
**Philippine Society of Maternal Fetal Medicine (PSMFM), Inc.**

**A Recognized Affiliate Subspecialty Society of the Philippine Obstetrical and Gynecological Society (POGS)**

# CLINICAL PRACTICE GUIDELINES on PRETERM LABOR AND BIRTH

**Fourth Edition**

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**Task Force on the Clinical Practice Guidelines on Preterm Labor and Birth**

# TABLE OF CONTENTS


**PART I: BACKGROUND**

1 Epidemiology ..... 1
*Valerie P. Tiempo-Guinto, MD and Maynila E. Domingo, MD*

2 Individualizing Risk Indicators for Preterm Birth ..... 7
*Anita Matilda F. Poblete, MD and Carmela G. Madrigal-Dy, MD*

3 Pathogenesis of Spontaneous Preterm Birth ..... 20
*Aurora Victoria A. Avelino, MD*

4 Clinical Diagnosis of Preterm Labor ..... 26
*Marie Scent Vera Fopalan-Benedicto, MD*

5 Predictors of Preterm Birth ..... 33
*Christine Vivienne Succor F. Tantoco, MD and Clarissa L. Velayo, MD*

6 Antimicrobial Agents in Preventing Preterm Labor ..... 70
*Valiant L. See, MD*

7 Antenatal Lower Genital Infection Screening Tests to Prevent Preterm Labor ..... 72
*Valiant L. See, MD*

**PART II: PREVENTION OF PRETERM BIRTH**

8 Progesterone Therapy ..... 75
*Joseph U. Olivar, MD*

9 Omega 3 and Fatty Acids ..... 88
*Valerie P. Tiempo-Guinto, MD*

**PART III: MANAGEMENT OF PRETERM LABOR: PHARMACOLOGIC AND NON-PHARMACOLOGIC INTERVENTIONS**

10 Cervical Cerclage ..... 100
*Marie Catheleen P. Santiago, MD*

11 Cervical Pessary ..... 105
*Marjorie I. Santos, MD*

12 Calcium Channel Blockers ..... 110
*Gumersinda Cruz-Javier, MD and Anna Konsuelo R. Chua, MD*

13 Betamimetics ..... 122
*Kristine Therese R. Elises-Molon, MD and Ireene G. Cacas-David, MD*

14 Oxytocin Receptor Antagonist ..... 133
*Edeliza Elvambuena-Amorin, MD and Joseph Carl M. Macalintal, MD*

15 Magnesium Sulfate ..... 138
*Zarinah G. Gonzaga, MD*

# TABLE OF CONTENTS

**PART IV: MANAGEMENT OF PRETERM LABOR: IMPROVING NEONATAL OUTCOMES**

16 Antenatal Corticosteroids ..... 143
*Leah Socorro N. Rivera, MD and Jacqueline Perote-Pedroso, MD*

17 Magnesium Sulfate for Neuroprotection ..... 156
*Marie Catheleen P. Santiago, MD*

18 Intrapartal Surveillance and Delivery ..... 161
*Jocelyn Cenizal-Bambalan, MD, Joanna Pauline Chua Ursua, MD, and Ma. Cresilda Paz B. Salamilao-Sabularce, MD*

**PART V: PRETERM LABOR IN SPECIAL CIRCUMSTANCES**

19 Preterm Labor in Special Circumstances ..... 170
*Maria Geraldine Assumption Gavina N. Castillo-Torralba, MD*

**PART VI: PERIVIABLE BIRTH**

20 Obstetrical Perspectives ..... 175
*Leslie R. Rigor, MD*

21 Neonatal Perspectives ..... 190
*Belen Amparo E. Velasco, MD*

**PART VII: OPTIMIZING MANAGEMENT OF PRETERM BIRTHS**

22 Government Initiatives ..... 211
*Mila D. Zaragoza-Ibay, MD and Ma. Lourdes A. Salaveria-Imperial, MD*

23 Care of Preterm Infants ..... 217
*Emilio A. Hernandez, Jr., MD*

APPENDICES

Appendix I ..... 231

Appendix II ..... 232

Chapter 1

# Epidemiology

Valerie P. Tiempo-Guinto, MD, MSc, FPOGS, FPSMFM, FPSUOG
Maynila E. Domingo, MD, FPOGS, FPSMFM, FPSUOG

The World Health Organization, American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) define ***preterm birth*** as delivery of an infant before 37 completed weeks (i.e., before completion of 259 days from the first day of the last normal menstrual period). It is further categorized to (a) ***extremely preterm birth***, which is delivery at less than 28 weeks age of gestation (AOG); (b) **very preterm birth**, which is delivery between 28 to 32 weeks AOG; and (c) **moderate to late preterm birth**, which is delivery at 32 to 36 6/7 weeks age of gestation. The ACOG defines **late preterm birth** as the delivery of an infant between 34 0/7 weeks and 36 6/7 weeks of gestation (i.e., 239 to 259 days after the first day of the LMP). This is considered an important category because late preterm infants still have higher morbidity and mortality rates compared to term infants because they are still physiologically and metabolically immature despite having a size and weight comparable to term newborns.[1]

Preterm birth remains a global health problem because it is still the leading cause of mortality in children less than 5 years of age around the world.[2] According to the latest global estimate, there are 15 million preterm births annually, indicating that 1 out of 10 newborns are delivered before 37 weeks.[3]

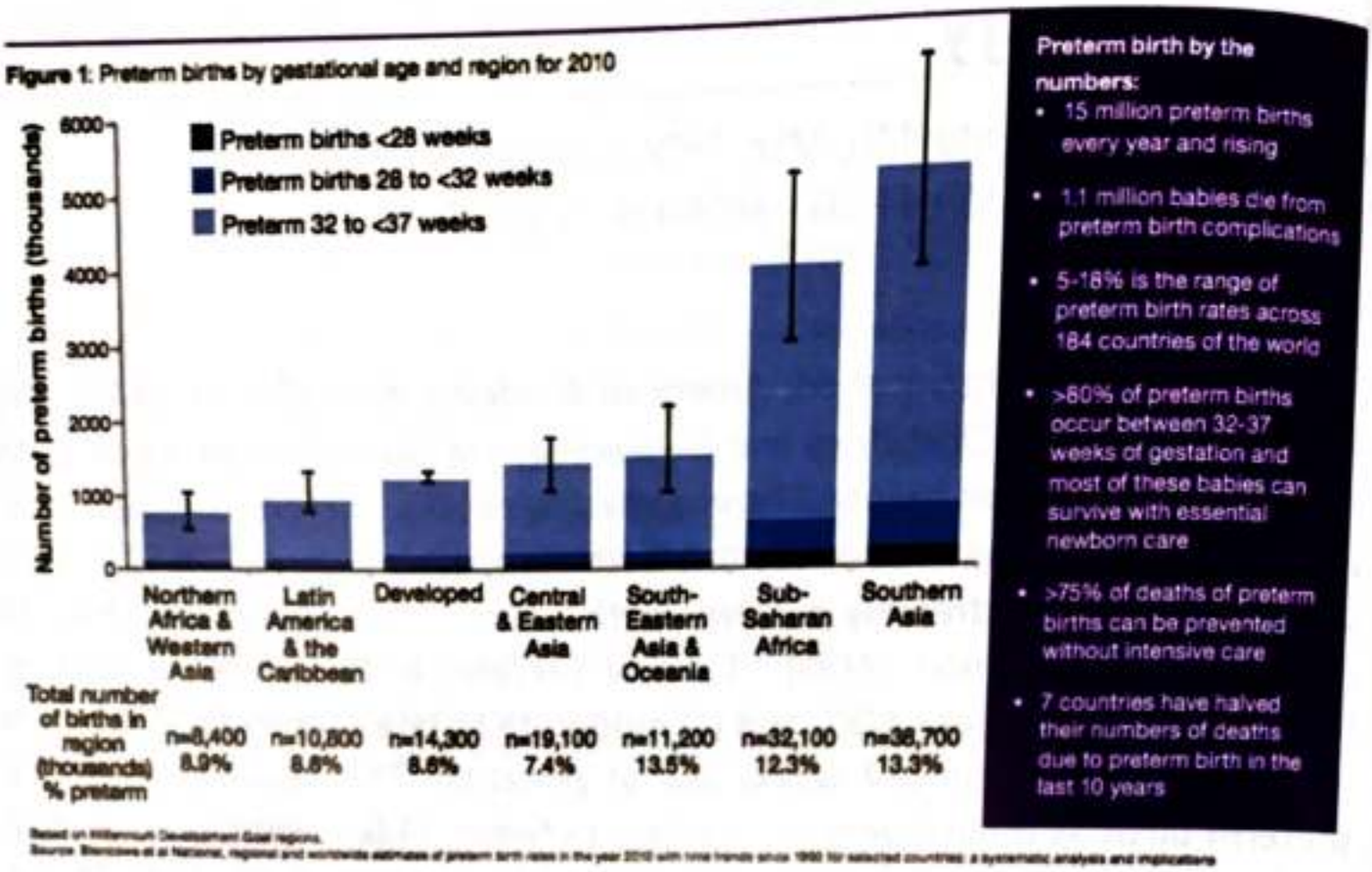


**FIGURE 1. PRETERM BIRTHS BY GESTATIONAL AGE AND REGION**

*Blencowe H, Cousens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013; 10 Suppl 1:S2.*


**FIGURE 2. ESTIMATED NUMBERS OF PRETERM BIRTHS IN 2014**

*Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019; 7:e37-e46.*

In 2010, WHO estimates that at least 60% of preterm births are from Africa and South Asia (Figure 2), with lower-income countries having higher rates compared to higher-income countries (12% vs 9%).[3] A new systematic review showed that in 2014, Asian and sub-Saharan African countries accounted for 78.9% of livebirths and 81.1% of preterm births worldwide.[4] The Philippines ranks 8th among the top 10 countries with the highest number of preterm births, with a reported **348 900** preterm deliveries in 1 year (Table 1).

**TABLE 1. TOP 10 COUNTRIES WITH HIGHEST NUMBER OF PRETERM BIRTHS (DATA FROM WORLD HEALTH ORGANIZATION)**

| COUNTRY | |
|---|---|
| **1. India** | 3, 519,1000 |
| **2. China** | 1,172,3000 |
| **3. Nigeria** | 773,600 |
| 4. Pakistan | 748,100 |
| 5. Indonesia | 675,700 |
| 6. United States of America | 517,400 |
| 7. Bangladesh | 424,100 |
| **8. Philippines** | **348,900** |
| 9. Democratic Republic of Congo | 341,400 |
| 10. Brazil | 279,300 |

Local data from the years 2014 to 2018 collected from accredited public and private training institutions of the Philippine Obstetrical and Gynecological Society (POGS) showed that preterm live birth rate in the Philippines ranges from 7% to 37%. The preterm stillbirth rate ranges from 32.22% to as high as 95.68%, recorded in 2014. Preterm neonatal death rate is from 27.13% to 73.78% (Table 2).

**TABLE 2. INCIDENCE OF PRETERM BIRTHS ACCORDING TO POGS FROM 2014 TO 2018**

| | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|
| **Total No. of Deliveries** | **32,912** | **71,630** | **96,382** | **128,070** | **163,724** |
| **Total No. of Livebirths** | **32,033** | **70,746** | **94,605** | **126,330** | **161,767** |
| Preterm Live Births | 2,510 (7.84%) | 4,941 (6.98%) | 34,587 (36.56%) | 9,479 (7.50%) | 13,979 (8.64%) |
| Term Live Births | 29,523 | 65,805 | 60,018 | 116,851 | 147,788 |
| **Total No. of Stillbirths** | **879** | **720** | **1072** | **943** | **796** |
| Preterm Stillbirths | 841 (95.68%) | 232 (32.22%) | 598 (55.78%) | 553 (58.64%) | 428 (53.77%) |
| Term Stillbirths | 38 | 488 | 474 | 390 | 368 |
| **Total No. of Neonatal Deaths** | **No data** | **164** | **705** | **797** | **1161** |
| Preterm Neonatal Deaths | No data | 121 (73.78%) | 262 (37.16%) | 217 (27.22%) | 315 (27.13%) |
| Term Neonatal Deaths | No data | 43 | 443 | 580 | 846 |

*POGS = Philippine Obstetrical and Gynecological Society*
*From POGS Annual Perinatal Statistics, 2014 - 2018*

Looking at the data from a tertiary referral center, University of the Philippines–Philippine General Hospital (UP-PGH), a higher preterm live birth rate of 22.80% to 25.29% is seen. Likewise, the preterm neonatal death rate is also higher, ranging from 68.3% to 80.5% (Table 3). This may be attributed to a higher incidence of preterm births in pregnancies complicated by other medical or surgical co-morbidities.

**TABLE 3. INCIDENCE OF PRETERM BIRTHS IN UP-PGH FROM 2014 TO 2018**

| | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|
| **Total No. of Deliveries** | **4893** | **4279** | **5126** | **5461** | **4253** |
| **Total No. of Livebirths** | **4787** | **4179** | **5035** | **5393** | **4203** |
| Preterm Live Births | 1130 (23.61%) | 1057 (25.29%) | 1148 (22.80) | 1238 (22.96%) | 1003 (23.86%) |
| Term Live Births | 3657 | 3122 | 3887 | 4155 | 3200 |
| **Total No. of Stillbirths** | **106** | **100** | **91** | **68** | **50** |
| **Total No. of Neonatal Deaths** | **127** | **123** | **123** | **72** | **60** |
| Preterm Neonatal Deaths | 93 | 99 | 99 | 52 | 41 |
| Preterm Neonatal Death Rate | 73.2 % | 80.5% | 80.5% | 72.2% | 68.3% |
| Term Neonatal Deaths | 34 | 24 | 24 | 20 | 19 |

*UP-PGH = University of the Philippines–Philippine General Hospital*
*From UP-PGH Perinatal Statistics, 2014 - 2018*

Among the preterm neonatal deaths, national data showed that approximately 10–20% are infants born under the category of moderate to late preterm (Table 4). On the other hand, data from UP-PGH showed that 20% of neonatal deaths are seen among infants born very preterm (Table 5). It can be inferred from this data that improvements in health care facilities, equipment and presence of well-trained specialists may improve survival of preterm infants, especially those who are under the category of moderate to late preterm.

**TABLE 4. PRETERM NEONATAL DEATHS ACCORDING TO AGE OF GESTATION ACCORDING TO POGS FROM 2014 TO 2018**

| AOG (in weeks) | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|
| 20 – 21 | No data | 3 | 8 | 7 | 10 |
| 22 – 27 | | 36 | 45 | 60 | 84 |
| 28 – 31 | | 38 | 93 | 65 | 100 |
| 32 – 36 | | 44 | 116 | 85 | 121 |
| 37 - 42 | | 42 | 440 | 571 | 834 |
| > 42 | | 1 | 3 | 9 | 12 |
| **TOTAL** | | **164** | **705** | **797** | **1161** |

*POGS = Philippine Obstetrical and Gynecological Society; AOG = age of gestation*
*POGS Annual Perinatal Statistics, 2014 - 2018*

**TABLE 5. PRETERM NEONATAL DEATHS ACCORDING TO AGE OF GESTATION ACCORDING TO UP-PGH FROM 2014 TO 2018**

| AOG (in weeks) | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|
| 20 – 27 6/7 | 35 | 31 | 30 | 18 | 13 |
| 28 – 33 6/7 | 42 | 55 | 53 | 23 | 21 |
| 34 – 36 6/7 | 16 | 13 | 16 | 11 | 7 |
| 37 – 40 6/7 | 31 | 21 | 20 | 19 | 17 |
| 41 – 42 6/7 | 3 | 3 | 2 | 1 | 2 |
| > 42 | 0 | 0 | 2 | 0 | 0 |
| **TOTAL** | **127** | **123** | **123** | **72** | **60** |

*UP-PGH = University of the Philippines–Philippine General Hospital; AOG = age of gestation*
*From UP-PGH Perinatal Statistics, 2014 - 2018*

Looking at the global and local data, it is evident that preterm birth remains a major health risk because it is associated with poor perinatal outcomes. Furthermore, it predisposes survivors to long term sequelae, including neurocognitive delay, physical disabilities and higher risk of metabolic disorders. All of these complications impose social and economic burden,

hence causing a significant impact to the society. Further local studies are needed to demonstrate the actual cost of treatment for preterm birth. Moreover, there is a need to come up with better data collection methods to show a more accurate statistics and have better analysis of the actual local situation. This can aid in health system analysis and can help public health leaders identify any gaps in the existing antenal care protocol. These gaps, if identified, can assist in designing guidelines or protocol to achieve the millennium sustainable goal of decreasing preterm births.

## References


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Chapter 2

# Individualizing Risk Indicators for Preterm Birth

Anita Matilda F. Poblete, MD, FPOGS, FPSMFM, FPSUOG
Carmela G. Madrigal-Dy, MD, FPOGS, FPSMFM, FPSUOG

Identification of women whose pregnancies are at higher than average risk of preterm labor and delivery would allow the possibility of providing the women with higher level antenatal care with the aim of preventing the preterm birth. The purpose of this chapter is to provide an overview of current knowledge about risk indicators for spontaneous preterm birth.

However, it must be emphasized that approximately 45–50% of all preterm births are idiopathic, occurring among women with no identifiable risk factors. In addition, the direct causality of risk factors has been difficult to establish, as some factors may show an association but may not necessarily be causative, and may involve co-factors to exert their effect, thus complicating the chain of causality.

Nevertheless, with promising progress in the realm of prevention, particularly regarding the role of progesterone among women with short cervix at mid-pregnancy, identification of risk factors currently known to be (or not to be) associated with preterm birth provides a meaningful step in the right direction towards curbing trends in the incidence of preterm birth, and as well may avoid unnecessary costly interventions or prohibitions for unproven risks.

| | |
|---|---|
| **QUESTION** | **What information in the clinical history would increase the likelihood of preterm birth?** |
| **RECOMMENDATION** | The risk factors enumerated in Tables 1 and 2 increase the likelihood of preterm birth and should be considered in the preconceptional counseling and prenatal management of women. |

# TABLE 1. RISK FACTORS THAT INCREASE THE LIKELIHOOD OF PRETERM LABOR

| | Risk Factor Details | | Comparator | Type of Risk Ratio | Risk Ratio | 95% CI | Author and Year | Type of Study |
|---|---|---|---|---|---|---|---|---|
| **MATERNAL DEMOGRAPHICS** | | | | | | | | |
| **Ethnicity** | Black | | Non-Black | RR | 1.51 | 1.39–1.69 | Oliveira[1] 2018 | Systematic Review and Meta-Analysis |
| | Black parents | | White parents | aOR | 1.78 | 1.59–2.00 | Srinivasjois[2] 2012 | Systematic Review and Meta-Analysis |
| | Asian | | Non-Asian | aOR | 1.40 | 1.38–1.42 | Ratnasiri[3] 2018 | Retrospective Cohort |
| | Filipino parents | | White parents | aOR | 1.37 | 1.33–1.40 | Kim[4] 2016 | Retrospective Cohort |
| | Filipino immigrant | | Other East Asian immigrants to Canada | RR | 2.91 | 2.27–3.73 | Bartsch[5] 2017 | Retrospective Cohort |
| **Maternal Age (years)** | Young maternal age <16 | | >16 "no restriction as to age range of comparator" | OR | 1.68 | 1.34–2.11 | Gibbs[6] 2012 | Systematic Review and Meta-Analysis |
| | Advanced maternal age | ≥ 35 | 20–34 | OR | 1.21 | 1.16–1.27 | Pinheiro[7] 2019 | Meta-Analysis |
| | | > 40 | 35–40 | OR | 1.18 | 1.10–1.27 | | |
| **Short Maternal Height** | Below reference height for population | | Normal height per population reference ("Short": < 150cm or <170cm depending on population studied) | RR | 1.23 | 1.11–1.37 | Han[8] 2012 | Systematic Review and Meta-Analysis |
| **Marital Status** | *Unmarried* | | *Married* | OR | 1.22 | 1.14–1.31 | Shah[9] 2011 | Systematic Review and Meta-Analysis |
| ***Pre-Pregnancy Body Mass Index (BMI)*** | *Underweight* | *BMI <18.5* | *Normal BMI* | OR | 1.30 | 1.13–1.49 | Liu[10] 2016 | Systematic Review |
| | *Obesity* | *Obese I BMI 30 to <35* | Normal BMI | OR | 1.54 | 1.09–2.16 | Faucher[11] 2016 | Meta-Analysis |
| | | *Obese II BMI 35 to <40* | Normal BMI | aOR | 1.33 | 1.12–1.57 | Torloni[12] 2009 | Systematic Review and Meta-Analysis |
| | | *Obese III BMI >=40* | Normal BMI | aOR | 2.27 | 1.76–2.94 | | |
| ***Low Socio-Economic Status*** | High deprivation quintile | | Low Deprivation Quintile | OR | 1.67 | 1.42–1.96 | Weightman[13] 2012 | *Systematic Review and Meta-Analysis* |
| **Intendedness of Pregnancy** | Unintended | | Intended | OR | 1.31 | 1.09–1.58 | *Shah[14] 2011* | *Systematic Review* |
| | Unwanted | | Wanted | OR | 1.50 | 1.41–1.61 | | |

| | Risk Factor Details | Comparator | Type of Risk Ratio | Risk Ratio | 95% CI | Author and Year | Type of Study |
|---|---|---|---|---|---|---|---|
| **OBSTETRIC FACTORS** | | | | | | | |
| **Inter-pregnancy Interval of <6 months** | Risk of extreme prematurity (< 32 weeks) | ≥ 6 months | aOR | 1.58 | 1.40–1.78 | Wendt [15] 2012 | Systematic Review |
| | Risk of any preterm (< 37 weeks) | | aOR | 1.09 | 1.01–1.18 | | |
| **Assisted Reproduction** | IVF-ICSI | Spontaneously conceived | OR | 1.75 | 1.50–2.03 | Cavoretto[16] 2018 | Systematic Review and Meta-Analysis |
| **History of Prior Preterm Birth** | History of one prior spontaneous preterm birth | No history | Effect Size (Percentage Higher Risk) | 30% (1.30) | 27–34% (1.27–1.34) | Phillips[17] 2017 | Systematic Review and Meta-Analysis |
| | | No history | Absolute Relative Risk | 20% (1.20) | 19.9–20.6% 1.199–1.206 | Kazemier[18] 2014 | Meta-Analysis |
| | History of two prior spontaneous preterm birth | No history | aRR | 10.57 | 9.05–12.34 | Laughon[19] 2014 | Retrospective Cohort |
| | History of prior indicated preterm birth | No history | OR | 2.79 | 1.45–5.40 | Meis[20] 1998 | Prospective Cohort |
| | History of prior medically indicated preterm birth | No history | aOR | 10.6 | 10.1–12.4 | Ananth[21] 2006 | Retrospective Cohort |
| | History of prior preterm twin pregnancy | Prior term twin | OR | 3.12 | 1.42–6.85 | Menzies[22] 2018 | Retrospective Cohort |
| | | | Absolute RR (Percentage Higher Risk) | 10% | 8.2–12.3% | Kazemier[18] 2014 | Meta-Analysis |
| **History of Previous Stillbirth** | Any stillbirth | No stillbirth | OR | 2.82 | 2.31–3.45 | Malacova [23] 2018 | Systematic Review and Meta-Analysis |
| **Previous Term Cesarean Delivery** | In first pregnancy | Previous term vaginal delivery | aOR | 1.12 | 1.01–1.24 | Zhang[24] 2019 | Systematic Review and Meta-Analysis |
| **History of D&C** | As treatment for miscarriage or termination of pregnancy | No prior D&C | OR | 1.29 | 1.17–1.42 | Lemmers[25] 2016 | Systematic Review and Meta-Analysis |
| **History of Multiple D&C** | As treatment for miscarriage or termination of pregnancy | No prior D&C | OR | 1.44 | 1.22–1.69 | | Systematic Review and Meta-Analysis |

| | Risk Factor Details | | Comparator | Type of Risk Ratio | Risk Ratio | 95% CI | Author and Year | Type of Study |
|---|---|---|---|---|---|---|---|---|
| **OBSTETRIC FACTORS (continued)** | | | | | | | | |
| **Multifetal Pregnancy** | Twins | IVF -CSI | Spontaneously conceived | RR | 1.54 | 1.47–1.62 | Pandey[26] 2012 | Systematic Review and Meta-Analysis |
| | Triplets | Triplets | Twins | RR | 4.11 | 2.89–5.83 | van de Mheen[27] 2014 | Retrospective Cohort |
| | | Dichorionic-Triamniotic triplets | Monochorionic triplets | OR | 4.6 | 1.6–11.8 | Adegbite[28] 2005 | Retrospective Cohort |
| **Male Fetal Gender** | Preterm birth (28–31 weeks) | | Female gender | RR | 1.5 | 1.3–1.7 | Peelen[29] 2015 | National Cohort 1,947,266 Births Netherlands |
| | High risk cohort male | | High risk cohort female | RR | 1.07 | 0.82–1.46 | Teoh[30] 2018 | High Risk Prospective Cohort (2,505) |
| **Inadequate Prenatal Care** | Percentage of recommended visits (among adolescents) | 0 | 75–100% of recommended visits | aOR | 7.4 | 5.7 – 9.7 | Debiec[31] 2010 | Retrospective Cohort |
| | | <25 | | aOR | 2.5 | 1.9 – 3.3 | | |
| | | 25 – 49 | | aOR | 1.5 | 1.2 – 1.8 | | |
| | | 50 – 74 | | aOR | 1.3 | 1.1 – 1.5 | | |
| ***Content and Timing of Prenatal Care in Pregnancy (CTP)*** | *CTP "sufficient"* | | *CTP lowest ("inadequate") category* | OR | 0.30 | 0.09 – 0.94 | Beeckman[32] 2013 | Prospective Cohort |
| | *CTP "appropriate"* | | | OR | 0.21 | 0.06 – 0.68 | | |
| ***Low Pregnancy Weight Gain*** | As per Institute of Medicine (IOM) | | Normal pregnancy weight gain | RR | 1.64 | 1.62 – 1.65 | Han[33] 2011 | Meta-Analysis |
| | | | | Likelihood Ratio (LR) | 1.8 | 1.5 – 2.3 | Honest[34] 2005 | Systematic Review and Meta-Analysis |
| | | | | OR | 1.70 | 1.32 – 2.20 | Goldstein[35] 2017 | Systematic Review and Meta-Analysis |

| | Risk Factor Details | | Comparator | Type of Risk Ratio | Risk Ratio | 95% CI | Author and Year | Type of Study |
|---|---|---|---|---|---|---|---|---|
| **NUTRITIONAL** | | | | | | | | |
| **Maternal Anemia** | In the first trimester | | No anemia | RR | 1.56 | 1.25–1.95 | Rahmati[36] 2019 | Systematic Review and Meta-Analysis |
| **Vitamin D Status** | Deficiency (< 30 nMol/L) | | No deficiency (≥ 30 nMol/L) | OR | 1.59 | 1.24–2.03 | Tous[37] 2019 | Systematic Review and Meta-Analysis |
| | Insufficiency (< 50 nMol/L) | | No insufficiency (≥ 50 nMol/L) | OR | 1.28 | 1.08–1.52 | | |
| **Maternal Omega-3 Fatty Acid status** | Lowest Quintile (<1.6% EPA/DHA % total fatty acids) | | Highest Quintiles (3rd to 5th) (>1.8%) | OR | 10.27 | 6.80–15.79 | Olsen[38] 2018 | Case-Control |
| **Poor Preconception Diet** | High-fat / sugar / takeaway (takeaway foods, potato chips, refined grains) | | High-protein / fruit (characterized by fish, meat, chicken, fruit, and some whole grains) or vegetarian-type (vegetables, legumes, whole grains) | aOR | 1.54 | 1.10–2.15 | Grieger[39] 2014 | Retrospective Cross-Sectional |
| **Consumption of Fruits and Vegetables** | Low (5 portions of fruits and vegetables a day less than once a week) | | Higher (5 portions of fruits and vegetables a day at least once a week) | RR | 1.31 | 1.03–1.66 | Smith[40] 2015 | Population-Based Case-Cohort |
| **LIFESTYLE / BEHAVIORAL** | | | | | | | | |
| **Smoking** | Smoking during pregnancy | | No smoking | OR | 1.27 | 1.21–1.33 | Shah[41] 2000 | Systematic Review and Meta-Analysis |
| **Passive Maternal Smoking (Second Hand Smoke)** | Passive maternal smoking | Exposed (Any place) | Not Exposed | sOR | 1.20 | 1.07–1.34 | Cui[42] 2016 | Meta-Analysis |
| | | Exposed (At home) | | sOR | 1.16 | 1.04–1.30 | | |
| **Alcohol** | Excess alcohol consumption (≥3 units/day) | | No Alcohol | RR | 1.23 | 1.05–1.44 | Patra[43] 2011 | Systematic Review and Meta-Analysis |
| **Illicit Drug Use** | Marijuana use during pregnancy | | No exposure | RR | 1.32 | 1.14–1.54 | Conner[44] 2016 | Systematic Review and Meta-Analysis |
| | Methamphetamine use during pregnancy | | No exposure | Mean Difference (weeks) | (-0.9) | (-0.11) – (-1.69) | Kalaitzopoulos[45] 2019 | Systematic review and Meta-Analysis |
| **Douching** | Vaginal douching during pregnancy | Early preterm birth (<34 weeks) | No douching | aOR | 6.9 | 1.7 – 28.2 | Luong[46] 2010 | Case Control |
| | | Preterm birth (<37 weeks) | No douching | aOR | 3.7 | 1.3 – 10.3 | | |

| | Risk Factor Details | Comparator | Type of Risk Ratio | Risk Ratio | 95% CI | Author and Year | Type of Study |
|---|---|---|---|---|---|---|---|
| **LIFESTYLE / BEHAVIORAL (continued)** | | | | | | | |
| **Work** | Long working hours during pregnancy (>40 hours/week) | Maximum 40 hours/week | OR | 1.25 | 1.01 – 1.54 | van Melick[47] 2014 | Systematic review and Meta-Analysis |
| | Lifting 5 kg/day | Less than 5 kg/day | OR | 1.29 | 1.05 – 1.57 | van Beukering[48] 2014 | Systematic Review and Meta-Analysis |
| | Standing and walking at work (>3 hours/day) | No standing and walking | OR | 1.33 | 1.11 – 1.59 | | |
| **Sleep-Disordered Breathing** | Obstructive sleep apnea (OSA) | No OSA | aOR | 1.6 | 1.2 – 2.2 | Warland[49] 2018 | Scope Review and Meta- Analysis |
| **INFECTIONS** | | | | | | | |
| **Chlamydia** | Prior Chlamydia trachomatis infection | No history of Chlamydia infection | OR | 2.2 | 1.0–4.8 | Ahmadi[50] 2018 | Systematic review and Meta-Analysis |
| **Bacterial Vaginosis (BV)** | Bacterial vaginosis infection during pregnancy Over-all | No BV | OR | 2.2 | 1.5–3.1 | Leitich[51] 2003 | Meta-Analysis |
| | <16 weeks of gestation | | | 7.55 | 1.80–31.65 | | |
| | <20 weeks of gestation | | | 4.20 | 2.11–8.39 | | |
| **Group B Streptococcus** | Maternal Group B Streptococcus colonization | Not colonized | RR | 1.21 | 0.99–1.48 | Bianchi-Jassir[52] 2017 | Systematic Review and Meta-Analysis |
| | | | OR | 1.85 | 1.24–2.77 | | |
| **Urinary Tract Infection** | Untreated asymptomatic bacteriuria (ASB) | Treated asymptomatic bacteriuria (ASB) | RR | 3.8 | 1.1–6.4 | Romero[53] 1989 | Meta-Analysis |
| **Candidiasis** | Candidiasis recurring in the 2nd trimester | Candidiasis occurring only in the 1st trimester | Percentage | 18% vs 10% | p=.0002 | Holzer[54] 2017 | Prospective Cohort |
| | Treatment of asymptomatic candidiasis colonization | Usual care | RR | 0.36 | 0.17–0.75 | Roberts[55] 2015 | Systematic Review and Meta-Analysis |
| **Periodontitis** | Periodontitis | No periodontitis | OR | 2.01 | 1.71–2.36 | Manrique-Corredor[56] 2019 | Systematic Review and Meta-Analysis |

| | Risk Factor Details | Comparator | Type of Risk Ratio | Risk Ratio | 95% CI | Author and Year | Type of Study |
|---|---|---|---|---|---|---|---|
| **PSYCHOSOCIAL FACTORS** | | | | | | | |
| **Anxiety** | Prenatal maternal anxiety | No maternal anxiety | OR | 1.70 | 1.33 – 2.18 | Rose[57] 2016 | Systematic Review and Meta-Analysis |
| **Depression** | Depression during pregnancy | No depression | RR | 1.39 | 1.19 – 1.61 | Grote[58] 2010 | Systematic Review and Meta-Analysis |
| | Depression during pregnancy (Untreated) | No depression | OR | 1.56 | 1.25 – 1.94 | Jarde[59] 2016 | Systematic Review and Meta-Analysis |
| | Antidepressant use for depression during pregnancy | No exposure during pregnancy | RR | 1.69 | 1.52 – 1.88 | Huang[60] 2014 | Systematic Review and Meta-Analysis |
| **Stress** | Maternal stress during pregnancy | Non-stressed | OR | 1.42 | 1.05 – 1.91 | Lima[61] 2018 | Systematic review and Meta-Analysis |
| **Intimate Partner Violence (IPV)** | Exposure to any form of intimate partner violence | Not exposed | OR | 1.42 | 1.21 – 1.63 | Hill[62] 2016 | Systematic Review and Meta-Analysis (19 studies) |
| | | Not exposed | OR | 1.91 | 1.60 – 2.29 | Donovan[63] 2016 | Systematic Review and Meta-Analysis (50 studies) |
| **History of Abuse Prior to Pregnancy** | Any abuse | No history | OR | 1.28 | 1.12 – 1.47 | Nesari[64] 2018 | Systematic Review and Meta-Analysis |

**Intimate partner violence (IPV)** refers to any maltreatment within an intimate relationship that leads to physical, psychological or sexual harm to those in the relationship
**Abuse** is defined as any attempt to control the behavior of another person and encompasses any direct or indirect physical, sexual or emotional maltreatment.
**RR** = relative risk
**OR** = odds ratio
**aOR** = adjusted odds ratio
**D&C** = dilatation and curettage
**IVF-ICSI** = in vitro fertilization - intracytoplasmic sperm injection
**EPA / DHA** = eicosapentaenoic acid / docosahexaenoic acid

**TABLE 2. RISK FACTORS STRATIFIED ACCORDING TO DEGREE OF MODIFIABILITY**

| Non-modifiable Antenatal Factors | |
|---|---|
| ***Demographic*** | ***Obstetric History*** |
| Ethnicity | History of prior preterm birth |
| Age | History of indicated preterm birth |
| Marital status | History of medically indicated preterm birth |
| Short maternal height | Pregnancy resulting from assisted reproductive technology |
| Intendedness of pregnancy | History of prior dilatation and curettage |
| Inter-pregnancy interval | Previous term cesarean delivery |
| Male fetal gender | |
| **Modifiable Factors** | |
| ***Behavioral*** | ***Nutrition*** |
| Smoking during pregnancy | Maternal underweight |
| Passive maternal smoking (second hand smoke) | Maternal obesity |
| Illicit drug use | Low pregnancy weight gain |
| Douching during pregnancy | Maternal anemia |
| Alcohol consumption (>3 units/day) | Vitamin D deficiency |
| | Low maternal omega-3 fatty acid status |
| | Low consumption of fruits and vegetables |
| **Unknown Modifiability** | |
| Socioeconomic status | |
| Prenatal maternal anxiety | |
| Maternal stress | |
| History of depression and/or use of anti-depressants | |
| History of intimate partner violence | |
| History of abuse | |
| **Potentially Modifiable Conditions** | |
| Long working hours | |
| Prolonged standing | |
| Lifting and carrying | |
| Short sleep duration | |
| Infections (Chlamydia, bacterial vaginosis, asymptomatic bacteriuria, periodontitis) | |

## SUMMARY

Many of the previously recognized risk factors for preterm birth are now being viewed in a new light. Risk ratios provided by the most recent meta-analysis studies give more accurate significant estimates of risk compared to simply citing one or a few trials, where risks may have been over or under-estimated. Factors receiving little attention can now be seen to confer risks not previously recognized. Evidence is also beginning to lay the ground for the many pieces of the complex and diverse pathways linking psychosocial factors to maternal and fetal outcome. Modifiable indicators such as short inter-pregnancy interval, vaginal and periodontal infection deserve closer attention in the local setting. With the knowledge of these indicators and their individual risk ratios, the clinician must be vigilant to screen for potential risks, even in the preconception period, so that they can counsel patients early enough and may be able to provide not only preventive or prophylactic interventions, but psychosocial as well as emotional support to their patients.

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Chapter 3

# Pathogenesis of Spontaneous Preterm Birth

Aurora Victoria A. Avelino, MD, FPOGS, FPSMFM, FPSUOG

Preterm births have been traditionally classified into two based on the circumstances surrounding the delivery.

- **Indicated preterm birth** – results from either induction of labor or cesarean section due to either a maternal or fetal illness
- **Spontaneous preterm birth** – occur either due to preterm labor with intact membranes or preterm prelabor rupture of membranes.[1] In a recent study with a more encompassing terminology, this may be associated with at least one of the following:
  1) preterm labor,
  2) preterm prelabor rupture of membranes, and
  3) cervical insufficiency[2]

This chapter focuses on the development of **spontaneous preterm births.** This involves three main processes known as the final common pathway of labor: 1) increased uterine contractility, 2) membrane rupture and 3) cervical ripening. These are the same processes that occur in term births, only that in cases of a preterm pregnancy, the activation of these is considered pathologic.[1] These processes may occur in no particular order and are intertwined and lead to one another. Rather than dictate recommendations, this chapter serves as a starting point for the clinician to understand how common risk factors eventually result in preterm labor at the molecular level, and hopefully result in future research on prevention, diagnosis, and management.

Preterm birth involves a number of pathways of different pathologies that may overlap resulting in the aforementioned final common pathway. The most commonly mentioned are these four major processes: 1) activation of the hypothalamic-pituitary-adrenal (HPA) axis; 2) infection and an inflammatory response; 3) decidual hemorrhage; 4) pathological uterine distention.[3] These processes are shown in Figure 1.

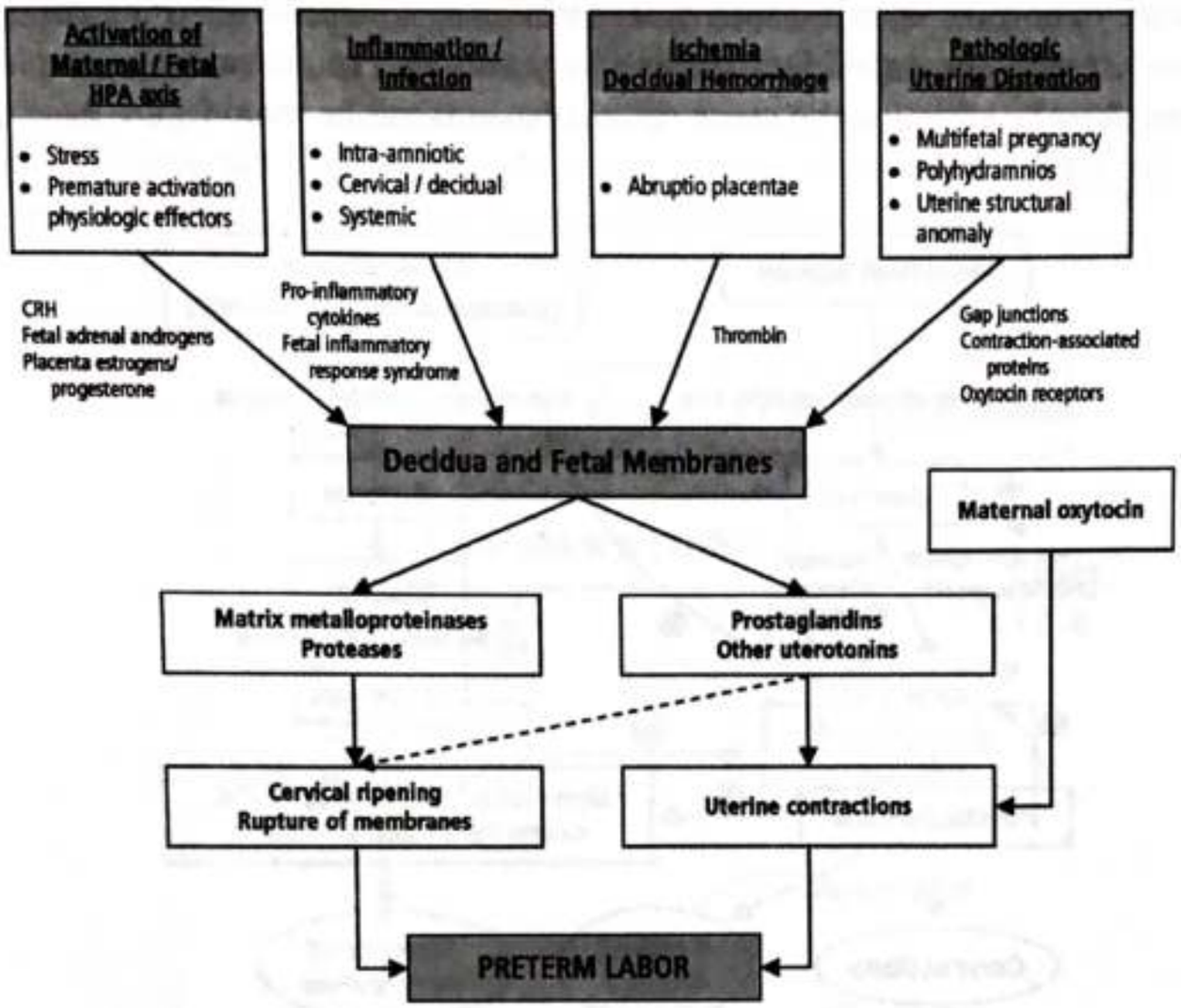


**FIGURE 1. OVERVIEW OF THE COMMONLY OCCURING PATHWAYS TO PRETERM BIRTH**

*Adapted from Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, editors. Preterm Birth: Causes, Consequences, and Prevention. Washington (DC): National Academies Press (US); 2007. 6, Biological Pathways Leading to Preterm Birth. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11353/. Figure 6-2. Overview of commonly occurring pathways to preterm birth.*

## *A. Preterm Activation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis*

Stress involves the production of cortisol. On the mother, this exhibits a negative feedback on the hypothalamus but stimulates placental production of corticotropin-releasing hormone (CRH), thereby further increasing the cortisol levels. Studies have shown that CRH modulates the production of prostaglandins, progesterone and estrogen, and affects myometrial contractility. In a prospective cohort study,[5] it was shown that increased stress levels measured by a scoring questionnaire and serial measurements of cortisol resulted in a 12% increase in preterm births.

Placental CRH also stimulates fetal adrenal zone. In one study, Salafia et al.[6] used fetal adrenal gland size as a predictor of preterm birth. Placental insufficiency

secondary to chronic villous or uteroplacental disease which causes intrauterine compromise and decreased fetal growth may also lead to activation of the fetal HPA axis thereby initiating the same series of events as shown in Figure 2.

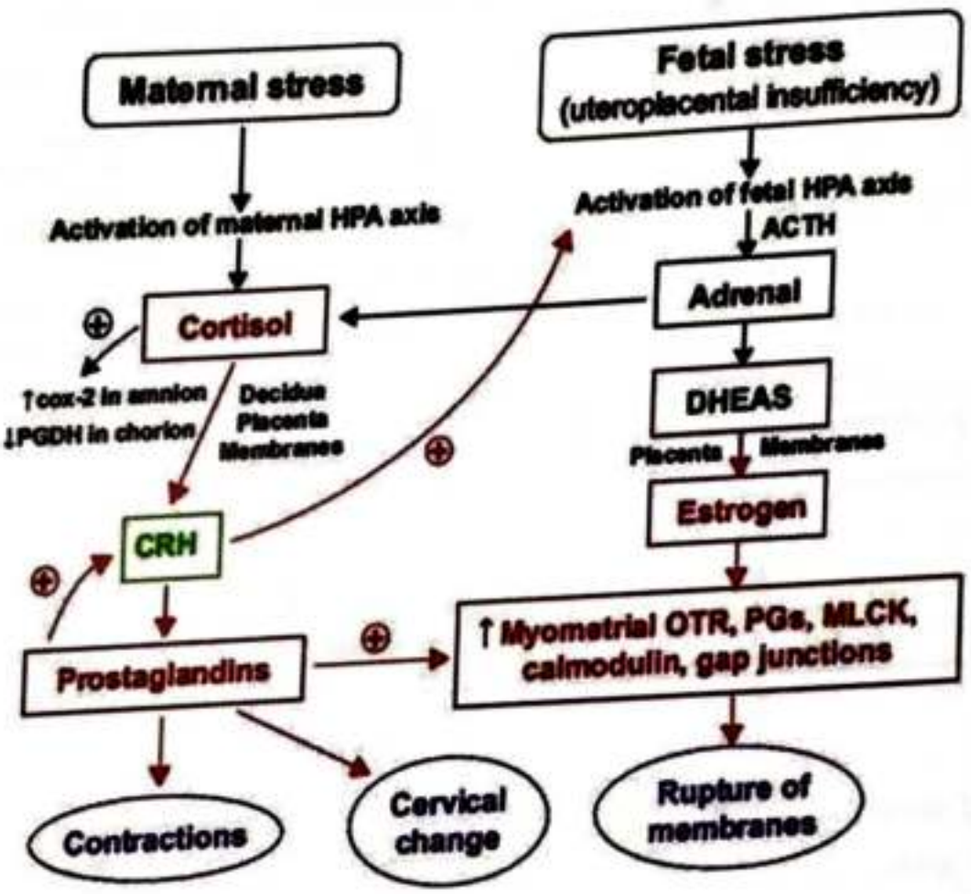


**FIGURE 2. PROPOSED PATHWAY OF STRESS-INDUCED PRETERM BIRTH**

*HPA Hypothalamic-Pituitary-Adrenal (HPA) Axis, COX-2 Cyclooxygenase 2; PGDH Prostaglandin dehydrogenase; ACTH Adrenocorticotropic hormone; CRH Corticotropin-releasing hormone; DHEAS 16-hydroxy-dehydroepiandrostendione sulfate; OTR oxytocin receptor; PG Prostaglandin; MLCK Myosin light chain kinase*

*Kota SK, Gayatri K, Jammula S, et al. Endocrinology of parturition. Indian J Endocrinol Metab 2013; 17:50-59. Figure 4, Maternal and fetal HPA axis and stress induced preterm birth; page 55.*

## *B. Infection and Inflammation*

Preterm birth is most commonly associated with infection. Pro-inflammatory cytokines such as IL-1β and TNF-α are central to infection-induced preterm birth.[1] Other pro-inflammatory mediators such as IL-6 were also found to be elevated in the amniotic fluid of women with PTL with intact membranes and these levels correlated well with positive results from culture of the amniotic fluid and fetal membranes.[8] IL-6 would then increase the amount of uterotonins such as prostaglandins and endothelins, thereby initiating uterine contractions.

The inflammatory response in preterm labor may also be secondary to certain bacteria, which produce proteases, collagenases, and elastases that can degrade the fetal membranes or produce cervical change. There is also an additive effect that the same bacteria also produce endotoxins and phospholipase A2, which stimulate uterine contractions that lead to preterm labor.[1]

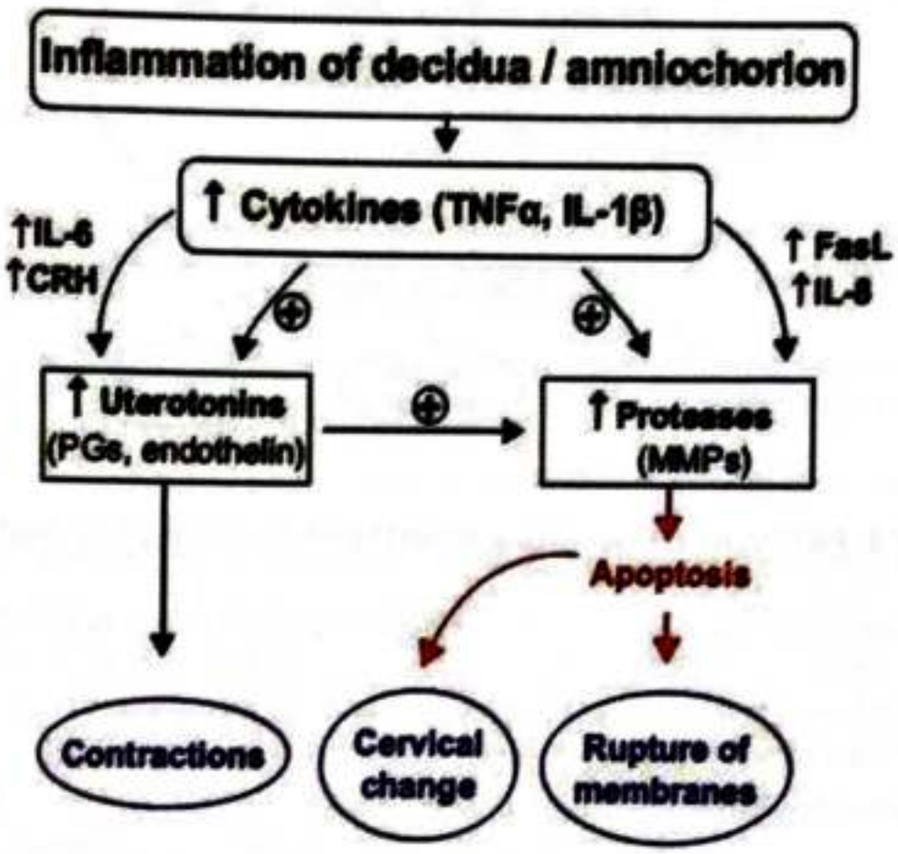


**FIGURE 3. AMNIOCHORIONIC INFECTION CAUSING PRETERM LABOR**

*TNFα Tumor necrosis factor alpha; IL interleukin; CRH Corticotropin-Releasing Hormone; FasL Fas ligand; PG Prostaglandin, MMP Matrix Metalloproteinase*

*Kota SK, Gayatri K, Jammula S, et al. Endocrinology of parturition. Indian J Endocrinol Metab 2013; 17:50-59. Figure 5, Inflammation of decidua -amniochorion and preterm labor; page 55.*

## *C. Decidual Hemorrhage*

Vaginal bleeding from decidual hemorrhage is associated with a high risk of preterm labor. In one study, even occult decidual hemorrhage was present in 38% of patients with PTB between 22 and 32 weeks of gestation due to PPROM and 36% of patients experiencing PTB secondary to PTL.[9] The presence of decidual hemorrhage releases a number of clotting factors including factor VIIa, tissue factor, and factor Xa, all of which may contribute to the initiation of contractions, as well as produce a cascade which leads to either cervical change or rupture of membranes.

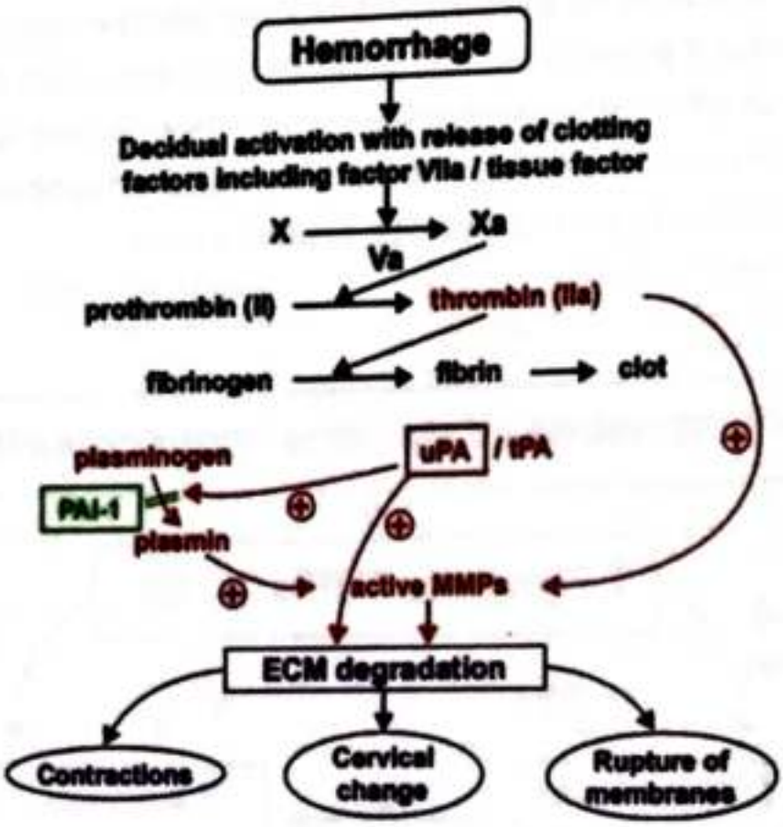


**FIGURE 4. PATHWAY OF DECIDUAL HEMORRHAGE LEADING TO PRETERM LABOR**

*uPA Urokinase plasminogen activator; tPA Tissue-type plasminogen activator; PAI-1 Plasminogen activator inhibitor 1; MMP Matrix Metalloproteinase; ECM Extracellular matrix*

*Kota SK, Gayatri K, Jammula S, et al. Endocrinology of parturition. Indian J Endocrinol Metab 2013; 17:50-59. Figure 6, Hemorrhage and preterm labor; page 55.*

## *D. Pathological Uterine Distension*

Pathological uterine distention may be secondary to polyhydramnios, multifetal gestation, or fetal macrosomia. These conditions distend both the uterus and the amniotic membrane, which is not as distensible as the former. Stretching of the myometrium beyond what is physiologic induces formation of gap junctions, which increases the response of oxytocin receptors, activates prostaglandin E2 and F2, as well as myosin light chain kinase producing uterine contractions and cervical ripening and dilatation.[3]

## CERVICAL INSUFFICIENCY

The previous pathways that lead to spontaneous preterm birth start with either preterm labor or preterm prelabor rupture of membranes leading to cervical remodeling and ripening. For cervical insufficiency, it is thought that cervical change occurs first. In these cases, a genetic factor may play a role. One study

showed that enhancing G13 allele in the anti-inflammatory IL-10.G microsatellite occurred more frequently in patients diagnosed with cervical insufficiency.[10]

The previous pathways that lead to spontaneous preterm births start with either preterm labor or preterm prelabor rupture of membranes leading to cervical remodeling and ripening. For cervical insufficiency, it is thought that cervical change occurs first but will still eventually trigger the other pathways to occur.[11]

## References


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Chapter 4

# Clinical Diagnosis of Preterm Labor

Marie Scent Vera Fopalan-Benedicto, MD, MBAH, FPOGS, FPSMFM, FPSUOG

Spontaneous preterm birth remains the leading cause of perinatal morbidity and mortality in many parts of the world, including the Philippines. The diagnosis of preterm labor is based on clinical criteria of regular uterine contractions before 37 weeks that are associated with cervical change.[1] Preterm labor is defined as uterine contractions (>4 contractions per 20 minute), cervical dilatation (>2 cm in a nulliparous and >3 cm in a multipara) and cervical effacement (>80%) or uterine contractions and cervical change.[2]

| **QUESTION 1** | **Among patients at high risk for preterm delivery, what is the contraction rate that can identify those women who are at increased risk for preterm birth?** |
|---|---|

**RECOMMENDATION**

1.1. A threshold rate of at least four contractions per hour on a monitor strip should be used to identify a patient at increased risk for preterm labor.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

1.2. Women reporting signs that they attribute to possible preterm labor or rupture of the membranes should be taken seriously and adequately evaluated. Self-perceived symptoms are poor predictors of preterm birth.[3]

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

1.3. Uterine activity should be assessed by palpation in all women presenting with any sign of preterm labor. The progression from subclinical preterm to overt preterm labor is

often gradual. Standard criteria for the diagnosis of preterm labor lack precision.[4]

*Quality of Evidence: Moderate*
*Strength of Recommendation: Moderate*

## SUMMARY OF EVIDENCE

In a randomized multi-center study by Bentley et al.,[5] an analysis was conducted to determine the association of at least four contractions per hour on a routine strip followed by at least four contractions per hour on a repeat tracing with subsequent preterm labor. Using this threshold, 70% of the patients were correctly classified. This contraction rate resulted in a sensitivity of 57%, a specificity of 80%, a positive predictive value of 72%, and a negative predictive value of 68%. A threshold rate of at least four contractions per hour on a monitor strip identifies a patient at increased risk for preterm labor (P=.003).

| **QUESTION 2** | **Among patients with uterine contractions, how accurate is cervical dilatation in diagnosing preterm labor?** |
|---|---|

**RECOMMENDATION** The traditional criteria for labor, persistent uterine contractions accompanied by dilatation or effacement of the cervix, or both, are reasonably accurate when the frequency is six or more contractions per hour, cervical dilatation is 3 cm or more, effacement is 80 percent or greater, and membranes rupture or bleeding occurs.[8]

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Glover et al.[6] conducted a secondary analysis of a multicenter randomized control trial (RCT) of women with singleton, non-anomalous pregnancies at 34 0/7 to 36 5/7 weeks gestation at high risk for preterm birth. The analysis showed that a cervical dilatation cut-off of >4cm was 60% sensitive and 68%

specific for preterm birth (area under the curve, AUC=0.64, 95% CI 0.61–0.68). A cervical effacement cut-off of >75% was 59% sensitive and 65% specific for preterm birth (AUC=0.62, 95% CI 0.58–0.65). Forty-one percent (41%) of women presenting with frequent uterine contractions and cervical dilatation and /or effacement at 34 to 36 5/7 weeks delivered at term.

The traditional criteria for labor, persistent uterine contractions accompanied by dilatation or effacement of the cervix, or both, are reasonably accurate when the frequency is six or more contractions per hour, cervical dilatation is 3 cm or more, effacement is 80 percent or greater, and membranes rupture or bleeding occurs. [7]

| **QUESTION 3** | **Among patients with uterine contractions, how accurate is transvaginal ultrasound cervical length assessment in diagnosing preterm labor?** |
|---|---|
| **RECOMMENDATION** | There is lack of compelling evidence for the use of cervical measurement alone in women with threatened preterm labor.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

A 2016 systematic review and meta-analysis of RCTs using individual patient-level data concluded that knowledge of cervical length in women with symptoms of acute preterm labor was associated with a significant reduction in preterm birth < 37 weeks gestation (RR 0.64,95% CI:0.44-0.94).[8] However, the other outcomes, which included preterm birth <36, <34, <32, <30, and <28 weeks gestation, time from randomization to delivery, time from evaluation to discharge, and other neonatal outcomes were not statistically different between those who had knowledge of cervical length and those who did not. Thus, the clinical impact of cervical measurement in this population remains unclear.

**RECOMMENDATION** Routine use of cervical length screening in low-risk population is not recommended

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

It has been shown in two RCTs that utilized universal screening in large cohorts,[9,10] that treatment with vaginal progesterone is associated with an approximately 40% reduction in the risk of preterm birth in women with short cervix (with inclusion criterion of a cervical length <15mm[4] or 10-20mm[3]). However, it is notable that the frequencies of a CL <15mm or CL 10-20mm in these mostly "low-risk" populations (about 80% of enrolled women had no prior preterm birth) were 1.7%[9] and 2.3%,[10] respectively. Furthermore, in subsequent studies of the implementation of universal cervical length screening programs, the frequency of a short cervix in women without a history of a prior preterm birth has ranged from 1% to 2% depending on the cervical length threshold used.[11-13]

There remains a significant debate about the utility of universal cervical length screening of women with singleton gestations but without prior preterm birth for the prevention of preterm birth given the relatively low frequency of a short cervical length in this population. Still, a large observational study showed that introduction of an institutional universal cervical length screening program was associated with a significant decrease in the frequency of preterm birth <37 weeks [6.7% vs. 6.0%; adjusted OR 0.82 (95% CI: 0.76-0.88)], <34 weeks [1.9% vs 1.7%; adjusted OR 0.74 (95% CI 0.64-0.85)], and <32 weeks gestation [1.1% vs 1.0%, adjusted OR 0.74 (95% CI:0.62-0.90)], and the reduction was primarily due to a reduction in spontaneous preterm birth.[14]

**QUESTION 4** **Among patients with regular uterine contractions, how accurate is fetal fibronectin assessment in diagnosing preterm labor?**

**RECOMMENDATION** Routine fetal fibronectin screening alone is not recommended in women with threatened preterm labor.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

A 2016 systematic review and meta-analysis of six RCTs with a low risk of bias that included 546 women with singleton gestations who presented with preterm labor symptoms found that those randomly assigned to the knowledge of fetal fibronectin results did not have reduced rates of preterm birth at <37 weeks, <32 weeks, or <28 weeks compared with the control group.[15] Women who were randomly assigned to fetal fibronectin results also had similar rate of hospitalization, use of tocolytics, and receipt of antenatal corticosteroids when compared with women without knowledge of fetal fibronectin results. Contrary to results, mean hospital costs were actually higher in the group randomly assigned to knowledge of fetal fibronectin (mean difference $153, 95% CI $24 to $282). There is no reason to justify the routine use of fetal fibronectin alone in women with threatened preterm labor.[16]

**QUESTION 5** **Among patients with regular uterine contractions, how accurate is fetal cervical length measurement in conjunction with fibronectin assessment in diagnosing preterm labor?**

**RECOMMENDATION** There is no high quality data to suggest addition of fibronectin determination to cervical length measurement in women with symptoms of preterm labor will significantly improve prediction and be helpful in the clinical management of preterm labor.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

The largest prospective cohort of 665 women with threatened preterm labor (≥3 contractions in 30 minutes, intact membranes, cervix <3cm dilated) were enrolled between 24 and 34 weeks gestation, and underwent cervical length and fetal fibronectin assessment at all 10 tertiary perinatal centers in the Netherlands. [17] They found that women with a cervical length ≥30 mm or those with a cervical length 15-30 mm and a negative fetal fibronectin result were at low risk (defined as <5% of spontaneous delivery within 7 days. Negative fetal fibronectin testing in women with a cervical length between 15 and 30 mm additionally classified 103 women (15% of the cohort) as low risk. However, the overall rate of delivery within 7 days was only 12%, and the combination of cervical length and fetal fibronectin only increased the PPV from 0.23 (95% CI;0.19-0.29) to 0.27 (95% CI 0.22-0.33). [18]

The positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms.[19]

No recommendations on the following can be made due to insufficient evidence:

1. Repeat cervical digital cervical assessment in asymptomatic women, while not harmful is not beneficial.
2. Self- testing of vaginal pH is not efficacious in the prevention of preterm delivery.

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Chapter 5

# Predictors of Preterm Birth

Christine Vivienne Succor F. Tantoco, MD, FPOGS, FPSMFM, FPSUOG
Clarissa L. Velayo, MD, PhD, FPOGS, FPSMFM, FPSUOG

The multifactorial etiology of preterm birth makes its accurate prediction challenging.

Current tests for prediction of preterm labor can be divided into three general categories:

1) Assessment of **risk factors**, which was already discussed extensively in chapter 2
2) Sonographic assessment of the **cervix**, and
3) Evaluation of **biochemical markers**

The last two categories will be tackled in this chapter.

## I. SONOGRAPHIC ASSESSMENT

### A. CERVICAL LENGTH

| QUESTION 1 | What is the clinical significance of a sonographically short cervix? |
|---|---|
| **RECOMMENDATION** | Screening of mid-trimester cervical length by transvaginal ultrasound is the best clinical predictor of spontaneous preterm birth.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

**SUMMARY OF EVIDENCE**

A short cervix, traditionally defined as a transvaginal sonographic cervical length (CL) ≤25 mm in the mid-trimester of pregnancy, is an important risk factor for spontaneous preterm birth and has emerged as one of the strongest and most consistent predictors of preterm birth in asymptomatic women with singleton or twin gestations.

Iams et al.[1] examined 2915 women at approximately 24 weeks of gestation and 2531 of these women again at approximately 28 weeks. Spontaneous preterm delivery (at less than 35 weeks) occurred in 126 of the women (4.3%) examined at 24 weeks. The length of the cervix was normally distributed at 24 and 28 weeks (mean [+/- SD], 35.2 +/- 8.3 mm and 33.7 +/- 8.5 mm, respectively). The relative risk of preterm delivery increased as the length of the cervix decreased. When women with shorter cervices at 24 weeks were compared with women with values above the 75th percentile, the relative risks of preterm delivery among the women with shorter cervices were as follows: 1.98 for cervical lengths at or below the 75th percentile (40 mm), 2.35 for lengths at or below the 50th percentile (35 mm), 3.79 for lengths at or below the 25th percentile (30 mm), 6.19 for lengths at or below the 10th percentile (26 mm), 9.49 for lengths at or below the 5th percentile (22 mm), and 13.99 for lengths at or below the 1st percentile (13 mm) (P<0.001 for values at or below the 50th percentile; P = 0.008 for values at or below the 75th percentile). For the lengths measured at 28 weeks, the corresponding relative risks were 2.80, 3.52, 5.39, 9.57, 13.88, and 24.94 (P<0.001 for values at or below the 50th percentile; P = 0.003 for values at the 75th percentile).

In a study by Owen et al.[2] in both the less than 25 mm and 25 to 29mm groups, the incidence of spontaneous mid-trimester birth (<26 weeks) was higher than the incidence of later (26–34 weeks) preterm birth (<25 mm group: 37% vs. 19%; 25-29 mm group: 16% vs. 3%, respectively) as compared with women with a shortest cervical length 30 mm or greater, who had rates of 1% and 9% respectively (P<.0001). Similarly, women who had an initial cervical length 30 mm or less and those who shortened their cervix to 30 mm or less before 22 weeks were also more likely to experience a mid-trimester than later preterm birth, whereas women who shortened their cervix 30 mm or less later (22-24 weeks) or who maintained a cervical length greater than 30 mm had lower rates of mid-trimester than later preterm birth (P<.0001).

Romero et al.[3] studied 303 women from six randomized controlled trials. One study, which included women with a cervical length between 20 and 25 mm, provided 74% of the total sample size. Vaginal progesterone, compared with placebo / no treatment, was associated with a statistically significant reduction in the risk of preterm birth < 33 weeks' gestation (31.4% vs. 43.1%; relative risk, [RR] 0.69; 95% confidence interval [CI] 0.51–0.93; moderate-quality evidence) and vaginal progesterone administration was associated with a significant decrease in the risk of preterm birth <35, <34, <32 and <30 weeks' gestation (RRs ranging from 0.47 to 0.83), neonatal death (RR 0.53; 95% CI 0.35–0.81), respiratory distress syndrome (RR 0.70; 95% CI 0.56-0.89), composite neonatal morbidity and mortality (RR 0.61;95% CI 0.34–0.98), use of mechanical

ventilation (RR 0.54; 95% CI 0.36–0.81) and birth weight <1500 g (RR 0.53; 95% CI 0.35-0.80) (all moderate-quality evidence).

| QUESTION 2 | Who are recommended to undergo routine transvaginal cervical length screening? |
|---|---|
| **RECOMMENDATION** | Women with a singleton pregnancy and history of prior spontaneous preterm birth should undergo routine transvaginal cervical length screening.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Fonseca et al.[4] in a European trial screened 24,640 women between 20 to 25 weeks of gestation. Only 1.7% of the women were found to have a cervical length less than or equal to 15 mm and were eligible for the trial. Those who had a very short cervical length (15 mm or less) demonstrated a lower risk of preterm birth when treated with vaginal progesterone suppository, 200 mg daily, compared with those who were treated with a placebo.

Hassan et al.[5] in a randomized trial of women with singleton gestations, found that vaginal progesterone gel, 90 mg daily, was associated with a decrease in spontaneous preterm birth at less than 33 weeks of gestation (9% vs. 16%; RR 0.55; 95% CI 0.33–0.92) and a decrease in composite neonatal morbidity and mortality (8% vs. 14%; RR 0.57; 95% CI 0.33–0.99) among asymptomatic women with a cervical length of 10–20 mm at 19–23 6/7 weeks of gestation.

| QUESTION 3 | What is the best sonographic cervical parameter to detect spontaneous preterm birth? |
|---|---|
| **RECOMMENDATION** | Functional cervical length appears to be the best single cervical parameter to predict spontaneous preterm birth.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

In a prospective cohort study by Guzman, et al.,[6] it was shown that cervical length was best in the prediction of preterm birth in women with a prior mid-trimester loss. An optimal cut-off of ≤ 1.5 cm had sensitivities for delivery at <28, <30, <32 and< 34 weeks' gestation of 100%, 100% 92% and 81%, respectively.

To et al.[7], in their study of cervical length and funneling in the prediction of spontaneous early preterm delivery, concluded that funneling did not provide a significant additional contribution to cervical length in the prediction of spontaneous delivery before 33 weeks (odds ratio for short cervix = 24.9, Z = 4.43, P < 0.0001; odds ratio for funneling = 1.8, Z = 0.84, P = 0.40).

| **QUESTION 4** | **What is the best ultrasonographic approach in measuring cervical length?** |
|---|---|
| **RECOMMENDATION** | The transvaginal route is the preferred route in the assessment of cervical length and morphology.<br><br>It is highly reproducible with a relatively low inter-observer variation rate of 5–10%. Measurements are not affected by maternal body-mass index, cervical position, and shadowing from maternal structures or fetal parts.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Hertzberg et al.[8] concluded that both transperineal and endovaginal ultrasonography can provide satisfactory images of the cervix, but endovaginal images are frequently superior to transperineal images. Transabdominal or transperineal ultrasonography can also be used, but if the cervix is not adequately depicted from these perspectives, endovaginal ultrasonography is indicated. Transperineal measurements of cervical length can be significantly shorter than endovaginal measurements before 20 weeks. Hence, short cervical

lengths documented at transperineal ultrasonography before 20 weeks should be confirmed by endovaginal ultrasonography.

In the study of Hernandez-Andrade et al.,[9] transabdominal measurement overestimated cervical length on average by 8 mm among women with a short cervix and resulted in the underdiagnosis of 57% of cases. Transvaginal US was also more reproducible (intraclass correlation coefficient [ICC] 0.96; 95% CI 0.94–0.97) based on comparisons between 2D images and immediately acquired 3D volume datasets relative to transabdominal US (ICC 0.71; 95% CI 0.57–0.84).

In their study published in 2001, Cicero et al.[10] found that at 22 to 24 weeks age of gestation (AOG) the cervix can be visualized adequately by translabial-transperineal sonography in about 80% of patients and the measurements of cervical length obtained by this approach are very similar to those obtained by transvaginal sonography.

| QUESTION 5 | Is universal screening for preterm birth recommended? |
|---|---|
| **RECOMMENDATION** | Implementation of this screening strategy may be viewed as reasonable and may be considered by individual practitioners.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

In a meta-analysis done by Romero et al.,[11] universal transvaginal cervical length screening at 18 to 24 weeks of gestation in women with a singleton gestation and the administration of vaginal progesterone for those with a sonographic short cervix were recommended.

A study by Son et al.[12] introduced screening from 18 to 24 weeks in women without a history of preterm birth (PTB) and recommended vaginal progesterone if the cervical length was ≤20 mm. There was a significant reduction in the frequencies of spontaneous PTB following the introduction of screening at <37, <34, <32 weeks. This is despite the prevalence of cervical length ≤25 mm of 0.89% at screening and the rate of spontaneous PTB <37 weeks AOG of 143 and <34 weeks of 500.

In the study of Newnham et al.,[13] the implementation of a multifaceted program in 2014 that included universal cervical length screening and treatment with vaginal progesterone to women with a cervical length ≤25 mm was followed by a statistically significant 7.6% reduction in the rate of preterm birth in 2015. The effect extended from the 28–31 week gestational age group onward. In both of these studies, surveillance of the projects was admirable and motivation of both staff and patients was high.

## QUESTION 6 What is the optimum cut-off for cervical length measurement in predicting preterm birth?

**RECOMMENDATION** For asymptomatic singleton pregnancies, cervical length at 24 weeks of gestation for preterm birth risk was defined as <25 mm. For symptomatic singleton pregnancies beyond 30 weeks gestation, short CL was defined as below 15 mm.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Iams et al.[14] published a seminal work that established norms for cervical length at 24 weeks' gestation, identifying cervical length <25 mm (the 10th centile) as a clinically important threshold in predicting spontaneous preterm birth, and cervical length at 24 weeks as the most predictive value. Short CL is considered one of the strongest risk factor for a spontaneous preterm birth with 37.3% sensitivity and 92.2% specificity. The positive predictive value (PPV) of a short cervical length is poor when assessed in a normal antenatal population including low- and high-risk women; only 18% of women in their study with cervical length <25 mm (at 22–25 weeks) delivered prior to 35 weeks gestation.

| QUESTION 7 | When is the best time to do cervical length measurement screening? |
|---|---|
| **RECOMMENDATION** | The cervix should be assessed between 16–24 weeks gestation. It is when initiation of therapies or interventions such as cerclage and progesterone may be done. Cervical length screening beyond 24 weeks AOG in asymptomatic women provides limited clinical value and there is absence of data to suggest that it improves outcomes.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Mella et al.[15], in his publication on cervical sonography published in 2009, emphasized that cervical length (CL) should not be routinely measured prior to 16 weeks of gestation since the lower uterine segment is underdeveloped, making it challenging to distinguish this area from the endocervical canal.

Greco et al.[16] noted that by using a combination of maternal characteristics and cervical length, screening for risk for spontaneous preterm birth may be done in the first trimester. The investigators estimated that the detection rate of preterm delivery was only 54.8% (95% CI 44.7–64.6), with a false-positive rate of 10%. Furthermore, the median cervical length multiples of the median (MoM), corrected for maternal characteristics, was significantly lower in the preterm (0.892 MoM, 95% CI 0.829–0.945) than in the term delivery group (0.994 MoM, 95% CI 0.919–1.082; $p < 0.0001$).

Berghella et al.[17] showed that before 14 weeks gestation, the sensitivity, specificity and positive and negative predictive values of a short cervix were 14%, 97%, 50%, and 82%, respectively (RR 2.8; 95% CI 1.4-5.6). The mean transvaginal sonographic cervical length before 14 weeks of gestation was 33.7 +/- 6.9 mm in pregnancies which delivered preterm (n=36), and 35.0 +/- 6.8 mm in those delivering at term (n=147) (P=0.3). Follow-up transvaginal ultrasound examination of the cervix to 24 weeks revealed that the average gestational age at which a short cervix was detected was 18.7 +/- 2.9 weeks. The investigators concluded that a cervical length <25 mm on transvaginal sonographic assessment rarely occurs before 14 weeks age of gestation and in high-risk

patients destined to deliver preterm, cervical changes predictive of preterm birth develop mostly after this gestational age.

| QUESTION 8 | How should the approach to cervical length screening differ for women with and without a prior preterm birth? |
|---|---|

**RECOMMENDATION**

Women with a history of spontaneous preterm birth should undergo cervical length screening with transvaginal ultrasound. Their serial assessment of cervical length is usually performed every 1–2 weeks from 16 until 24 weeks of gestation.

For patients at highest risk for preterm delivery (prior to 24 weeks delivery in a previous pregnancy, second trimester losses), an initial examination at 15 to 16 weeks should be considered. For patients at a lower risk (cone biopsy, uterine malformations), a first exam could be obtained during the 18 to 20 weeks anatomy scan.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Owen et al.,[18] in a multi-center randomized trial of cerclage for preterm birth prevention, showed that birth less than 24 weeks (P=.03) and perinatal mortality (P=.046) were less frequent in the cerclage group. There was a significant interaction between cervical length and cerclage. Birth less than 35 weeks (P=.006) was reduced in the less than 15 mm stratum with a null effect in the 15–24 mm stratum. The investigators concluded that in women with a prior spontaneous preterm birth less than 34 weeks and cervical length less than 25 mm, cerclage reduced previable birth and perinatal mortality but did not prevent birth less than 35 weeks, unless cervical length was less than 15 mm.

Owen et al.[19] concluded that birth <35 weeks occurred in 16% of the ≥25 mm cohort. The relationship between cervical lengths ≥25 mm and birth gestational age was null (p=0.15). In the <25 mm group, progressively shorter cervical lengths predicted birth <35 weeks (p<0.001) while this relationship was null in the ≥25 mm group (p=0.17).

| QUESTION 9 | Is cervical length measurement by serial transvaginal ultrasound recommended? |
|---|---|

**RECOMMENDATION**

In women found to have a short cervix (≤25 mm) during routine screening, have a history of prior preterm birth or have previously received surgical interventions (cerclage, LEEP, cold knife excision), there is insufficient data showing clinical benefit of serial measurement and surveillance. Although there may be a psychological benefit to both patient and provider to serially visualize and measure the cervix outside routine evaluation in these women, the initiation of proper medical intervention (progesterone) is more effective.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Carvalho et al.[20] concluded that there is a spontaneous shortening in the pregnant cervix from the first to the second trimester of pregnancy. The shortening is more rapid in pregnant women who deliver prematurely and who have a history of previous preterm delivery.

Guzman et al.[21] showed the rate of endocervical canal length shortening of incompetent cervices diagnosed between 15 and 19 weeks gestation was -0.52 cm/week (P <.001). The rate of endocervical canal length shortening in incompetent cervices diagnosed between 20 and 24 weeks gestation was significant and varied from -0.49 cm/week to -0.80 cm/week at 20 and 24 weeks gestation, respectively (P <0.001). The models describing the rate of cervical shortening in the two groups of incompetent cervices were significantly different (P <.001).

In the study of Yoshizato et al.,[22] it was concluded that rapid cervical length shortening occurred between 16–20 and 21–25 weeks in the early group and between 21–25 and 26–30 weeks in the late group. In nulliparous women, cervical dilatation velocity in the early and late groups was more rapid than in the controls.

Meath et al.[23] concluded that cervical length was predicted to decrease by 0.6 mm per week in singletons, 0.9 mm in twins and 1.2 mm in triplets.

Miller et al.[24] showed mean cervical length was shorter (4.2 ± 0.9 cm vs 4.5 ± 0.9 cm, $P < .001$) and the proportion of women with a short cervix was higher (6.5% vs 1.5%, $P < .001$) in women with a prior cervical excisional procedure. In multivariable regression, both a short cervix (adjusted odds ratio [aOR], 6.19; 95% CI 3.85–9.95) and a prior cervical excisional procedure (aOR, 1.53; 95% CI 1.04–2.25) were significantly associated with preterm birth. Both a prior cervical excisional procedure and a short cervix were independently associated with preterm birth. These data suggest that the risk of preterm birth associated with a prior loop electrosurgical excision procedure or cold knife cone is not merely due to postsurgical shortening of the cervix.

Conner et al.[25] concluded that LEEP itself may not be an independent risk factor for preterm birth. The meta-analysis showed LEEP was associated with an increased risk of preterm birth before 37 weeks of gestation (pooled RR 1.61, 95% CI 1.35–1.92). However, no increased risk was found when women with a history of LEEP were compared with women with a history of cervical dysplasia but no cervical excision (pooled relative risk 1.08, 95% CI 0.88–1.33).

| **QUESTION 10** | **When is cervical length (CL) measurement for multiple pregnancies recommended?** |
|---|---|
| **RECOMMENDATION** | Routine cervical length screening in multiple pregnancies is not recommended.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Romero et al.,[26] in a systematic review and meta-analysis of individual patient data of women with a twin gestation and a mid-trimester sonographic cervical length ≤25 mm, showed that vaginal progesterone, compared with placebo/no treatment, was associated with a statistically significant reduction in the risk of preterm birth <33 weeks' gestation (31.4% vs. 43.1%; RR 0.69; 95% CI 0.51–0.93); moderate-quality evidence). Moreover, vaginal progesterone

administration was associated with a significant decrease in the risk of preterm birth <35, <34, <32 and <30 weeks' gestation (RRs ranging from 0.47 to 0.83).

For twin pregnancies, transvaginal sonographic cervical length measurement at 20-24 weeks' gestation appears to be a good predictor of spontaneous preterm birth in asymptomatic women with twin pregnancies as shown in the study of Conde-Agudelo et al.[27]. In his study, asymptomatic women with a cervical length of ≤20 mm at 20-24 weeks gestation was most accurate in predicting preterm birth <32 and <34 weeks' gestation (pooled sensitivities, specificities, and positive and negative likelihood ratios of 39% and 29%, 96% and 97%, 10.1 and 9.0, and 0.64 and 0.74, respectively). A cervical length ≤25 mm at 20-24 weeks' gestation had a pooled positive likelihood ratio of 9.6 to predict preterm birth <28 weeks' gestation.

Liem et al.[28] concluded that there is limited evidence on the accuracy of cervical length measurement testing in the prediction of preterm birth in symptomatic women with a twin pregnancy, especially on the most important outcome, that is, delivery within 7 days.

Goldenberg et al.[29], in a prospective screening among twin as compared with singleton pregnancies, showed a cervical length ≤25 mm was more common at both 24 and 28 weeks, a statistically significant difference. There were no significant differences in most other risk factors. Of the factors evaluated by means of univariate analysis at 24 weeks, only a short cervix (≤25 mm) was consistently associated with spontaneous preterm birth. The odds ratio and 95% confidence interval for spontaneous preterm birth at <32 weeks, <35 weeks, and <37 weeks were 6.9 (2.0 to 24.2), 3.2 (1.3 to 7.9), and 2.8 (1.1 to 7.7). At 28 weeks, a cervical length ≤25 mm was not a strong predictor of spontaneous preterm birth. At both 28 weeks (OR 9.4; 95% CI 1.0–67.7) and 30 weeks (OR 46.1; 95% CI 4.2–1381), a positive fetal fibronectin result was significantly associated with spontaneous preterm birth at <32 weeks. Most known risk factors for spontaneous preterm birth were not significantly associated with spontaneous preterm birth of twins. At 24 weeks, cervical length ≤25 mm was the best predictor of spontaneous preterm birth at <32 weeks, <35 weeks, and <37 weeks. Of the risk factors evaluated at 28 weeks, fetal fibronectin was the only statistically significant predictor of spontaneous preterm birth at <32 weeks.

| QUESTION 11 | **Is cervical length measurement screening for women with uterine anomalies recommended?** |
|---|---|

**RECOMMENDATION** Routine cervical length screening should be performe in women with uterine anomalies at 24 weeks gestatio or the mid-trimester.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Airoldi et al.[30] showed that a short cervical length on transvagina ultrasonography in women with uterine anomalies has a 13-fold risk for preterm birth. Unicornuate uterus had the highest rate of cervical shortening and preterm delivery. The overall incidence of spontaneous preterm birth at less than 35 weeks was 11%. Sixteen percent (16%) of women had short cervical length and 50% had spontaneous preterm birth.

| QUESTION 12 | **Should women with a history of treatment for cervical dysplasia (in the absence of a prior preterm birth) undergo routine serial cervical length screening?** |
|---|---|

**RECOMMENDATION** Low-risk women who have undergone treatment for cervical dysplasia or have a history of dysplasia do not require additional evaluation.

There is insufficient evidence to support additional screening for women with a previous electrosurgical procedure (loop electrical excision procedure, LEEP) or cold knife cone for cervical dysplasia.

A large retrospective cohort study, as well as a systematic review and meta-analysis, found that while average CL is shorter in women after a procedure, most nevertheless have a normal mid-trimester CL and more importantly, the increased risk of spontaneous PTB in this population appears related to the history of cervical

dysplasia, not the procedure itself. Therefore, these otherwise low-risk women who have undergone treatment for cervical dysplasia or have a history of dysplasia do not require additional evaluation beyond that which would routinely be offered to women without a history of a prior preterm birth.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Miller et al.[24] showed the mean cervical length was shorter (4.2 ± 0.9 cm vs 4.5 ± 0.9 cm, $P < .001$) and the proportion of women with a short cervix was higher (6.5% vs 1.5%, $P < .001$) in women with a prior cervical excisional procedure. In multivariable regression, both a short cervix (adjusted OR 6.19; 95% CI 3.85–9.95) and a prior cervical excisional procedure (adjusted OR 1.53; 95% CI 1.04–2.25) were significantly associated with preterm birth. Both a prior cervical excisional procedure and a short cervix were independently associated with preterm birth. These data suggest that the risk of preterm birth associated with a prior loop electrosurgical excision procedure or cold knife cone is not merely due to postsurgical shortening of the cervix.

Conner et al.[31] concluded that LEEP itself may not be an independent risk factor for preterm birth. LEEP was associated with an increased risk of preterm birth before 37 weeks of gestation (pooled RR 1.61; 95% CI 1.35–1.92). However, no increased risk was found when women with a history of LEEP were compared with women with a history cervical dysplasia but no cervical excision (pooled RR 1.08; 95% CI 0.88–1.33).

| **QUESTION 13** | **Should women undergo routine cervical length screening after cerclage placement?** |
|---|---|

**RECOMMENDATION** There is insufficient data to support routine cervical length screening after cerclage placement.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

Rana et al.[32] followed up patients with the diagnosis of cervical incompetence with cervical sonography after placement of prophylactic McDonald cerclage. During the first year of study, 3 out of 12 patients treated with prophylactic cerclage demonstrated funneling of the internal cervical os when examined with cervical sonography; all 3 had premature deliveries. During the last 3 years of the study, 8 of 27 patients treated with prophylactic cerclage demonstrated funneling. With active intervention, neonatal survival improved to 100%. Sonography aids in the management of patients with cervical incompetence and improves outcome even after placement of cervical cerclage.

Fox et al.[33] explored the hypothesis that serial transvaginal ultrasonography identifies early evidence of suture failure and that repeat cerclage delays delivery. Forty-six percent (46%) developed cervical changes at scan and underwent repeat cerclage. The median gestation at delivery for the women who had repeat cerclage was 35 (22–39) weeks compared with 38 (36–40) weeks for those who had a single suture ($p>0.05$). The median interval from the detection of cervical changes at scan to delivery was 13 (4–19) weeks. Serial transvaginal ultrasonography after cervical cerclage identifies a group of women who are more likely to deliver preterm, and provides an opportunity for intervention (repeat cerclage) which appears to delay delivery by an average of 7 weeks.

Dijkstra et al.[34] showed that an increase in cervical length after cerclage is not predictive of term delivery. Serial CL measurements in the late second or early third trimester predict preterm birth but could provide earlier warning in patients with a prophylactic cerclage than in patients with urgent cerclage. These were noted in the evaluation of 80 women whose primary physician determined that a prophylactic (n=50) or urgent cerclage (n=30) was indicated. The patients had transvaginal ultrasonographic evaluation before and after cerclage. Thereafter, most women had three additional transvaginal ultrasound examinations until 32 weeks gestation.

Funai et al.[35] in a study published in 1999, showed that prophylactic cerclage resulted in measurable increases in cervical length, which might have contributed to the success of the procedure, but further evaluation was needed to determine whether the degree of cervical lengthening after cerclage predicts term delivery. Twenty-one (21) Shirodkar and 10 McDonald operations were included. The mean (+/- standard deviation) pre-cerclage cervical length was 2.7+/-0.9 cm and the post-cerclage cervical length was 3.6+/-0.9 cm ($P<.001$, paired t test).

| QUESTION 14 | **What is the role of cervical length screening to predict preterm birth for women in other clinical scenarios?** |
|---|---|

**RECOMMENDATION** Routine transvaginal cervical length screening is not recommended for women with cervical cerclage, multiple gestation, preterm prelabor rupture of membranes (PPROM), or placenta previa.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

***Threatened Preterm Labor***

Transvaginal ultrasound cervical length measurement may serve as an adjunct to digital cervical examination in the assessment of women with symptoms of acute preterm labor.

Gomez et al.[36] showed the prevalence of preterm delivery was 37.3%. Receiver-operator characteristic curve and logistic regression analyses indicated a significant relationship between the occurrence of preterm delivery and ultrasonographic cervical parameters ($p < 0.005$ for each) but not with the results of digital examination of the cervix. Survival analysis demonstrated a shorter admission-to-delivery interval for patients with an abnormal cervical index or endocervical length ($p < 0.005$ for each). Endovaginal ultrasonographic examination of the uterine cervix is more accurate than digital examination of the cervix in the assessment of the risk for preterm delivery in patients with preterm labor and intact membranes.

Okitsu et al.[37] revealed that transvaginal ultrasound was superior, because the transabdominal technique usually requires a full bladder, which causes deformation and elongation of the cervix. Digital examination showed dilatation of the internal os in 38.5% of patients in whom it had previously been shown by transvaginal sonography. Transvaginal ultrasonography has the advantage of providing natural and objective information on the cervix. Shortening of the cervical length by -1.5 SD or more was associated with an increased risk of preterm delivery (11.3% vs. 2.8%, $p < 0.01$). A dilated internal os of more than 5 mm before 30 weeks of gestation was associated with preterm delivery more often than an undilated internal os (33.3% vs.

3.5%, p < 0.01). From these data, dilatation of the internal os on transvaginal ultrasonography was proved to be an early and important predictor of preterm delivery.

***Preterm Prelabor Rupture of Membranes***

Rizzo, et al.[38] suggested that the combined use of the amniotic fluid interleukin-6 assay and the cervical index in patients with preterm premature rupture of membranes provides a good prediction of the interval from admission to delivery.

Gire et al.[39] suggested that the use of transvaginal ultrasonography for cervical length measurement among singleton preterm premature rupture of membranes may predict an early delivery but cannot anticipate the risk of chorioamnionitis or neonatal sepsis. The median time interval between admission and delivery (latency period) was 48 hours. A cervical length of less than 20 mm was associated with a significant risk of early delivery (mean latency period was 59.44 +/- 159.93 hours vs. 240.94 +/- 364.67 hours; P < 0.05).

Mehra et al.[40], in a study of singleton pregnancies with PPROM, noted that delivery within 7 days occurred in 48% of pregnancies. Median duration (interquartile range) from PPROM to delivery and transvaginal cervical length (TVCL) to delivery was 8 days (4.0-16.0) and 8 days (3.0-15.0), respectively. Using multiple regression, TVCL as a continuous variable (odds ratio [OR] 0.65; 95% CI 0.44-0.97; P < .05) and AFI ≤5 cm (OR 4.69; 95% CI 1.58–13.93; P < .01) were determined to be independent predictors of delivery within 7 days. A shorter TVCL and an AFI ≤5 cm independently predict delivery within 7 days in women presenting with PPROM. The combination of an AFI >5 cm and TVCL >2 cm greatly improved the potential to remain undelivered at 7 days following cervical length assessment.

Carlan et al.[41] studied 92 singleton pregnancies complicated by PPROM at 24-34 weeks' gestation and assigned them randomly to groups having no vaginal sonography (n=47) or having endovaginal ultrasound (n=45). This study showed incidence of chorioamnionitis among those in the no-probe and probe groups (28% vs. 20%). The incidence of endometritis (6% vs. 9%) and neonatal infection (17% vs. 20%) were also similar between groups.

***Placenta Previa***

All studies used a cervical length cutoff of 30mm to define the cervix as 'short,' and reported that those with a short cervical length were more likely to have hemorrhage and emergent delivery. These three studies demonstrate that (1) there may be an association between shortened cervical length and preterm birth in the setting of placenta previa, (2) there are no prospective studies testing a management strategy based on cervical length, and (3) there is insufficient data to suggest a proven clinical benefit of routine cervical length measurement or surveillance.

Stafford et al.[42] noted that in pregnancies with placenta previa, a third-trimester cervical length of 30 mm or less is associated with increased risk for hemorrhage, uterine activity, and preterm birth. Women with previa and a short cervix were more likely to require delivery for hemorrhage, 79% compared with 28%, and to deliver preterm, 69% compared with 21% (both P<.001). Tocodynamometer evidence of regular uterine contractions was more common with a short cervix than with a longer cervix, 69% compared with 21% (P<.001). Conversely, 64% with a cervical length greater than 30 mm had no bleeding episodes and progressed to term.

Ghi et al.[43] showed that transvaginal sonographic cervical length predicts the risk of emergency. The mean +/- SD gestational age at ultrasound was 30.7 +/- 2.7 weeks and the cervical length was 36.9 +/- 8.8 mm. Cesarean delivery was performed in all cases, at a mean gestational age of 34.7 +/- 2.3 weeks. Twenty-nine (49.1%) of the women presented with prepartum bleeding and 12 (20.3%) required an emergency cesarean section prior to 34 completed weeks due to massive hemorrhage. Cervical length did not differ significantly between cases with and those without prepartum bleeding (35.3 +/- 9.3 mm vs. 38.4 +/- 8.2 mm; P = 0.18), but was significantly shorter among patients who underwent emergency cesarean section < 34 weeks due to massive hemorrhage compared with patients who underwent elective cesarean section (29.4 +/- 5.7 mm vs. 38.8 +/- 8.5 mm; P = 0.0006).

Zaitoun et al.[44], in a study of cases with confirmed diagnosis of complete placenta previa, showed antepartum bleeding was observed in 51.4% (n=18) of 35 patients with cervical length measurements ≤30 mm, of whom 88.9% (16 out of 18) had showed severe attack that necessitated emergency cesarean delivery before 36 weeks, versus 21.1% (n=4) of 19 patients with cervical length ≥30 mm. By combining cervical length with lower placental edge thickness measurement sensitivity, specificity, positive predictive value (PPV) negative predictive value (NPV) and accuracy increased to 83.3, 78.4, 53.4, 79.8 and 89.7%, respectively for the

prediction of antepartum bleeding and emergency cesarean section <36 weeks using receiver-operating characteristics curve with area under the curve 0.882.

## B. OTHER SONOGRAPHIC MARKERS

| QUESTION 15 | What are the additional ultrasound parameters for predicting preterm birth? |
|---|---|

**RECOMMENDATION**

The development of new ultrasound techniques was shown to be effective in the prediction of preterm birth but functional cervical length remains to be the superior predictive tool among them. These new techniques include: amniotic fluid sludge (AFS), cervical consistency index, assessment of cervical elastography (strain elastography and shear wave elastography), uterocervical angle (UCA), uterine artery pulsatility index (PI) during peak uterine contraction, placental strain ratio, and measurement of the central zone of fetal adrenal gland.

**SUMMARY OF EVIDENCE**

***Amniotic Fluid Sludge***

Adanir et al. [45], in a study of patients at high risk for spontaneous preterm delivery, evaluated for the presence of amniotic fluid sludge with transvaginal ultrasonography. The study showed that the prevalence of amniotic fluid sludge in the study population was 19.6%. The rates of spontaneous preterm delivery <37 weeks of gestation were 66.7% for the patients with sludge and 27.0% for the patients without sludge. Patients with sludge had a higher rate of spontaneous preterm delivery ($p = 0.002$). The amniotic fluid sludge is an independent risk factor for spontaneous preterm delivery among asymptomatic patients at high risk for spontaneous preterm delivery.

Fuchs et al.[46] noted that amniotic fluid sludge was observed in 7.4% of patients in a case-control study including singleton pregnancies between 15-32 weeks of gestation. It was associated with shorter cervical length, greater

body mass index, cervical cerclage and preterm birth before 28 weeks, but after adjustment, it was no longer associated with preterm delivery before 32 or 34 weeks.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## ***Cervical Consistency Index***

The cervical consistency index is computed using the formula:

Cervical consistency index = (AP1/AP) x 100

where AP = anteroposterior cervical diameter before (AP)
AP 1= anteroposterior cervical diameter after

Baños et al.[47] showed that cervical consistency index, determined using antero-posterior diameter measurements of the cervix with and without cervical pressure, has been shown to be a predictor at least comparable to cervical length for preterm birth, although external validation and larger sample sizes need to be considered to further assess clinical utility.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## ***Assessment of Cervical Elastography***

Strain elastography and shear wave elastography, when combined with cervical length, are promising predictive measurements although there are still limitations in their technical implementation.

Oturina et al.[48], in 30 cases resulting in preterm birth and 30 gestational age-matched controls, showed that when vaginal ultrasound examination with cervical length and elastography measurement were performed, an association between the value of the strain ratio that was calculated from the ROIs placed side by side in the middle of the anterior lip (SR4), and preterm delivery ($P<0.001$) was observed. The predictive values of cervical length and SR4 were comparable (AUC 0.7394; AUC 0.8322), respectively.

Wang et al.[49] showed in a meta-analysis and systematic review that cervical elastography is a promising and reliable method to predict preterm delivery. In this study, cervical elastography showed better diagnostic performance to predict preterm delivery than cervical length measurement. This meta-analysis showed that cervical elastography had a sensitivity of 0.84 [95% CI 0.68–0.93], a specificity of 0.82 (95% CI 0.63–0.93), a diagnostic odds ratio of 25 (95% CI 7–93), and an area under the curve (AUC) of SROC of 0.90 (95% CI 0.87–0.93). Cervical length measurement showed that the AUC of SROC was 0.60 (95% CI 0.56–0.64).

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

***Uterocervical Angle***

Daskalakis et al.[50] showed that uterocervical angle is measured between lower uterine segment and cervical canal. In the systematic review that included 3,018 women, the existing data supported that second trimester uterocervical angle measurement might be useful as a predictive factor of preterm birth <34 weeks, as at least two studies in unselected singleton pregnancies and two studies in pregnancies with an ultrasonographically shortened cervix supported the hypothesis. The most commonly reported cut-off values were 105° and 95°.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

***Uterine Artery Pulsatility Index***

Olgan et al.[51] studied the use of uterine artery doppler velocimetry during peak uterine contraction for patients exhibiting symptoms of preterm labor for the identification of pregnant women at risk of preterm delivery. In 172 patients admitted with preterm (24–35 weeks gestation) uterine contractions, uterine artery PI during the peak of contractions was significantly higher in patients who delivered within 7 days than in those who did not ($P < 0.001$).

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

***Placental Strain Ratio***

Albayrak et al.[52] included 70 pregnant women wherein placental real time sonoelastography measurements were performed. Two different real time sonoelastography measurements were performed by taking two different tissues as references. The real time sonoelastography value measured when taking the rectus abdominis muscle as a reference was termed the muscle-to-placenta strain ratio (MPSR), while the real time sonoelastography value measured when taking subcutaneous tissue as a reference was termed the fat-to-placenta strain ratio (FPSR). Women whose gestational age at birth was less than 37 weeks 0 days were accepted as spontaneous preterm birth. There was a low-level negative correlation between MPSR and gestational age at birth (r=-0.300, P=.012) and there was a moderate-level negative correlation between FPSR and gestational age at birth (r=-0.513, P<.001). The multivariate linear regression analysis showed that the FPSR (β=0.609, P=.002) was the significant predictor for the spontaneous preterm birth.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

***Measurement of Central Zone of Adrenal Gland***

Lemos et al.[53] conducted a prospective cross-sectional study of pregnant women between 24 and 36 weeks of gestation. An ultrasound exam was performed for each participant to obtain the cervical length measurement (transvaginal route) and fetal adrenal gland biometry. The prevalence of delivery within 7 days was 35.8%, which showed a statistically significant difference from the depth of the central zone of the fetal adrenal gland (p = 0.036). The cutoff for the depth of the central zone of the fetal adrenal gland was 7.2 mm (sensitivity 66.7%, specificity 61.8% and accuracy 63.5%). These values were not significantly different than the cutoffs for cervical length measurement: 20 mm (p = 0.267) and 9 mm (p = 0.118). The biometry for the central zone of the fetal adrenal gland predicted delivery within 7 days in pregnant women with spontaneous preterm birth and had a predictive accuracy similar to that of cervical length measurement.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## II. BIOMARKERS

## A. CERVICAL FLUID

| QUESTION 16 | What are the approaches in the prediction of preterm birth screening using cervical fluid? |
|---|---|

**RECOMMENDATION**

The following cervical fluid biomarkers may be useful in the prediction of preterm birth.

1. Fetal fibronectin (fFN)
2. IL-6 and IL-8 levels in cervicovaginal fluid
3. Placental alpha macroglobulin-1 (PAMG-1)
4. Insulin-like growth factor binding protein-1 (IGFBP-1)

### SUMMARY OF EVIDENCE

#### *Fetal Fibronectin*

The qualitative fetal fibronectin test has traditionally been used as a test for detecting imminent delivery in women with threatened preterm labor. The greatest value of this qualitative test lies in its high negative predictive values, and so it can be a useful test in reassuring women with a negative result.

Jun et al.[54], in a prospective study including 85 women with symptomatic preterm labor of a singleton pregnancy, showed that their approach using the fetal fibronectin (fFN) test could not improve the ability to predict preterm birth (PTB), but it could identify women at risk for delivery before 34 or 37 weeks of gestation. Thirty-six and-a-half percent showed a positive fFN and 51.8% had a short CL. PTB occurred within 7 and 14 days of testing and before 34 and 37 weeks of gestation in 17.6, 20.0, 23.5 and 49.4% of the women, respectively. The fFN and CL results showed low predictive effectiveness for the studied outcomes with $LR^+$ (fFN, 1.5–1.9; CL, 1.0–1.5) and $LR^-$ (fFN, 0.7; CL, 0.7–0.9). The combined use of fFN and CL could not improve these results ($LR^+$, 1.4–2.3; $LR^-$, 0.7–0.9). However, the risk of PTB before 37 weeks was increased in women with positive fFN but not CL shortening compared to the reference group (OR 3.8; 95% CI 1.1–1.3). The risk of PTB before 34 weeks was increased in both positive fFN and CL compared to the reference group (OR, 8.1; 95% CI 1.9–34.5).

Abbott et al.[55] in a prospective cohort study of women in threatened preterm labor showed that fetal fibronectin (fFN) concentration correlated with risk of preterm delivery. For fFN levels <10 ng/mL, there was a negative predictive value of 98.2% for delivery before 34 weeks, whereas levels >200 ng/mL were associated with a positive predictive value of 37% for delivery before 34 weeks. The additional risk stratification of quantitative fFN may help to guide clinicians on identifying women requiring intervention and admission.

Watson et al.[56] recommended the QUiPP app, a clinical prediction tool for spontaneous preterm birth, which defines a percentage risk of preterm birth based on gestation, obstetric history and quantitative fetal fibronectin. The app has been shown to accurately guide management at certain risk thresholds to avoid unnecessary intervention in low-risk women. The advantage of the app is that it combines clinical history and interrogates risk across the whole range of fibronectin and cervical length.

Bruijn et al.[57], in a systematic review, reported that although the accuracy of fetal fibronectin in predicting spontaneous preterm birth varied, it is most accurate in predicting preterm birth in women with threatened preterm labor without advanced cervical dilatation within 7-10 days after testing.

Berghella et al.[58], in a meta-analysis, reported that fetal fibronectin testing in singleton gestations was not associated with prevention of preterm birth or improved perinatal outcomes, reporting that preterm birth incidences before 28 weeks, 32 weeks, 34 weeks, and 37 weeks did not change despite its higher costs. While testing fetal fibronectin, blood-stained swabs were still effective in predicting preterm birth; however, they had higher false positive rates.

Several observational studies have noted that the combination of cervical length and fetal fibronectin (fFN) assessment may improve prediction of preterm birth among women with symptoms of acute preterm labor.

Gomez et al.[59] showed the prevalence of spontaneous preterm delivery within 48 hours, 7 days, and 14 days of admission, and delivery </=32 and </=35 weeks were 7.9% (17/215), 13.0% (28/215), 15.8% (34/215), 8.9% (9/101), and 15.8% (34/215), respectively. ROC curve analysis and contingency tables showed a significant relationship between the occurrence of preterm delivery and both cervical length and fetal fibronectin results ($P < .01$ for each). Both tests performed comparably in the prediction of spontaneous preterm delivery. However, when fetal

fibronectin results were added to those of cervical length (<30mm significant improvement in the prediction of preterm delivery was achieved

Ness et al.[60], in a randomized trial of women with threatened preter labor, showed knowledge of cervical length and fetal fibronectin wa associated with reduction in length of evaluation in women with cervica length > or = 30 mm and in incidence of spontaneous preterm birth all women with preterm labor.

Van Baaren et al.[61] showed that a combination of cervical length screenin and fetal fibronectin testing in "symptomatic" patients shows that feta fibronectin does not add to preterm birth prediction in women with a ver short (30 mm) cervical length. In these situations, fetal fibronectin may be discarded because the NPV of cervical length 30 mm alone is high (9 100%). When used in combination with CL screening, FFN may be mos useful in women with cervical length of 20-29 mm (e.g. the "grey zone"); i this situation a "negative test" (80% of cases) may allow for no treatmen while a positive test would suggest the need for intervention (antenata corticosteroids, transfer to tertiary center, etc.).

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## ***Interleukin-6 (IL-6) and Interleukin -8 (IL-8) Levels***

Jung et al.[62] showed IL-6 and IL-8 levels in cervicovaginal fluid were associated with preterm birth within 7 days and successful when especially combined with cervical length. Combination of IL-8 levels and cervical length had a specificity of 92.8% for predicting preterm birth in 7 days; however, its relatively low sensitivity (56.4%) was a limitation for its clinical use.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

## ***Placental Alpha Macroglobulin-1 (PAMG-1)***

Oskovi et al.[63] showed placental alpha macroglobulin-1 (PAMG-1) was compared with fetal fibronectin and cervical length measurement and it was reported that PAMG-1 was more accurate in predicting preterm birth within 7 days with 80% sensitivity and 95% specificity and it was reported it had the greatest utility in patients when cervical length was 15–35mm.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## ***Insulin-like Growth Factor Binding Protein-1 (IGFBP-1)***

Eleje et al.[64] reported that a triple biomarker of native and total IGFBP-1 and IL-6 was as a successful test with 87.1% sensitivity, 92.4% specificity, 84.4% PPV, 100% NPV, and 95% accuracy in predicting preterm birth in 7 days.

Bruijn et al.[65], in this study 350 women were tested, of whom 20% delivered within seven days. Eighty-four women had a positive IGFBP-1 test and 162 women a positive fetal fibronectin (fFN) test, of whom 64% and 39% delivered within seven days, respectively. Ninety-seven women had a cervical length below 15 mm, of whom 52% delivered within seven days. Sensitivity, specificity, positive and negative predictive values of combining cervical length with the IGFBP-1 test or the fFN test were 91%, 75%, 47% and 97%, and 96%, 58%, 36% and 98%, respectively.

Fuchs et al.[66] noted that, among 180 women, 11.7% had a positive phIGFBP-1 test. Spontaneous preterm birth occurred within 7 days, 14 days of testing and before 34 weeks and 37 weeks in 7.8%, 10.6%, 12.9% and 28.8%, respectively. The phIGFBP-1 test alone or in combination with cervical length has a low predictive accuracy to predict preterm birth in symptomatic women.

Melchor et al.[67], in a meta-analysis where a bivariate mixed model pooled sensitivity of PAMG-1, fetal fibronectin, and phosphorylated (IGFBP-1) in symptomatic women was used, PAMG-1 was reported to have the highest positive predictive value and positive likelihood ratio (LR+) while negative predictive value and LR- remained similarly high within the three biomarkers. The areas under the receiver-operating characteristics (ROC)

curves for PAMG-1, fFN and phIGFBP-1 for sPTB ≤ 7 days were 0.961, 0.874 and 0.801, respectively.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

| QUESTION 17 | **Can fetal fibronectin testing be used for prevention of preterm birth in asymptomatic women with a prior preterm birth or for other at-risk populations such as multiple gestations?** |
|---|---|

**RECOMMENDATION**

Fetal fibronectin is of no benefit in the management of asymptomatic women with a prior preterm birth or for other at risk populations, such as twin gestations.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Berghella et al.[68], in a systematic review and meta-analysis of randomized controlled trials, concluded that fetal fibronectin testing in singleton gestations with threatened preterm labor is not associated with the prevention of preterm birth or improvement in perinatal outcome but is associated with higher costs.

Dos Santos et al.[69] stated in a systematic review that currently no evidence supporting the use of fetal fibronectin (fFN) testing in asymptomatic women. This review suggests that in women with singleton pregnancies without risk factors for preterm birth, a positive fFN may be predictive of preterm birth but should be used with caution. Further good quality research is needed to determine the usefulness of fFN testing in the pathway of care for women without risk factors who are asymptomatic for preterm birth.

## B. AMNIOTIC FLUID

**QUESTION 18** **What are the approaches in the prediction of preterm birth screening using amniotic fluid?**

**RECOMMENDATION** The following screening tests using amniotic fluid showed significant results in their respective studies, but not enough clinical studies to recommend their use.

1. Low amniotic fluid glucose
2. Interleukin-6 (IL-6)
3. Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PGF) and Soluble VEGF Receptor-1 (sFlt-1)
4. Interleukin-1β (IL-1β)
5. Neutrophil Elastase
6. IL-8 and Annexin-A2

### ***Low Amniotic Fluid Glucose***

Ozgu et al.[70] concluded that amniotic fluid glucose levels were significantly lower in patients with preterm delivery than term deliveries (P = 0.01). Although this result is significant and notable, there is not enough clinical evidence to recommend their use as a screening test for preterm delivery and intrauterine growth retardation (IUGR) in routine practice.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

### ***Interleukin-6 (IL-6)***

Oz et al.[71] concluded IL-6 levels in the amniotic fluid were significantly higher in the preterm delivery group, and there was a statistically significant negative correlation between IL-6 concentrations in the amniotic fluid and gestational age at delivery (correlation coefficient (CC): -18.5%, $p < 0.05$). A negative correlation was also detected between CRP levels in the amniotic fluid and gestational age at delivery, but the correlation was not statistically significant ($p = 0.068$). The investigators concluded that measuring IL-6 in the amniotic fluid can identify women at risk of preterm delivery. Because it is not acceptable to perform amniocentesis for this screening, it is more convenient for patients in whom genetic amniocentesis is performed.

Kesrouani et al.[72] in another prospective study did not find significant difference in terms of IL-6, matrix metalloproteinase-9 (MMP-9), glucose, and C-reactive protein (CRP) in mid-trimester amniotic fluid. They noted that mid-pregnancy amniotic fluid biomarker levels do not correlate with preterm delivery. Larger studies are needed before advising routine measurement of these markers.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## ***Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PGF), and Soluble VEGF Receptor-1 (sFlt-1)***

Lee et al.[73], in a prospective study, explained that elevated levels of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are suggestive of angiogenesis and tendency of inflammation at midtrimester, are predictive of preterm delivery, and their availability is maximized by downregulation of soluble VEGF receptor-1 (sFlt-1). The levels of VEGF and PlGF in the preterm group were significantly higher than in the control group (30.48 ± 8.57 pg/mL vs. 26.06 ± 8.24 pg/mL and 28.83 ± 7.83 pg/mL vs. 25.35 ± 8.26 pg/mL, respectively) ($p = 0.017$ and 0.048, respectively). In terms of sFlt-1, the levels were decreased in the preterm group (10,478.51 ± 4012.56 pg/mL vs. 12,544.05 ± 4140.96 pg/mL) ($p = 0.021$).

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## ***Interleukin-1β (IL-1β)***

Nadeau-Vallee et al.[74] showed interleukin (IL)-1 has a central role in preterm labor. Elevated levels of interleukin-1β (IL-1β) due to possible infection or inflammation, in amniotic fluid and cervicovaginal fluid, were suggested as a potential predictor of preterm birth. However, investigations do not have an active role yet in clinical practice in prediction of preterm birth and further studies are needed for clinical use of IL-1 targeting therapies for prevention of preterm birth.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## ***Neutrophil Elastase***

Hatakeyama et al.[75] investigated neutrophil elastase levels in amniotic fluid for predicting preterm birth, following emergent cerclage. Duration of pregnancy was reported significantly longer in patients after emergent cerclage when neutrophil elastase levels in amniotic fluid were <180 ng/mL. This optimal cut-off predicted pregnancy continuation beyond 30, 34, and 36 weeks of gestation was 180 ng/mL; this cut-off value had a sensitivity, specificity, positive predictive value, and negative predictive value of 84.0, 77.8, 91.3, and 63.7% beyond 30 weeks of gestation; 87.5, 80.0, 91.5, and 72.3% beyond 34 weeks of gestation; and 85.0, 71.4, 80.9, and 76.9% beyond 36 weeks of gestation, respectively. Thus, this may serve as a useful marker for predicting the duration of continued pregnancy after cervical cerclage.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## ***IL-8 and Annexin-A2 levels***

Jia et al.[76] showed amniotic fluid IL-8 and annexin-A2 levels are associated with the occurrence of preterm premature rupture of membranes (PPROM) and preterm labor (PTL). Combined detection of IL-8 and Annexin-A2 levels in identifying preterm delivery within 2 weeks in PTL and PPROM is of possible clinical and predictive value. Their levels were measured in amniotic fluid that developed preterm delivery <32 weeks either with or without preterm premature rupture of membranes (PPROM); and combination of amniotic fluid IL-8 and Annexin-A2 for predicting preterm delivery within 2 weeks was reported to have a sensitivity of 81.25%, specificity of 88.89%, and positive predicting value (PPV) of 92.86%.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## C. MATERNAL SERUM MARKERS

**QUESTION 19** **What are the approaches in the prediction of preterm birth screening using maternal markers?**

**RECOMMENDATION** The following screening tests using maternal markers showed significant results in their respective studies, but not enough clinical studies to recommend their use.

1. Maternal Serum Calponin 1
2. Ratio of Maternal Serum Alpha Fetoprotein (AFP)/Amniotic Fluid AFP
3. Maternal Serum Progesterone-Induced Blocking Factor (PIBF)
4. Maternal Plateletcrit Count (PCT)
5. Maternal Salivary Estriol

### ***Maternal Serum Calponin 1***

Cetin et al.[77] showed maternal serum calponin 1 was found significantly high in patients who delivered preterm within 7 weeks and for whom the test was requested as biomarker for a short-term prediction of preterm birth in addition to cervical length measurement. The threshold value of 2 ng/mL for maternal serum calponin 1 predicted delivery within 7 days with 61.1% sensitivity and 62.2% specificity. The general accuracy values for maternal cervical length measurement (≤25 mm), serum calponin 1 level (>2 ng/mL) and the combination of two tests to predict delivery within 7 days was found to be 64.4%, 61.6% and 72.1%, respectively.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

### ***Ratio of Maternal Serum Alpha Fetoprotein (AFP)/Amniotic Fluid AFP***

Sharony et al.[78] suggested the ratio of maternal serum alpha fetoprotein (AFP)/amniotic fluid AFP as a potential predictor for intrauterine growth restriction and preterm delivery in a small sample sized study (n= 160). A significant correlation was found between the ratio and intrauterine growth restriction (IUGR) and week of delivery.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## Maternal Serum Progesterone-Induced Blocking Factor (PIBF)

Hudić et al.[79] showed maternal serum progesterone-induced blocking factor (PIBF) concentrations taken within 5 days before labor started were significantly lower than in those obtained more than 5 days before labor (5/11, 45.5%; the mean interval between sampling and the onset of labor was 4.1 ± 1.8 days). This data suggests that pregnancy termination can be predicted by lower than normal pregnancy PIBF values within 5 days before labor and can contribute to the diagnosis of preterm birth.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## Maternal Plateletcrit Count (PCT)

Isik et al.[80] showed plateletcrit is the volume occupied by platelets in the blood as a percentage and calculated according to the formula:

PCT = platelet count × MPV / 10,000

Under physiological conditions, the number of platelets in the blood is maintained in an equilibrium state by regeneration and elimination. Plateletcrit was found significantly higher in patients who delivered preterm; a cut-off value of 0.201%, with a sensitivity of 95.6% and specificity of 87.5%, was reported.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## Maternal Salivary Estriol

In a study of maternal salivary estriol at 25-34 weeks, Sogra et al.[81] had 82% negative predictive value on identifying women who will not deliver preterm, which could be used for avoiding unnecessary interventions to prevent preterm birth. In this study, salivary estriol levels equal to or higher than the cut-off point (2.6 ng m(-1)) were considered as the estriol (+) group and those lower than 2.6 ng mL(-1) were considered as the estriol (-) group. Findings showed that 18.3% subjects in the estriol (+) group and 8.2% subjects in the estriol (-) group had preterm deliveries. There was a significant relationship between salivary estriol levels and preterm birth ($\chi 2 = 10.636$, $p = 0.001$).

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

Currently, there are no tools that enable early prediction of those women susceptible to preterm birth and more research is needed to develop new strategies to identify women who may benefit from prophylactic therapy.

Not a single biomarker has been evolved to date, which possesses sensitivity as well as reliability for the detection of spontaneous preterm birth. The variability in results of the studies may be caused by different study designs and diversities in the study population. Study on a large sample size is needed to confirm the effectiveness of a biomarker.

A single biomarker or even in combination, if found for the prediction of preterm birth, can decrease the hospital cost and restrict the treatment. Identification of risk factors early in pregnancy is an essential component of clinical obstetric care, since early interventions may be effective in reducing the risk of preterm birth.

Pre-conceptional counselling regarding these factors may further reduce the risk of preterm birth. Differentiation of severity of risk factors is important to assess the best strategy to prevent preterm birth. The prevention of preterm birth is a major public health priority.

The workup that is obtained depends on clinical resources available and local practice patterns. Available resources may vary based on time of day, day of the week, and/or provider availability.

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Chapter 6

# Antimicrobial Agents

Valiant L. See, MD, FPOGS, FPIDSOG

Evidence shows that the presence of maternal infection and the production of inflammatory mediators can contribute to the pathogenesis of preterm birth.

The pathophysiology by which infections cause preterm birth include:

1. Ascending infection to the placenta and fetus
2. Transplacental passage of infection to the fetus
3. Systemic blood-borne infection
4. Activation of pro-inflammatory cytokines that activate prostaglandin production

Symptomatic maternal infections like urinary tract infection, vaginitis, cervicitis or pneumonia warrant specific antibiotic therapy. On the other hand, while subclinical or asymptomatic infection has a well-established role in the pathogenesis of preterm labor, evidence regarding its treatment is inconsistent.

| **QUESTION 1** | **Should antimicrobials be administered to patients with idiopathic spontaneous preterm labor?** |
|---|---|
| **RECOMMENDATION** | Administration of antibiotics in pregnant women with idiopathic spontaneous preterm labor without clinical signs and symptoms of infection does not significantly decrease the incidence of preterm birth and therefore is not recommended.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

According to the World Health Organization (WHO) recommendations[1] on routine antibiotic administration for women in preterm labor with intact amniotic membranes published in November 2015, routine antibiotic administration is not recommended for women in preterm labor with intact amniotic membranes and no clinical signs of infection. The evidence against the use of antibiotics for women in preterm labor was based on a Cochrane

systematic review of 14 randomized controlled trials involving more than 7800 women. The results showed that there was no clear evidence that administration of prophylactic antibiotics result in prolongation of pregnancy. No statistically significant differences were observed in birth prior to 36 or 37 weeks (RR 0.98, 95% CI 0.92–1.05; 10 studies, 7387 women), birth within 48 hours of randomization (RR 1.04, 95% CI 0.89–1.23; 4 studies, 6800 women), birth within 7 days of randomization (RR 0.98, 95% CI 0.87–1.10; 8 studies, 7053 women) or gestational age at birth (mean difference 0.53 weeks, 95% CI 0.00–1.06; 10 studies, 986 women).

Another study by Stetzer, et al.,[2] showed that resistance of microorganisms may develop when antibiotics are used without specific aim or when a specific bacterium is undertreated. They further stated that prenatal and intrapartum antibiotic use is associated with an increased risk for antibiotic resistant neonatal sepsis. Thus, they discourage the administration of antibiotics among women in preterm labor for the purpose of prolonging pregnancy. Treatment should be only for those with specific indications such as intrapartum group B streptococci prophylaxis and those with urinary tract infection.

This was further supported by the study of Bowes,[3] which stated that the use of antibiotics in treating women with idiopathic spontaneous preterm labor does not significantly decrease the incidence of preterm birth and may result in an increased risk of neonatal developmental abnormalities. A published clinical trial by Kenyon et al.[4] showed that antibiotics should not be routinely prescribed for women with spontaneous preterm labor without evidence of clinical infection.

These studies all agree with the recommendation of the American College of Obstetricians and Gynecologists (ACOG) [5] that women in preterm labor should not be treated with antibiotics for the sole purpose of preventing preterm delivery.

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Chapter 7

# Antenatal Lower Genital Infection Screening Tests to Prevent Preterm Labor

Valiant L. See, MD, FPOGS, FPIDSOG

Recent evidences suggest that infection may be implicated in a substantia proportion of cases of preterm delivery. The normal microbial flora present i the vagina usually plays a significant role in preventing lower genital infections Organisms such as *Ureaplasma*, Group B *Streptococcus*, *Gardnerella Bacteroides fragilis, Mycoplasma, Escherichia coli* and *Candida* can present as abnormal vaginal flora that can lead to the development of sexually transmitted diseases, yeast infections, cervico-vaginitis, and urinary tract infections. Screening for lower genital infection during pregnancy to prevent preterm labor still has no universally accepted recommendation for obstetricians and may have some adverse effects with increased cost.

| QUESTION 1 | Does antenatal lower genital tract infection screening reduce preterm labor? |
|---|---|
| RECOMMENDATION | There are few data supporting that antenatal lower genital tract infection screening may reduce preterm labor. This is due to the circumstance that lower genital tract infections often are asymptomatic and prompt recognition with immediate treatment reduces mortality and morbidity from the effect of premature labor and birth.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

A prospective and retrospective observational study by Dr. Pinnamaneni Siddhartha[1] involved 116 women in preterm labor. Clinical examination, ultrasound, urine culture and sensitivity and vaginal swabs were taken. Urinary tract infection was seen in 27.58% women. *E. coli* was the most common

microorganism isolated in urine (15.51%). Vaginal infections were seen in 33.62% of the cases. *Candida* was the most common microorganism isolated in cultures. The study concluded that screening for genitourinary infections in pregnancy is necessary especially in high-risk cases.

Another study by Vrishali et al.,[2] found that urogenital infection was 3.77 times (34%) more likely in women with preterm labor compared to the full term laboring patients group (9%). This suggests a significant association of urogenital infections with preterm labor. Thus, it was recommended that early screening and treatment may prove beneficial in the reduction of mortality and morbidity resulting from premature labor and birth.

A conflicting study was published by Kumari et al.[3] wherein they stated that screening for abnormal vaginal flora cannot be generalized, but may be safely carried out in pregnant women who had a previous history of preterm labor. Routine screening of asymptomatic pregnant women who are at low risk of having preterm labor is not advocated as there is little evidence that it helps in preventing preterm labor.

Based on the Cochrane systematic review authored by Sangkomkamhang et al. in 2016, there is evidence from one trial that infection screening and treatment programs for pregnant women before 20 weeks gestation reduce preterm birth and preterm low birth weight. They recommended future trials to evaluate the effects of different types of infection screening programs. [4]

| **QUESTION 2** | **What screening test could be done to document subclinical infections?** |
|---|---|
| **RECOMMENDATION** | 1. Asymptomatic bacteriuria (ASB) – Urine culture and sensitivity<br>2. Cervicitis<br>a. *Neisseria gonorrhea* – Nucleic acid amplification test<br>b. *Chlamydia trachomatis* - Nucleic acid amplification test<br>3. Vaginitis – Gram stain |

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Chapter 8

# Progesterone Therapy

Joseph U. Olivar, MD, FPOGS, FPSMFM

After almost four centuries,[1] the role of ovarian steroids is still clear; progesterone inhibits while estrogen promotes the events leading to parturition.

But how does progesterone maintain tranquility of the uterus? The mechanism by which progesterone maintains uterine quiescence is unknown but several actions are enumerated in a journal[2] published by the Society for Maternal-Fetal Medicine (SMFM).

**TABLE 1**
**Proposed mechanisms of action reported for progestogens to prevent preterm birth[9-17]**

| |
|---|
| Stimulate transcription of ZEB1 and ZEB2, which inhibit connexin 43 (gap-junction protein that helps synchronize contractile activity) and oxytocin-receptor gene |
| Decrease prostaglandin synthesis, infection-mediated cytokine production (antiinflammatory effects) by fetal membranes/placenta |
| Changes in PR-A and PR-B expression (decreased PR-A/PR-B ratio keeps uterus quiescent) |
| Membrane-bound PR in myometrium |
| PRs, when stimulated by progesterone, help selected gene promotion, or prevent binding of other factors |
| Interfere with cortisol-mediated regulation of placental gene expression |
| Nongenomic pathways |
| Reduce cervical stromal degradation in cervix |
| Alter barrier to ascending inflammation/infection in cervix |
| Reduce contraction frequency in myometrium |
| Attenuate response to hemorrhage/inflammation in decidua |
| Alter estrogen synthesis in fetal membranes/placenta |
| Alter fetal endocrine-mediated effects |

*PR*, progesterone receptor; *ZEB1*, zinc finger E-box binding homeobox protein 1; *ZEB2*, zinc finger E-box binding homeobox protein 2.

*SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.*

Phase 1 of parturition (from conception up to around 32 weeks of gestation) is characterized by progesterone predominance starting from the corpus luteum then from the placenta. This explains uterine tranquility at this time. But at around 33 weeks, phase 1 shifts to phase 2 which is now characterized by estrogen predominance with subsequent decline in progesterone activity (not serum level). This shift in the ratio of progesterone and estrogen is the most

accepted phenomenon explaining parturition. It is postulated that this is probably the same mechanism, i.e. loss of progesterone activity, that explains spontaneous preterm labor. It therefore follows theoretically that the progesterone supplementation may block the onset of preterm labor.

Numerous studies have been done to determine the role of progesterone in the prevention of preterm labor and in this chapter, the evidences will be presented.

| **QUESTION 1** | **Does progesterone prevent preterm birth in a singleton gestation with history of prior preterm delivery?** |
|---|---|

**RECOMMENDATIONS**

- Women with singleton gestation and a history of prior spontaneous preterm singleton birth should be given progesterone supplementation from 16 to 36 weeks of gestation to reduce the risk of another spontaneous preterm birth.[3]
- Choice of progesterone:
  - 17-hydroxyprogesterone caproate (17-OHPC) 250 mg intramuscularly weekly or micronized progesterone 200 mg intravaginally once a day
  - Oral micronized progesterone 200 mg taken once a day at bedtime is an alternative.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

The pivotal study was done by Meis [4] in 2003 when he recruited women with prior history of spontaneous preterm birth (PTB). One group was given intramuscular (IM) progesterone against a group who received placebo from 16 to 36 weeks. The primary outcome was preterm birth less than 37 weeks. The result was significant. Treatment with 17-hydroxyprogesterone caproate (OHPC) significantly reduced the risk of delivery at <37 weeks age of gestation (AOG) (incidence, 36.3% in the progesterone group vs. 54.9% in the placebo group; relative risk, [RR] 0.66; 95% confidence interval [CI], 0.54 to 0.81), delivery at

<35 weeks AOG (incidence, 20.6% vs. 30.7%; RR, 0.67; 95% CI, 0.48–0.93), and delivery at <32 weeks AOG (11.4% vs. 19.6%; RR, 0.58; 95% CI, 0.37–0.91). Infants of women given 17-OHPC also had significantly lower incidence of birth weight less than 2.5 kg (RR, 0.66; 95% CI, 0.51–0.87), need for supplemental oxygen (RR, 0.62; 95% CI, 0.42–0.92); intraventricular hemorrhage (IVH) of any grade (RR, 0.25; 95% CI, 0.08–0.82) and necrotizing enterocolitis (NEC).

In the same year, da Fonseca[5] from Brazil also made a randomized controlled trial (RCT) involving 142 women with prior history of PTB. One group was given vaginal progesterone (100 mg) while the other group was given placebo. All patients underwent uterine contraction monitoring with an external tocodynamometer once a week for 60 minutes between 24 to 34 weeks AOG. Significant differences in uterine activity were found between the progesterone and placebo groups (23.6% vs. 54.3%; $P$ <.05) and in preterm birth between progesterone and placebo (13.8% vs. 28.5%; $P$ <.05). More women delivered <34 weeks in the placebo group (18.5%) than in the progesterone group (2.7%) ($P$ <.05).

These findings led the American College of Obstetricians and Gynecologists (ACOG) and SMFM in 2008 to recommend treatment with either 17-OHPC or vaginal progesterone in women with a history of prior spontaneous PTB to prevent recurrence of PTB.

In 2017, a meta-analysis[6] of RCTs compared the efficacy and side effects of vaginal progesterone and 17-OHPC. Three RCTs (680 women) were included. Women who were given vaginal progesterone had significantly lower incidence of spontaneous preterm delivery <34 weeks (17.5% vs. 25.0%; RR, 0.71; 95% CI, 0.53–0.95); and <32 weeks (8.9% vs. 14.5%; RR, 0.62; 95% CI, 0.40–0.94); compared with women who received 17-OHPC. There were no significant differences in the rates of spontaneous preterm birth at <37 weeks, <28 weeks and <24 weeks. The incidence of women who reported adverse drug reactions was significantly lower in the vaginal progesterone group compared with the 17-OHPC group (7.1% vs. 13.2%; RR, 0.53; 95% CI, 0.31–0.91). Regarding neonatal outcomes, vaginal progesterone was associated with a lower rate of admissions to the neonatal intensive care unit (NICU) compared with 17-OHPC (18.7% vs. 23.5%; RR, 0.63; 95% CI, 0.47–0.83). This meta-analysis concluded that daily vaginal progesterone (either suppository or gel) started at about 16 weeks AOG is an effective, if not better, alternative to weekly 17-OHPC injection for the prevention of another spontaneous preterm birth in women with singleton gestations and prior history preterm delivery. On a practical standpoint, 17-OHPC is not readily available locally.

The 2018 updated meta-analysis[3] by Romero et al. affirmed that in women wit short cervix, even in that subgroup with prior history or spontaneous preter birth, vaginal progesterone therapy is effective in preventing another preter delivery.

In 2019, another meta-analysis[7] was published which assessed the efficacy o the oral route for micronized progesterone. Three trials on oral progesteron (OP) versus placebo (involving 386 patients: 196 in OP and 190 in placebo) me the inclusion criteria. The meta-analysis demonstrated a significant decrease i the risk of preterm birth at <37 weeks AOG (42% vs. 63%; P=0005; RR, 0.68; 95% CI, 0.55–0.84), preterm birth at <34 weeks AOG (29% vs. 53%; P<.00001; RR, 0.55; 95% CI, 0.43–0.71), and increased gestational age of delivery (mean difference, 1.71 weeks; 95% CI, 1.11–2.30) with oral progesterone compared with placebo. There was a considerable lower rate of perinatal death (5% vs. 17%; P=001; RR 0.32; 95% CI, 0.16–0.63), neonatal intensive care admission (RR, 0.39; 95% CI, 0.25–0.61), respiratory distress syndrome (RR, 0.21; 95% CI, 0.05–0.93), and higher birth weight (mean difference, 435.06 g; 95% CI, 324.59–545.52) with oral progesterone. There was however, a higher rate of maternal side effects with OP which included dizziness (RR, 2.95; 95% CI, 1.47–5.90), somnolence (RR, 2.06; 95% CI, 1.29–3.30), and vaginal dryness (RR, 2.37; 95% CI, 1.10–5.11); but no serious adverse effects were noted.

| **QUESTION 2** | **Does progesterone prevent preterm birth in asymptomatic women with short cervix?** |
|---|---|

**RECOMMENDATIONS**

- Asymptomatic women with a singleton gestation and a short cervix (cervical length [CL] ≤25mm) should be offered daily progesterone supplementation from the diagnosis of short cervix up to 36 6/7 weeks of gestation to reduce the risk of spontaneous preterm birth.[3]
- Choice of progesterone:
  - Vaginal micronized progesterone 200 mg or 90 mg gel suppository
  - Oral micronized progesterone is an alternative

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

In 2007, da Fonseca conducted another RCT[8] where pregnant women with short cervical length (CL ≤15mm) were randomized to receive either 200 mg vaginal micronized progesterone or placebo from 24 to 34 weeks gestation. Results revealed that the rate of spontaneous preterm delivery <34 weeks AOG was significantly less in the progesterone group compared to placebo (19.2% vs. 34.4%; RR, 0.56; 95% CI 0.36–0.86). Progesterone was likewise associated with a non-significant reduction in neonatal morbidity (8.1% vs. 13.8%; RR, 0.59; 95% CI, 0.26–1.25; P=0.17). No serious adverse events were associated with the use of progesterone.

In 2012, a meta-analysis[9] of individual patient data (IPD) confirmed the initial findings of da Fonseca. Five high quality trials were included with a total of 775 women and 827 infants. Vaginal progesterone supplementation was significantly associated with a reduction in the rate of preterm birth <33 weeks (RR, 0.58; 95% CI, 0.42–0.80), <35 weeks (RR, 0.69; 95% CI, 0.55–0.88), and <28 weeks (RR, 0.50; 95% CI, 0.30–0.81); respiratory distress syndrome (RDS) (RR, 0.48; 95% CI, 0.30–0.76); composite neonatal morbidity and mortality (RR, 0.57; 95% CI, 0.40–0.81); birth weight <1500 g (RR, 0.55; 95% CI, 0.38–0.80); admission to NICU (RR, 0.75; 95% CI, 0.59–0.94); and the need for mechanical ventilation (RR, 0.66; 95% CI, 0.44–0.98). No significant differences between the vaginal progesterone and placebo groups were found with regard the rate of adverse maternal events or fetal congenital anomalies.

In 2016, however, the OPPTIMUM Study[10] came out. This study tested the effect of 200 mg vaginal micronized progesterone on women at risk of preterm delivery due to three risk factors, namely: previous history of PTB, short cervix and positive fibronectin. The three primary outcomes measures were: obstetric (birth before 34 weeks or fetal death), neonatal (death, brain injury or bronchopulmonary dysplasia) and childhood (cognitive score at age of 2 years). Results revealed that although progesterone is safe during pregnancy and there is a tendency to decrease neonatal brain injury due to its anti-inflammatory effect, there is no significant difference with placebo with regard to obstetric, neonatal and childhood outcome.

This created uncertainty on the efficacy of vaginal progesterone in reducing the rate of spontaneous preterm birth. Thus, in the same year (2016), Romero and Nicolaides updated their meta-analysis[11] which now included the data from the OPPTIMUM study. The authors provided the following conclusions:

- Even with the data from the OPPTIMUM trial included, the combined results still favored vaginal progesterone with a significant 34% reduction in preterm birth < 34 weeks.
- This did not alter the other significant results from the 2012 IPD meta-analysis.

The authors explained why the OPPTIMUM STUDY did not give any significant result favoring vaginal progesterone.

- The OPPTIMUM study lacks power to detect an important difference between vaginal progesterone and placebo in the subgroup of women with CL <25mm
- The OPPTIMUM study is high risk for the following bias: incomplete outcome data, reporting bias and low compliance (68.6%) which could have affected the trial's statistical power to determine the effects of the intervention

In 2018, Romero et al.[3] published another meta-analysis to include a more rigorous subgroup analysis especially addressing women with prior history of preterm birth. This included five trials involving 974 women who were randomized to receive either vaginal progesterone or placebo. The primary outcome was preterm delivery <33 weeks AOG. The secondary outcomes included preterm delivery at different ages of gestation and varied neonatal outcomes. Vaginal progesterone was again proven to significantly reduce the risk of preterm delivery <33 weeks AOG (RR, 0.62; 95% CI, 0.47–0.81; P=.0006; high-quality evidence). Moreover, vaginal progesterone significantly reduced the risk of preterm birth at <36, <35, <34, <32, <30, and <28 weeks AOG; spontaneous preterm delivery at <33 and <34 weeks AOG; RDS; composite neonatal morbidity and mortality; birth weight <1500 and <2500 grams; and admission to the NICU (RR from 0.47–0.82; high-quality evidence for all). There were seven (7 or 1.4%) neonatal deaths seen in the vaginal progesterone group compared with 15 (3.2%) in the placebo group (RR, 0.44; 95% CI, 0.18–1.07; P=.07; low-quality evidence). Between the two groups, maternal adverse events, fetal congenital anomalies, and adverse neurodevelopmental and health outcomes at age of two years did not differ.

| QUESTION 3 | **Does progesterone prevent preterm birth in asymptomatic women with twin gestation?** |
|---|---|

**RECOMMENDATIONS**

- Asymptomatic women with twin gestation and a short cervix (cervical length (CL) ≤25mm) should be offered twice daily progesterone supplementation from the diagnosis of short cervix up to 36 weeks of gestation to reduce the risk of spontaneous preterm birth. [14]
- Choice of progesterone:
  - Vaginal micronized progesterone 200 mg twice daily

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

In 2012, a meta-analysis of individual patient data (IPD) [12] reported on the efficacy of vaginal progesterone in preventing spontaneous preterm birth and neonatal morbidity and mortality in asymptomatic women with twin gestation and a short cervix (CL ≤25 mm) in the mid-trimester. Fifty-two (52) women (104 fetuses/infants) from three RCTs were included in the meta-analysis. Although the use of vaginal progesterone was associated with a significant 44% reduction in the risk of composite neonatal morbidity and mortality (RR, 0.56; 95% CI, 0.30–0.97), there was a 30% non-significant reduction in the risk of preterm birth <33weeks' gestation (RR, 0.70; 95% CI, 0.34–1.44).

The 2015 Philippine Society of Maternal Fetal Medicine (PSMFM) Clinical Practice Guidelines on Preterm Labor[13] therefore concluded that progesterone is not recommended for multiple gestation (twins and higher order gestation), with normal or short cervical length, because it does not prolong gestation and does not improve perinatal outcome.

However, in 2017, an updated meta-analysis [14] of individual patient data (IPD) from RCTs comparing vaginal progesterone with placebo/no treatment in women with a twin gestation and a mid-trimester short cervical length ≤25mm was published. The primary outcome measure was preterm birth <33weeks' gestation. The meta-analysis concluded that vaginal progesterone supplementation was associated with a statistically significant reduction in the risk of preterm birth <33 weeks' AOG (31.4% vs. 43.1%; RR, 0.69; 95% CI, 0.51–

0.93). In addition, vaginal progesterone administration was associated with a significant decrease in the risk of preterm delivery <35, <34, <32 and <30 weeks gestation (RRs ranging from 0.47 to 0.83), neonatal death (RR, 0.53; 95% CI 0.35–0.81), respiratory distress syndrome (RR, 0.70; 95% CI, 0.56–0.89), composite neonatal morbidity and mortality (RR, 0.61; 95% CI, 0.34–0.98), use of mechanical ventilation (RR, 0.54; 95% CI, 0.36–0.81) and birth weight <1500 grams (RR, 0.53; 95% CI, 0.35–0.80). Between the vaginal progesterone and placebo groups, there were no significant differences in neurodevelopmental outcomes at 4–5 years of age.

## QUESTION 4 — Is progesterone effective in acute preterm labor?

**RECOMMENDATIONS**

- There is no robust evidence supporting the hypothesis that the administration of micronized progesterone decreases preterm birth or improves neonatal outcome in women with preterm labor.[15]
- Based on low quality evidence, combining daily micronized progesterone with a tocolytic agent may prove beneficial.[16]
- Choice of progesterone:
  - Micronized progesterone 400 mg every 8 hours intravaginally

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

In 2014, a randomized double-blind placebo controlled trial [15] randomly allocated participants to daily vaginal progesterone 200 mg versus placebo within 48 hours of starting tocolysis for acute preterm labor. The main outcome included delivery <37 weeks AOG. Secondary outcomes included delivery <32 and <34 weeks, adverse side effects, duration of tocolysis, re-admissions for preterm contractions, length of hospital stay, and neonatal morbidity and mortality. This study ended prematurely based on results of the intermediate analysis. Preterm birth occurred in 42.5% of women in the progesterone group versus 35.5% in the placebo group (RR, 1.2; 95% CI, 0.93–1.5). Delivery at <32 and <34 weeks was not different between the two groups ([12.9 vs. 9.7%; RR 1.3; 95% CI 0.7–2.5] and ([19.7 vs. 12.9%; RR 1.5; 95% CI 0.9–2.4], respectively).

The duration of tocolysis, hospitalization, and recurrence of preterm labor were comparable between two groups. Neonatal morbidity was found in 44 (22.8%) cases on progesterone versus 35 (18.8%) cases on the placebo group (RR, 1.2; 95% CI, 0.82–1.8), whereas there were 4 (2%) neonatal deaths in each study group.

On the same year, a meta-analysis[16] on the use of progestational agents for treating threatened or established preterm labor was published by the Cochrane Pregnancy and Childbirth group. The use of progestational agents (micronized progesterone but not IM progesterone) resulted in a statistically significant reduction in preterm deliveries at less than 37 weeks of gestation (average RR 0.62, 95% CI 0.39 to 0.98, I2 = 57%, Tau2 = 0.11). This meta-analysis concluded that there is now encouraging data to show that progesterone, when used with another tocolytic agent, results in a reduction of preterm births at less than 37 weeks of gestation and increase in neonatal birth weight.

| **QUESTION 5** | **After arrested preterm labor, is progesterone effective for maintenance tocolysis?** |
|---|---|

**RECOMMENDATIONS**

- Maintenance tocolysis in the form of micronized progesterone is associated with prevention of preterm birth, significant prolongation of pregnancy, and lower neonatal sepsis.[17]
- Choice of progesterone:
  - Micronized vaginal progesterone 200 mg administered 2–3x a day
  - Oral micronized progesterone once a day

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

A publication[18] in the International Journal of Gynecology and Obstetrics (FIGO) evaluated the effectiveness of oral micronized progesterone for maintenance tocolysis in cases of arrested preterm labor. Ninety (90) women between 24–34 weeks AOG, singleton pregnancy with intact membranes and arrested uterine contractions were randomly allocated to receive oral micronized progesterone (n = 45) or placebo (n = 45) daily up to 37 weeks or delivery, whichever comes first. Outcomes were compared using Student t test, $x^2$test, Fisher exact test, and log-rank $x^2$test. The RCT revealed that micronized progesterone taken orally

significantly prolonged the latent period (33.29 ± 22.16 vs. 23.07 ± 15.42 days; P=0.013). Log-rank analysis result revealed a meaningful difference in mean time to delivery between 2 groups (P=0.014). There were significantly lesser preterm births (33% vs. 58%; P=0.034) and low birth weight neonates (37% vs. 64%; P=0.017), and significantly higher mean birth weight (2.44 ± 0.58 vs. 2.14 ± 0.47 kg; P=0.009) in the oral micronized progesterone group. Perinatal outcomes and adverse effects were similar both groups.

In 2015, a meta-analysis[17] tried to evaluate the effectiveness of vaginal progesterone as maintenance tocolysis compared to control (placebo or no treatment) in singleton gestations with arrested preterm labor (PTL). Five RCTs including 441 singleton pregnancies were analyzed. Women who received vaginal progesterone for maintenance tocolysis had a significantly lower incidence of preterm birth <37 weeks (42% versus 58%; RR, 0.71; 95% CI, 0.57-0.90; 3 trials, 298 women). Women who received vaginal progesterone had significantly longer latent period (mean difference 13.80 days; 95% CI, 3.97-23.63; 4 trials, 368 women), later AOG at delivery (mean difference 1.29 weeks; 95% CI, 0.43-2.15; 4 trials, 368 women), lower rate of recurrent PTL (24% versus 46%; RR, 0.51; 95% CI, 0.31-0.84; 2 trials, 122 women), and lower incidence of newborn sepsis (2% vs. 7%; RR, 0.34; 95% CI, 0.12-0.98; 4 trials, 368 women). This meta-analysis concluded that maintenance tocolysis with vaginal progesterone is associated with prevention of preterm birth, significant prolongation of gestation, and lower newborn sepsis.

In 2018, a randomized, double-blind, single-center study[19] performed between 2012 and 2015 was published. Thirty women who had preterm labor between 24 0/7 - 33 6/7 weeks were randomly allocated to receive either 400 mg vaginal progesterone or a placebo 48 hour after acute tocolysis. EMG measurements were recorded prior to and 1 hour and 2 hours following treatment. Mann–Whitney U tests were used to compare EMG power density, spectrum peak frequency and peak amplitude, propagation velocity of EMG signals, and duration and number of EMG bursts in 30-minute recordings between the groups ($P < 0.05$). Results showed that EMG propagation velocity was greater in patients given placebo compared to those who received progesterone at 1 hour (27.83 ± 10.66 vs. 15.60 ± 2.94 cm/s) and 2 hours (26.97 ± 13.39 versus 15.12 ± 2.58 cm/s) following treatment ($P = 0.001$). PDS peak frequencies were higher in the placebo compared to the progesterone group at 2 hours following treatment (0.54 ± 0.11 vs. 0.44 ± 0.06 Hz; $P = 0.003$). This RCT concluded that the administration of 400 mg of vaginal micronized progesterone for maintenance tocolysis significantly reduces the propagation velocity of electrical signals within the myometrium and is associated with a shift toward lower uterine electrical signal frequencies.

| QUESTION 6 | Can progesterone be used in preterm prelabor rupture of membranes (PPROM)? |
|---|---|

**RECOMMENDATION**

- There is not enough evidence to recommend the use of any progestogens in PPROM.[2]

*Quality of Evidence: Low to Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

The publication of the Society for Maternal-Fetal Medicine (SMFM) on progesterone and prevention of preterm birth concluded that there is no sufficient evidence to assess effect of progesterone in women with PPROM.[2]

In another study [20] of 69 women with singleton gestations and PPROM at 24-30 weeks, 17-OHPC 250 mg IM is associated with no effect on interval to delivery, gestational age at delivery, or neonatal mortality and morbidity compared to placebo.

| QUESTION 7 | Is progesterone supplementation safe during pregnancy? |
|---|---|

**RECOMMENDATION**

All forms of progesterone (intramuscular, vaginal and oral) are considered safe in pregnancy. [21,22,23]

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Current evidence suggests that in-utero exposure to progesterone (IM, vaginal and oral) does not have an effect on the neurodevelopmental outcomes at least until 2 years of age, and possibly until 6 years of age.[3] Overall, the OPPTIMUM study[10] found that there were no significant differences in neurodevelopmental outcomes at 2 years of age between children exposed in utero to vaginal progesterone and those exposed to placebo. O'Brien et al.[25] assessed

neurodevelopmental outcomes at 6, 12, and 24 months of age in children born to women enrolled in their trial [26] and found similar frequencies of suspected developmental delay in the vaginal progesterone and placebo groups. Similar findings have been reported in children born to mothers participating in trials that compared vaginal progesterone and placebo in unselected twin gestations,[27,28] at a mean age of 56 months.[29,30] Therefore, there is no evidence that vaginal progesterone has adverse effects on childhood neurodevelopmental outcomes.

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Chapter 9

# Omega-3 Long Chain Polyunsaturated Fatty Acids for the Prevention of Preterm Labor

Valerie P. Tiempo-Guinto, MD, MSc, FPOGS, FPSMFM, FPSUOG

Alpha-linolenic acid (ALA; 18:3omega-3) and linoleic acid (LA; 18:2omega-6) are essential fatty acids that are obtained solely from the diet, since they cannot be manufactured by our body. ALA is the parent compound of the long chain polyunsaturated fatty acids (LCPUFA) eicosapentaenoic acid (EPA;20:5omega-3), docosapentaenoic acid (DPA;22:5omega-3) and docosahexaenoic acid (DHA;22:6omega-3) through a series of desaturation and elongation reactions. The efficiency of this process of conversion in humans, however, is very low; thus, LCPUFAs are better obtained from diet. The omega-3 LCPUFAs are now linked to downregulation of inflammatory processes in our body. On the other hand, LA is converted to arachidonic acid (AA; 20:4omega-6) which gives rise to the proinflammatory 2-series of prostanoids (prostaglandins and thromboxanes) and the 4-series leukotrienes. It is the balance of these opposing factors that regulate inflammation.[1]

Observational studies in the 1980s have reported longer pregnancy duration in fish-eating communities.[1] Subsequent randomized controlled trials supported this observation.[1,2] Although the exact mechanism of action is still unknown, results of studies have supported the suggestions that omega-3 LCPUFAs modulate prostaglandin synthesis and inhibit palmitate-induced inflammatory cascade, both of which act in prolonging gestation.[1]

| | |
|---|---|
| **QUESTION 1** | **Among pregnant women at risk for preterm labor and delivery, does administration of omega-3 LCPUFAs versus no supplementation improve perinatal outcomes?** |
| **RECOMMENDATION** | Supplementation with omega-3 LCPUFAs significantly decrease the risk of preterm delivery at < 37 weeks and < 34 weeks age of gestation (AOG).<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

To answer the question of whether omega-3 LCPUFAs prevent preterm labor and delivery, a Pubmed search was conducted using the keywords "preterm labor" and "omega-3 long chain polyunsaturated fatty acids". Studies considered to have the strongest level of evidence were selected. The Cochrane Systematic Review on "Omega-3 Fatty Acid Addition During Pregnancy", published in 2018, investigated the effect of supplementation with omega-3 LCPUFAs on a variety of maternal and perinatal outcomes. Randomized controlled trials (RCTs) comparing omega-3 LCPUFA supplementation with placebo or no supplementation were included in the meta-analysis. Seventy (70) RCTs that involved 19,927 women at low, medium and high risk of poor pregnancy outcomes were included. The primary outcome measures evaluated were preterm birth < 37 weeks, preterm birth < 34 weeks and prolonged gestation > 42 weeks. The secondary outcomes studied which are relevant to this CPG were length of gestation, maternal adverse effects, serious morbidity and mortality, and hemorrhage for the mother; stillbirths, low birth weight, large for gestational age, and several complications of prematurity for the neonate; long-term morbidities for the infant/child; and, use of health service resources.[3]

The results were as shown below:

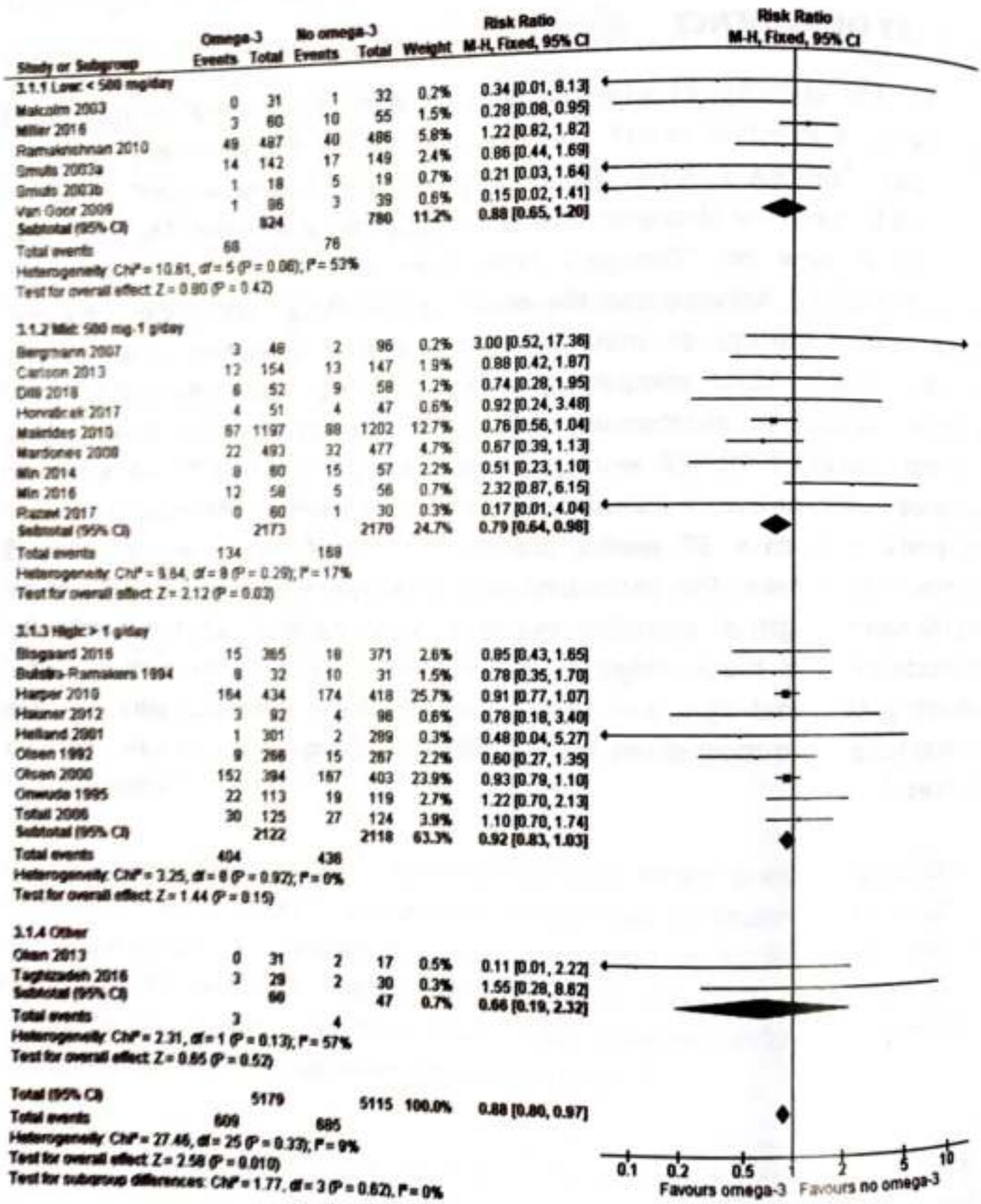



**Figure 1. Forest plot of risk of preterm delivery <34 weeks with supplementation with LCPUFAs in different doses**

As seen in Figure 1, Omega-3 LCPUFAs significantly decreased the risk of preterm delivery at less than 37 weeks (RR 0.88, 95% CI 0.80-0.97), with the best results for doses of 500 mg to 1 g/day (RR 0.79, 95% CI 0.64-0.98).[3]

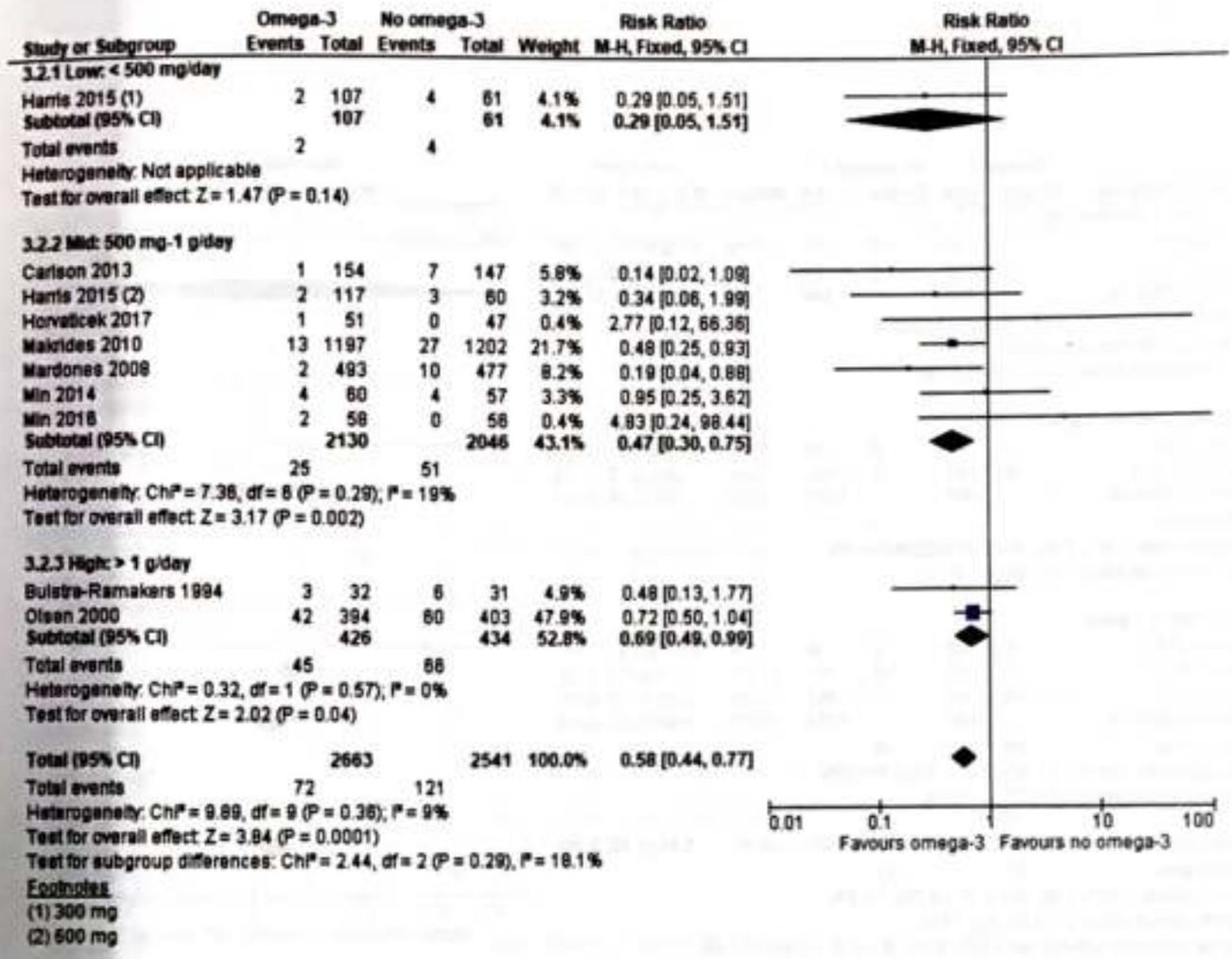



**Figure 2. Forest plot of risk of preterm delivery <34 weeks with supplementation with LCPUFAs in different doses**

As seen in Figure 2, omega-3 LCPUFAs also significantly decreased the risk of preterm delivery at less than 34 weeks age of gestation (AOG) (RR 0.58, 95% CI 0.44-0.77). The best results were seen at doses between 500 mg and 1 g/day (RR 0.47, 95% CI 0-30, 0-75).[3]

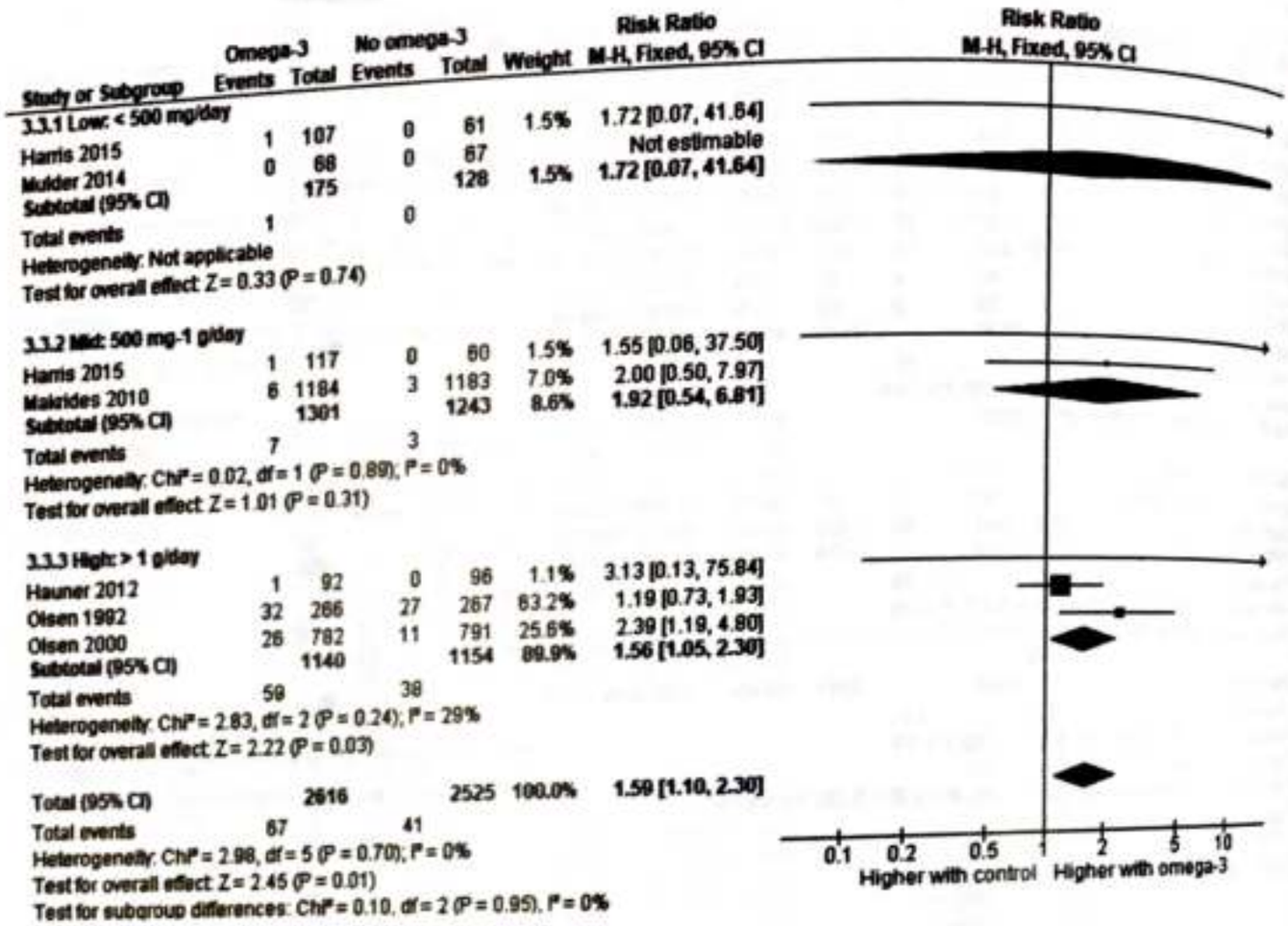



**Figure 3. Forest plot of risk of prolonged gestation with supplementation with LCPUFAs in different doses**

As Figure 3 shows, the Cochrane systematic review further concluded that supplementation with omega-3 LCPUFAs did not significantly prolong gestation to > 42 weeks AOG.[3]

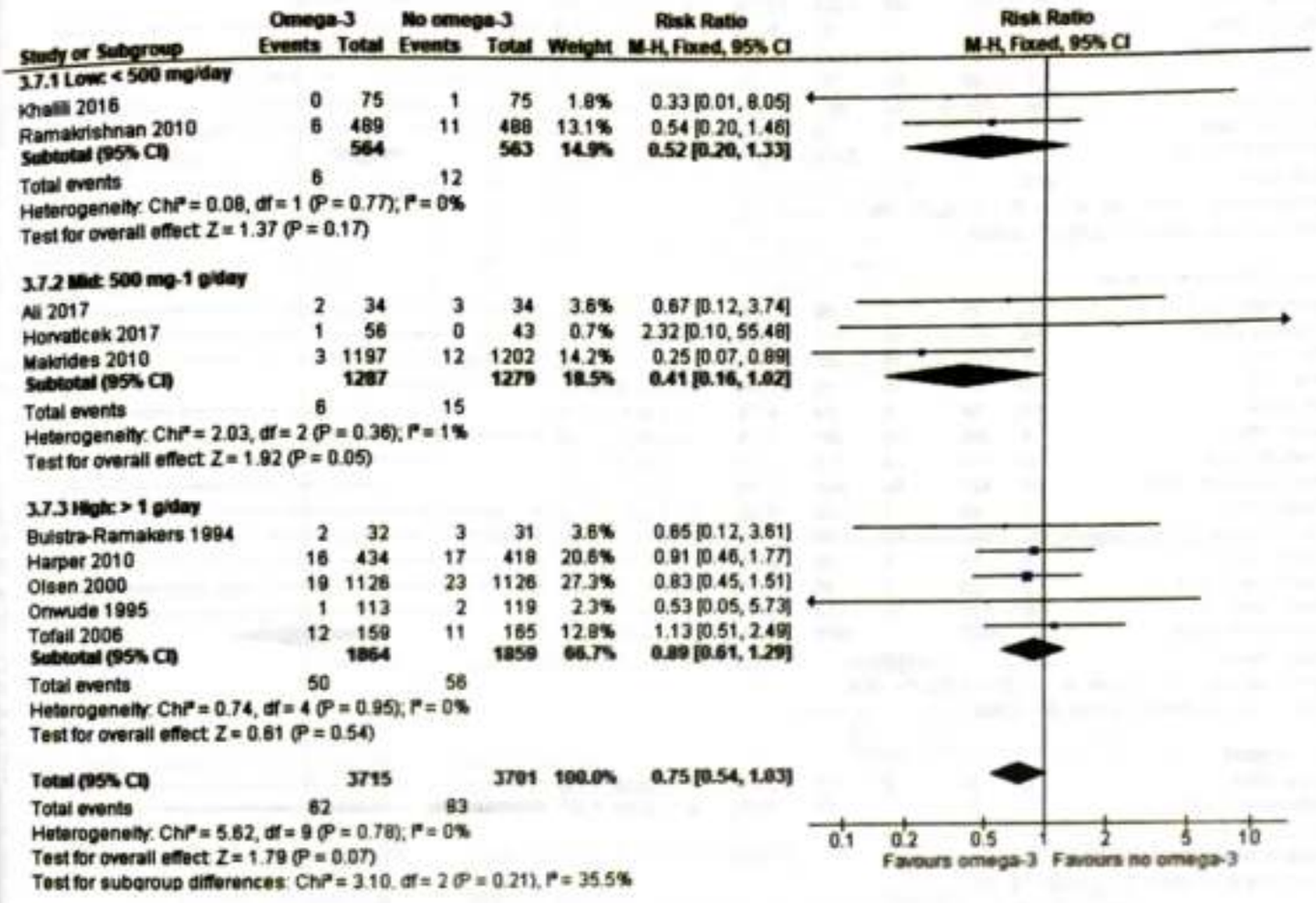



**Figure 4.** Risk of perinatal death with supplementation with omega-3 LCPUFAs in different doses

Figure 4 shows that perinatal death was also not significantly affected by the supplementation with omega-3 LCPUFAs.[3]

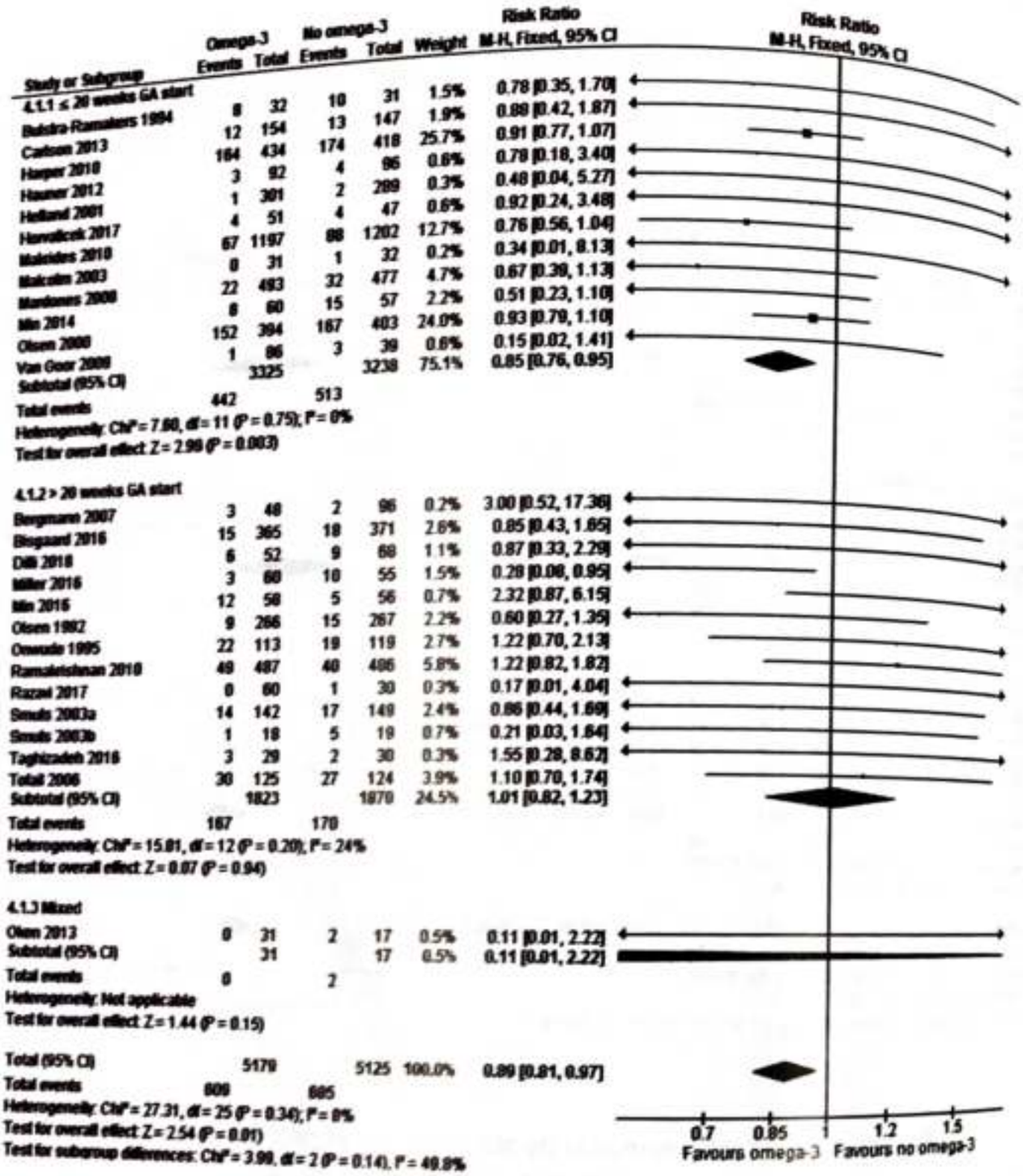



**Figure 5. Risk of preterm delivery according to time of initiation of omega-3 LCPUFAs supplementation**

**QUESTION 2** **Among pregnant women at risk for preterm labor and delivery, when should supplementation with omega-3 LCPUFAs be started to achieve best outcomes?**

**RECOMMENDATION** In preventing preterm birth, omega-3 LCPUFAs work best if given < 20 weeks age of gestation.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Figure 5 illustrates that in preventing preterm birth, omega-3 LCPUFAs work best if they are given ≤ 20 weeks age of gestation (RR 0.85, 95% CI 0.76-0.95).[3]

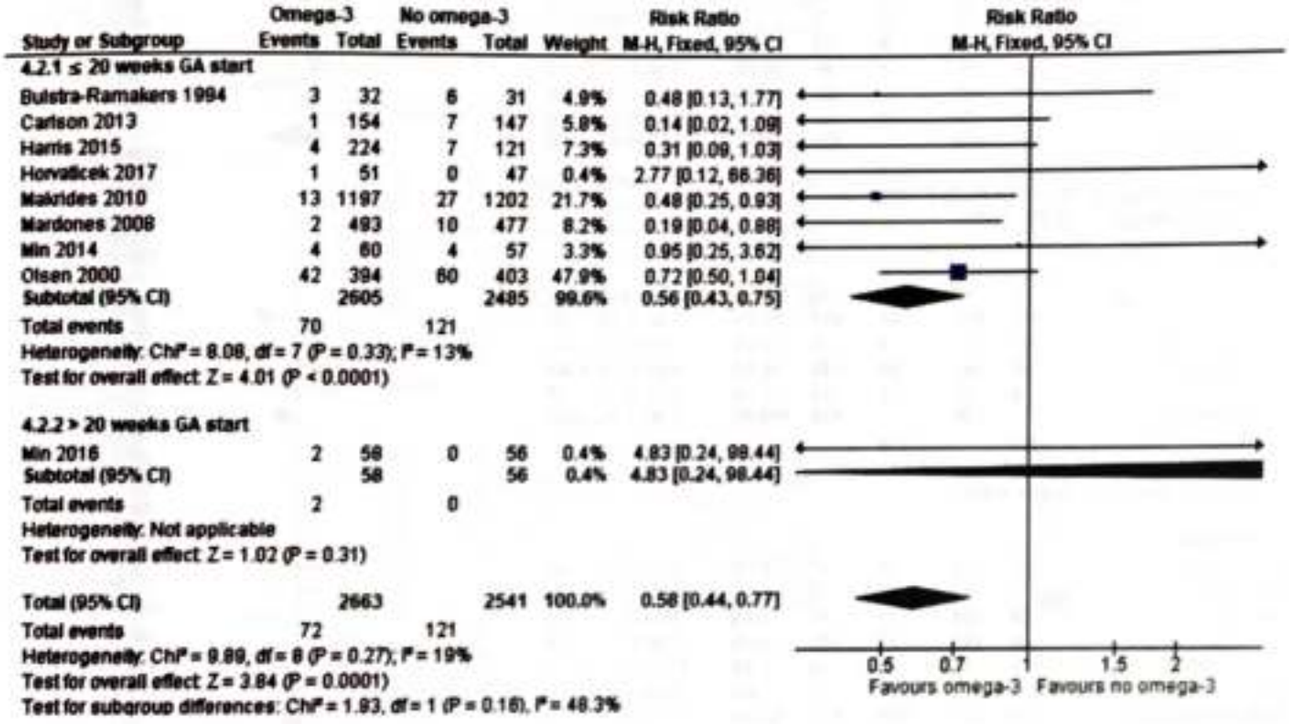
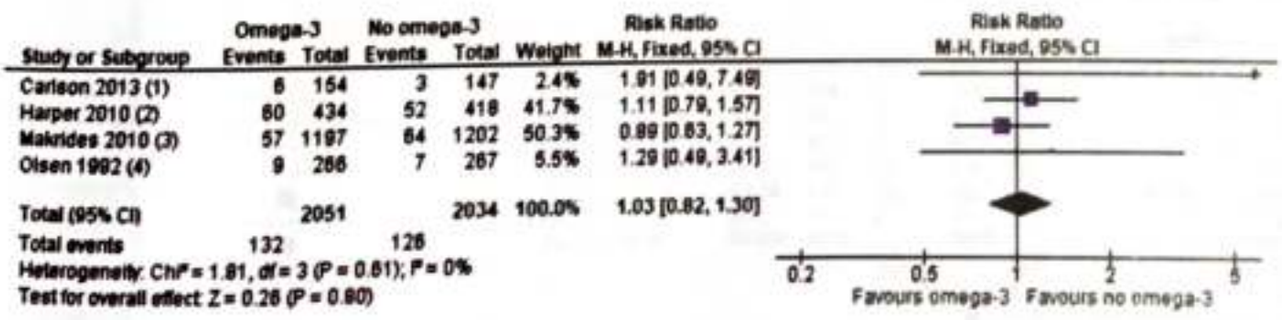
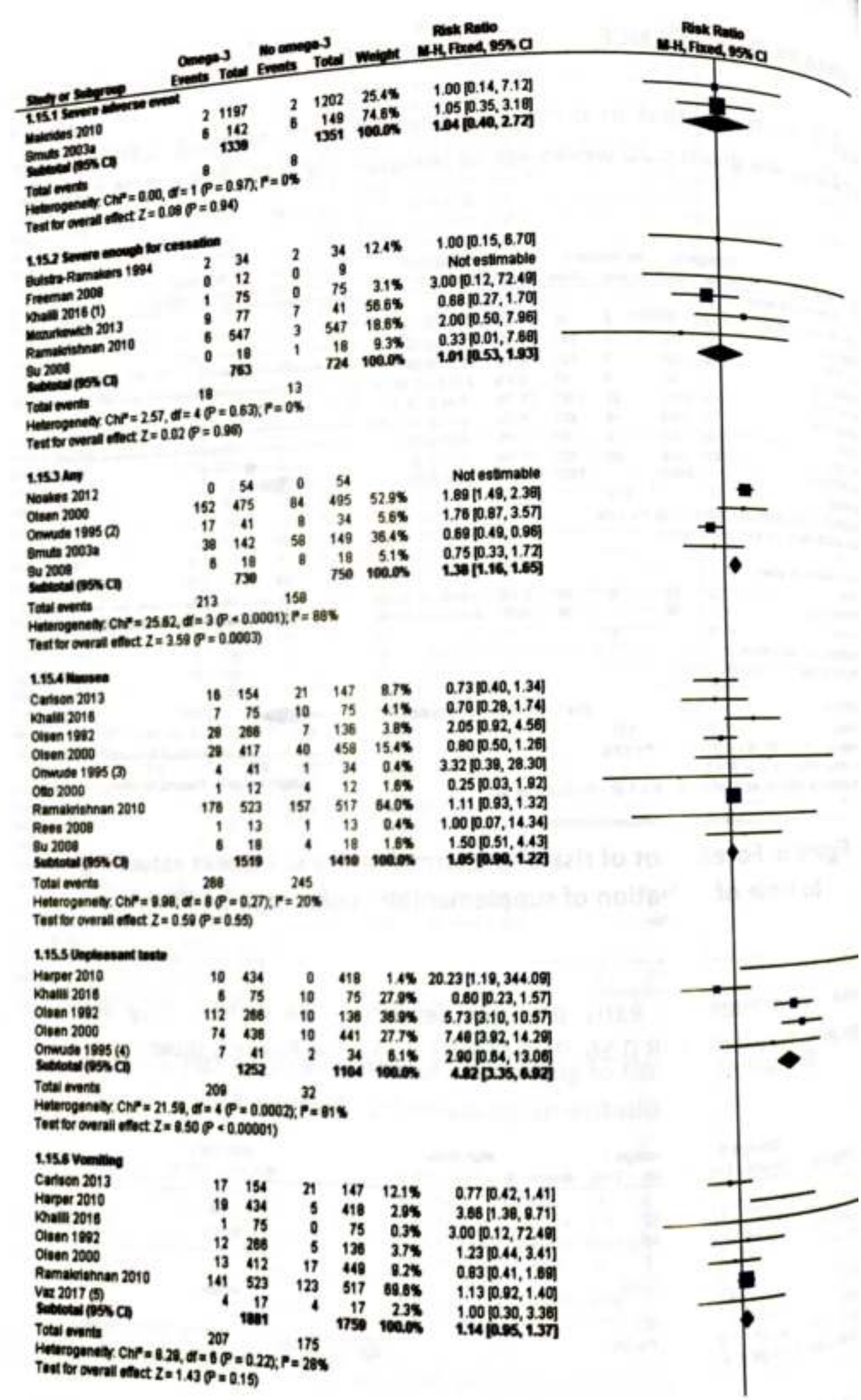


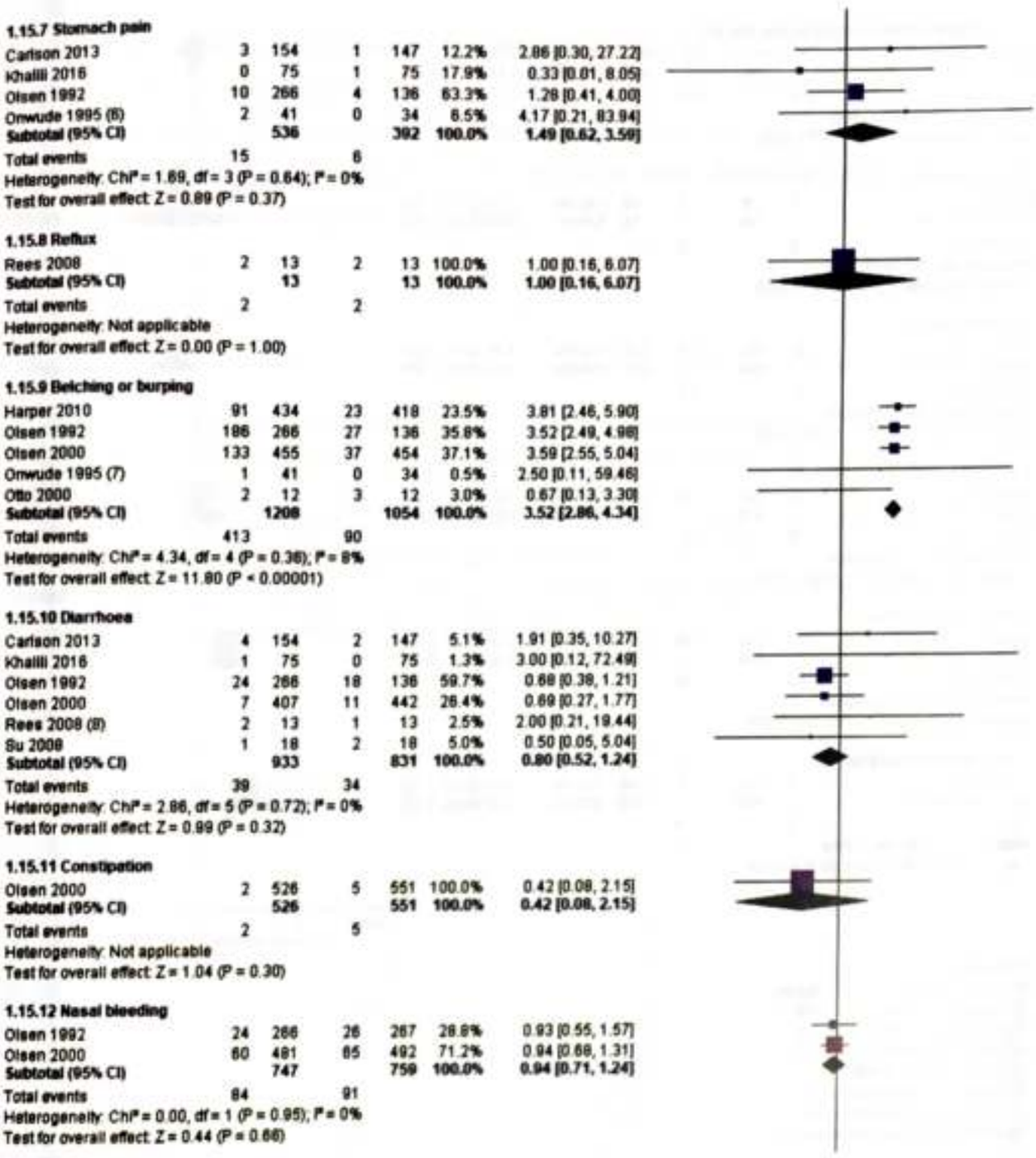

**Figure 6. Forest plot of risk of preterm delivery <34 weeks according to time of initiation of supplementation of omega-3 LCPUFAs**

Likewise, in preventing early preterm delivery (< 34 weeks), they are best started at ≤ 20 weeks (RR 0.56, 95% CI 0.43-0.75),[3] as Figure 6 shows.




Footnotes
(1) vaginal blood loss
(2) vaginal blood loss or blood loss after caesarean
(3) vaginal blood loss or blood loss after caesarean
(4) vaginal blood loss


Study or Subgroup
Omega-3 Events Total
No omega-3 Events Total
Weight
Risk Ratio M-H, Fixed, 95% CI
Risk Ratio M-H, Fixed, 95% CI
1.15.1 Severe adverse event
Makrides 2010 2 1197 2 1202 25.4% 1.00 [0.14, 7.12]
Smuts 2003a 6 142 6 149 74.6% 1.05 [0.35, 3.16]
Subtotal (95% CI) 1339 1351 100.0% 1.04 [0.40, 2.72]
Total events 8 8
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
1.15.2 Severe enough for cessation
Buistra-Ramakers 1994 2 34 2 34 12.4% 1.00 [0.15, 6.70]
Freeman 2008 0 12 0 9 Not estimable
Khalili 2016 (1) 1 75 0 75 3.1% 3.00 [0.12, 72.49]
Mozurkewich 2013 9 77 7 41 56.6% 0.68 [0.27, 1.70]
Ramakrishnan 2010 6 547 3 547 18.8% 2.00 [0.50, 7.96]
Su 2008 0 18 1 18 9.3% 0.33 [0.01, 7.66]
Subtotal (95% CI) 763 724 100.0% 1.01 [0.53, 1.93]
Total events 18 13
Heterogeneity: Chi² = 2.57, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)
1.15.3 Any
Noakes 2012 0 54 0 54 Not estimable
Olsen 2000 152 475 84 485 52.9% 1.89 [1.49, 2.39]
Onwude 1995 (2) 17 41 8 34 5.6% 1.76 [0.87, 3.57]
Smuts 2003a 38 142 58 149 36.4% 0.69 [0.49, 0.96]
Su 2008 6 18 8 18 5.1% 0.75 [0.33, 1.72]
Subtotal (95% CI) 730 750 100.0% 1.38 [1.16, 1.65]
Total events 213 158
Heterogeneity: Chi² = 25.82, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 3.59 (P = 0.0003)
1.15.4 Nausea
Carlson 2013 16 154 21 147 8.7% 0.73 [0.40, 1.34]
Khalili 2016 7 75 10 75 4.1% 0.70 [0.28, 1.74]
Olsen 1992 28 266 7 136 3.8% 2.05 [0.92, 4.56]
Olsen 2000 28 417 40 458 15.4% 0.80 [0.50, 1.26]
Onwude 1995 (3) 4 41 1 34 0.4% 3.32 [0.39, 28.30]
Otto 2000 1 12 4 12 1.6% 0.25 [0.03, 1.92]
Ramakrishnan 2010 178 523 157 517 64.0% 1.11 [0.93, 1.32]
Rees 2008 1 13 1 13 0.4% 1.00 [0.07, 14.34]
Su 2008 6 18 4 18 1.6% 1.50 [0.51, 4.43]
Subtotal (95% CI) 1519 1410 100.0% 1.05 [0.90, 1.22]
Total events 288 245
Heterogeneity: Chi² = 9.98, df = 8 (P = 0.27); I² = 20%
Test for overall effect: Z = 0.59 (P = 0.55)
1.15.5 Unpleasant taste
Harper 2010 10 434 0 418 1.4% 20.23 [1.19, 344.09]
Khalili 2016 6 75 10 75 27.9% 0.60 [0.23, 1.57]
Olsen 1992 112 266 10 136 36.9% 5.73 [3.10, 10.57]
Olsen 2000 74 436 10 441 27.7% 7.48 [3.92, 14.29]
Onwude 1995 (4) 7 41 2 34 6.1% 2.90 [0.64, 13.06]
Subtotal (95% CI) 1252 1104 100.0% 4.82 [3.35, 6.92]
Total events 209 32
Heterogeneity: Chi² = 21.58, df = 4 (P = 0.0002); I² = 81%
Test for overall effect: Z = 8.50 (P < 0.00001)
1.15.6 Vomiting
Carlson 2013 17 154 21 147 12.1% 0.77 [0.42, 1.41]
Harper 2010 19 434 5 418 2.9% 3.66 [1.36, 9.71]
Khalili 2016 1 75 0 75 0.3% 3.00 [0.12, 72.49]
Olsen 1992 12 266 5 136 3.7% 1.23 [0.44, 3.41]
Olsen 2000 13 412 17 449 9.2% 0.83 [0.41, 1.69]
Ramakrishnan 2010 141 523 123 517 69.6% 1.13 [0.92, 1.40]
Vaz 2017 (5) 4 17 4 17 2.3% 1.00 [0.30, 3.36]
Subtotal (95% CI) 1881 1759 100.0% 1.14 [0.95, 1.37]
Total events 207 175
Heterogeneity: Chi² = 8.28, df = 6 (P = 0.22); I² = 28%
Test for overall effect: Z = 1.43 (P = 0.15)



**1.15.7 Stomach pain**

| | | | | | | |
|---|---|---|---|---|---|---|
| Carlson 2013 | 3 | 154 | 1 | 147 | 12.2% | 2.86 [0.30, 27.22] |
| Khalili 2016 | 0 | 75 | 1 | 75 | 17.9% | 0.33 [0.01, 8.05] |
| Olsen 1992 | 10 | 266 | 4 | 136 | 63.3% | 1.28 [0.41, 4.00] |
| Onwude 1995 (6) | 2 | 41 | 0 | 34 | 6.5% | 4.17 [0.21, 83.94] |
| **Subtotal (95% CI)** | | **536** | | **392** | **100.0%** | **1.49 [0.62, 3.59]** |
| Total events | 15 | | 6 | | | |

Heterogeneity: Chi² = 1.69, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

**1.15.8 Reflux**

| | | | | | | |
|---|---|---|---|---|---|---|
| Rees 2008 | 2 | 13 | 2 | 13 | 100.0% | 1.00 [0.16, 6.07] |
| **Subtotal (95% CI)** | | **13** | | **13** | **100.0%** | **1.00 [0.16, 6.07]** |
| Total events | 2 | | 2 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

**1.15.9 Belching or burping**

| | | | | | | |
|---|---|---|---|---|---|---|
| Harper 2010 | 91 | 434 | 23 | 418 | 23.5% | 3.81 [2.46, 5.90] |
| Olsen 1992 | 186 | 266 | 27 | 136 | 35.8% | 3.52 [2.49, 4.98] |
| Olsen 2000 | 133 | 455 | 37 | 454 | 37.1% | 3.59 [2.55, 5.04] |
| Onwude 1995 (7) | 1 | 41 | 0 | 34 | 0.5% | 2.50 [0.11, 59.46] |
| Otto 2000 | 2 | 12 | 3 | 12 | 3.0% | 0.67 [0.13, 3.30] |
| **Subtotal (95% CI)** | | **1208** | | **1054** | **100.0%** | **3.52 [2.86, 4.34]** |
| Total events | 413 | | 90 | | | |

Heterogeneity: Chi² = 4.34, df = 4 (P = 0.36); I² = 8%
Test for overall effect: Z = 11.80 (P < 0.00001)

**1.15.10 Diarrhoea**

| | | | | | | |
|---|---|---|---|---|---|---|
| Carlson 2013 | 4 | 154 | 2 | 147 | 5.1% | 1.91 [0.35, 10.27] |
| Khalili 2016 | 1 | 75 | 0 | 75 | 1.3% | 3.00 [0.12, 72.49] |
| Olsen 1992 | 24 | 266 | 18 | 136 | 59.7% | 0.68 [0.38, 1.21] |
| Olsen 2000 | 7 | 407 | 11 | 442 | 28.4% | 0.69 [0.27, 1.77] |
| Rees 2008 (8) | 2 | 13 | 1 | 13 | 2.5% | 2.00 [0.21, 19.44] |
| Su 2008 | 1 | 18 | 2 | 18 | 5.0% | 0.50 [0.05, 5.04] |
| **Subtotal (95% CI)** | | **933** | | **831** | **100.0%** | **0.80 [0.52, 1.24]** |
| Total events | 39 | | 34 | | | |

Heterogeneity: Chi² = 2.86, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)

**1.15.11 Constipation**

| | | | | | | |
|---|---|---|---|---|---|---|
| Olsen 2000 | 2 | 526 | 5 | 551 | 100.0% | 0.42 [0.08, 2.15] |
| **Subtotal (95% CI)** | | **526** | | **551** | **100.0%** | **0.42 [0.08, 2.15]** |
| Total events | 2 | | 5 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)

**1.15.12 Nasal bleeding**

| | | | | | | |
|---|---|---|---|---|---|---|
| Olsen 1992 | 24 | 266 | 26 | 267 | 28.8% | 0.93 [0.55, 1.57] |
| Olsen 2000 | 60 | 481 | 65 | 492 | 71.2% | 0.94 [0.66, 1.31] |
| **Subtotal (95% CI)** | | **747** | | **759** | **100.0%** | **0.94 [0.71, 1.24]** |
| Total events | 84 | | 91 | | | |

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)

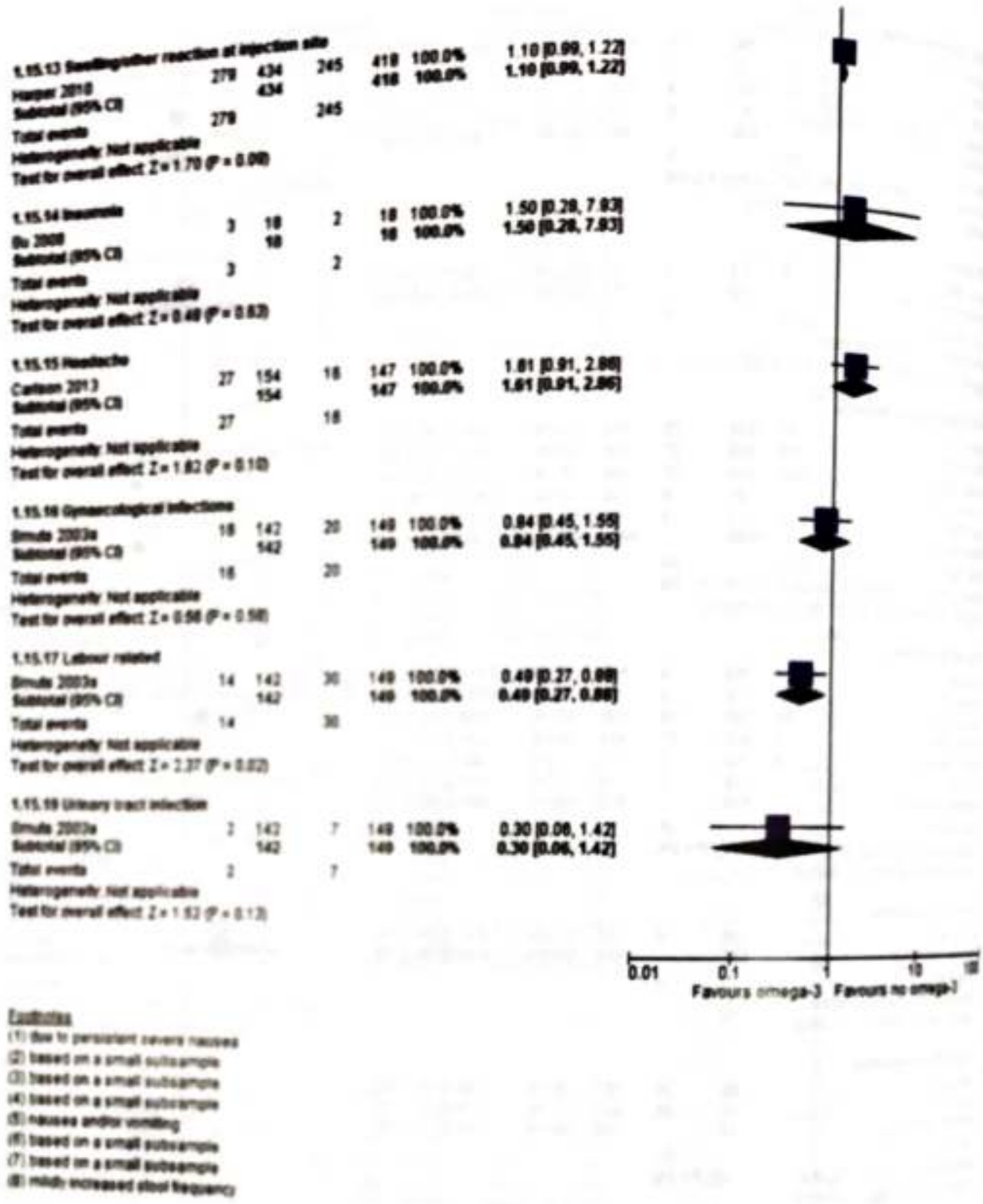



**Figure 7. Forest plot of risk of adverse maternal events with supplementation of omega-3 LCPUFAs**

Figure 7 illustrates that omega-3 LCPUFAs were easily tolerated. Overall, there was no significant increase in postpartum hemorrhage (RR 1.03, 95% CI 0.83-1.30), severe maternal adverse events (RR 1.04, 95% CI 0.4-2.72) or in events severe enough to cause cessation of the medication (RR 1.01, 95% CI 0.53-1.95) although there were increased complaints of vomiting, belching or burping.[8]

From this meta-analysis, it may be concluded that omega-3 LCPUFA supplementation, started early in pregnancy, at a dose of 500 mg to 1g/day, is effective in preventing preterm labor and delivery with little or no significant adverse effects and with relatively low cost to the mother.

Although the Cochrane reviewers did not recommend further studies comparing omega-3 LCPUFAs supplementation and placebo in preventing preterm labor and delivery, they proposed that further studies be conducted on the effect of omega-3 LCPUFA supplementation on growth and development and longer-term outcomes for the mother and child.[3]

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Chapter 10

# Cervical Cerclage for Prevention of Preterm Birth

Marie Catheleen P. Santiago, MD, FPOGS, FPSUOG, FPSMFM

## DEFINITION OF TERMS

- **PRETERM BIRTH** – birth between 20 and 36 6/7 weeks[1]
- **SHORT CERVIX** – cervical length of less than 25 mm, measured at the mid-trimester, via transvaginal or translabial ultrasound[2]
- **CERCLAGE** – a procedure in which sutures are used to close the cervix during pregnancy to prevent pregnancy loss or preterm birth. The approach may be transvaginal, transabdominal or laparoscopic[3]
- **HISTORY-INDICATED CERCLAGE** – cerclage performed because of a woman's increased risk for preterm delivery secondary to her obstetric or gynecologic history[4]
- **ULTRASOUND-INDICATED CERCLAGE** – cerclage performed in asymptomatic women, where the cervix is seen to be shortened in transvaginal ultrasound[4]
- **RESCUE CERCLAGE** – cerclage performed as an emergency measure in cases of cervical dilatation with exposed fetal membranes, after discovery through ultrasound or pelvic examination[4]

| QUESTION 1 | When should history-indicated cerclage be offered? |
|---|---|
| **RECOMMENDATION** | History-indicated cerclage may be offered to women with history of 3 or more previous preterm deliveries and /or second trimester losses [4].<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Three randomized control trials (RCT)[5,6,7] compared the outcome of history-indicated cerclage against expectant management. There were fewer deliveries before 33 weeks in the cerclage group matched up against those with no

cerclage (13% against 17%, RR 0.75, 95% CI 0.58–0.98). While there was no significant difference between the two groups in the total number of miscarriages, stillbirths and deaths following live births, subgroup analyses revealed that women with a history of 3 more pregnancies ending before 37 weeks benefited from cerclage , with delivery before 33 weeks decreased by half in the cerclage group (15% vs. 32%, P <0.05). No effect was seen in those with only one or two previous early deliveries.

| **QUESTION 2** | **When should ultrasound-indicated cerclage be offered?** |
|---|---|
| **RECOMMENDATION** | Cerclage may be offered to pregnant women with history of spontaneous second trimester losses or preterm births, who, on transvaginal ultrasound surveillance, were found to have a cervical length of 25 mm or less before 24 weeks of gestation.[4]<br><br>It is not recommended in women:<br>1. Without a history of spontaneous preterm delivery or mid-trimester loss who have an incidental finding of a short cervix on ultrasound<br>2. With funneling of the cervix where the cervical length is 25 mm or longer [4]<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Owen et al., in a randomized controlled trial [8] and Berghella et al. [9], in a meta-analysis, both found that those with history of preterm births and mid-trimester losses plus a cervical length at or less than 25 mm on sonographic surveillance at or before 24 weeks, benefited from cerclage compared to those treated with expectant management (RR 0.57; 95% CI 0.33–0.99 and RR 0.61; 95% CI 0.4–0.92, respectively).

To et al.[10] measured the cervical length of 47,123 women with risk factors for preterm birth at 22–24 weeks AOG. Four-hundred seventy (470) women were found to have a cervix measuring 1.5 cm or less. Fifty-four percent (54%) of

these women agreed to be randomized to either the performance of a cerclage or expectant management. There was no significant difference in the incidence of preterm birth in the cerclage versus expectant management group (22% versus 26%). There is no overall evidence of benefit for cerclage in women with a shortened cervix with no other risk factors.

## QUESTION 3 When should a rescue cerclage be considered?

**RECOMMENDATION** The choice to place a rescue cerclage should be individualized, since the risks of preterm delivery and neonatal mortality are high. Advanced dilatation of the cervix of 4 cm or more or prolapse of the membrane beyond the external cervical os is associated with a high incidence of cerclage failure.[4]

*Quality of Evidence: Moderate*
*Strength of Recommendation: Weak*

### SUMMARY OF EVIDENCE

There is only one RCT comparing rescue cerclage and bed rest alone. Althusius et al. studied 23 women who were seen to have dilated cervices and prolapsed membranes at a mean gestation of 22–23 weeks.[11] All of them were hospitalized and on bed rest until 30 weeks of gestation. Those allocated to the cerclage group were given preoperative indomethacin. Those in the cerclage group delivered on average 4 weeks later than those in the bed rest group and a significant reduction in delivery before 34 weeks (53% vs. 100%, P=0.02). There was no data provided on the incidence of chorioamnionitis or neonatal morbidity.

## QUESTION 4 When is cerclage contraindicated?

**RECOMMENDATION** The performance of a cervical cerclage is not recommended in the following circumstances:[4]

- Active preterm labor
- Evidence of chorioamnionitis
- Continuous vaginal bleeding
- Preterm prelabor rupture of membranes
- Evidence of fetal compromise
- Lethal fetal congenital defect
- Fetal demise [4]

*Quality of Evidence: Low*
*Strength of Recommendation: Weak / GPP*

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| QUESTION 1 | Can cervical pessary prevent preterm birth in singleton pregnancies with a sonographically short cervix? |
|---|---|

**RECOMMENDATION** The use of cervical pessary for the prevention of preterm birth in women with a sonographically short cervix may be beneficial in certain populations. Further studies are needed to validate its potential benefits as current studies show inconsistent results.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

The first multicenter randomized controlled trial (RCT)[9] on the use of the pessary included 385 unselected women who were screened by transvaginal ultrasound (TVUS). The study showed that in women with a short cervical length (<25 mm) between 18 and 22 weeks age of gestation (AOG), the pessary prolonged the pregnancy and reduced the rate of poor outcome compared with controls. The women were randomized to receive a pessary (*n*=192) or expectant management (*n*=193). In the pessary group, there were fewer births before 34 weeks (6% versus 27%; RR 0.24; 95% CI 0.13–0.43), before 37 weeks (27% versus 59%; RR 0.36; 95% CI 0.27–0.49) and before 28 weeks (2% versus 8%; RR; 95% CI 0.09–0.73), showing a significant difference in the occurrence of composite poor neonatal outcome.

A smaller RCT that involved 108 Asian women with singleton pregnancy and a cervical length <25 mm on routine second-trimester transvaginal scan showed a similar trend favoring the use of cervical pessary. The mean gestational age at delivery was 38.1 weeks in the pessary group compared with 37.8 weeks in the expectant group, with no significant differences in the rates of delivery before 28, 34 or 37 weeks.[10]

A single-center parallel-group RCT by Saccone et al.[11] included 300 women with asymptomatic pregnancies and without prior spontaneous preterm birth but with short cervical length (<20 mm) on transvaginal ultrasound. The subjects were randomized to receive a cervical pessary (intervention group) or no pessary (control group). Women in both groups were prescribed vaginal progesterone 200 mg suppositories daily until 36 weeks and 6 days of gestation. No recommendation was made about bed rest, activity or vaginal intercourse.

The primary outcome was spontaneous preterm birth at less than 34 weeks of gestation. The results showed that spontaneous preterm birth at <34 weeks occurred in 11 women (7.3%) in the pessary group and 23 women (15.3%) in the control group (between-group difference, -8.0%; 95% CI, -15.7% to -0.4%). The study therefore concluded that among women without prior spontaneous preterm birth who had asymptomatic singleton pregnancies and short transvaginal cervical length, cervical pessary use resulted in a lower rate of spontaneous preterm birth at < 34 weeks of gestation.

The secondary outcome measures in Saccone's study[11] also favor the use of cervical pessary as it was associated with lower rate of spontaneous preterm birth at < 37 weeks gestation, a longer gestational age at delivery and latency from randomization to delivery, higher birth weight, lower rates of admission to the neonatal intensive care unit (NICU) and a lower incidence of adverse perinatal outcome compared to group that had no pessary.

Interestingly, in the systematic review and meta-analysis conducted by Saccone et al. in 2017[12] where 3 RCTs (n= 1420) were included, cervical pessary use did not reduce the rate of spontaneous preterm delivery or improve perinatal outcome. However, individual patient data meta-analysis may indicate whether cervical pessary could be beneficial in certain subgroups of women (singleton pregnancies without prior history of spontaneous preterm birth but have short cervices on transvaginal ultrasound).

The multicenter RCT conducted in 2016 by Nicolaides et al.,[13] also supported the finding that the use of cervical pessary showed no significant difference in the rate of spontaneous delivery before 34 weeks, perinatal death, adverse neonatal outcome or neonatal special care compared with the control group managed expectantly.

| QUESTION 2 | **Can cervical pessary prevent preterm birth in twin gestations with a sonographically short cervix?** |
|---|---|
| **RECOMMENDATION** | The use of cervical pessary in twin pregnancies with short cervical length on transvaginal ultrasound at 16–24 weeks is not recommended because it does not prevent spontaneous preterm birth or improve perinatal outcome.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

In 2017, a meta-analysis evaluated the effectiveness of cervical pessary for preventing spontaneous preterm birth (SPTB) in twin pregnancies with an asymptomatic transvaginal ultrasound cervical length (TVU CL) in the second trimester. Three RCTs that included 481 twin pregnancies with a sonographically short cervix in the second trimester (16–24 weeks) compared the use of cervical pessary with expectant management. Two RCTs used a TVU CL ≤ 25 mm and one used TVU CL ≤ 38 mm as cut-off. The meta-analysis concluded that the use of cervical pessary was not associated with prevention of spontaneous preterm birth, and the mean gestational age at delivery and the mean latency were similar in the pessary group compared to the control group. Similarly, no benefits were noticed in the neonatal outcomes in the pessary group. [14]

Thangatorai et al.[15] conducted another systematic review and meta-analysis in 2018 to assess the effectiveness of cervical pessary in the prevention of preterm births. They were likewise unable to show benefit of using cervical pessary in twin pregnancies with a short cervix.

| QUESTION 3 | **Should women receive supplemental vaginal progesterone after cervical pessary insertion?** |
|---|---|

**RECOMMENDATION** Vaginal progesterone may be given to women after cervical pessary insertion to lower the rate of preterm delivery.

*Quality of Evidence: Weak*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

In a retrospective cohort study of 202 women with singleton pregnancies managed in two tertiary medical centers, one center used a combination of cervical pessary and supplemental vaginal progesterone (study group) and the second used only vaginal progesterone in women who had a short cervix on TVUS done between 15 and 29 weeks gestation (control group). Ninety-four (94 or 46.5%) women were included in the study group and 108 (53.5%) women were included in the control group.

The study showed that the combined treatment of cervical pessary and vaginal progesterone had a lower rate of preterm delivery <34 weeks of gestation and was able to prolonged gestation when compared to those women who were treated with only vaginal progesterone; however, more randomized control studies are needed to validate these results.[16]

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Chapter 12

# Calcium Channel Blockers

Gumersinda Cruz-Javier, MD, FPOGS, FPSMFM, FPSUOG
Anna Konsuelo R. Chua, MD, FPOGS

Calcium channel blocker is one of the most commonly used tocolytics. It acts by reducing smooth muscle contractility by decreasing the influx of calcium into cells. Nifedipine, which has been widely used in the treatment of hypertension, has been extensively studied in the management and control of preterm labor. To improve neonatal outcomes, it is recommended that women with imminent preterm labor receive tocolytic therapy and antenatal corticosteroids and deliver in a tertiary center. The goal of initial tocolysis is to delay delivery for at least 48 hours, allowing completion of a course of corticosteroids for fetal lung maturation and maternal transfer to a tertiary center with capable neonatal intensive care unit (NICU) facilities.[1]

| QUESTION 1 | **Which tocolytic agent is most effective at delaying delivery for 48 hours to allow the administration of antenatal corticosteroids?** |
|---|---|
| **RECOMMENDATIONS** | Nifedipine had the highest probability of delaying delivery by 48 hours, improving neonatal outcomes and with relatively low maternal side effects and therefore it is recommended for practice.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

The work of Hass and colleagues [2] utilizes network meta-analysis methodology for the assessment of different tocolytic therapies. This is the first of its kind in obstetrics because it allows direct and indirect comparisons of tocolytic treatments among different trials. It was concluded that prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery by 48 hours and improving neonatal outcomes and with relatively low maternal side effects.

Prostaglandin inhibitors, magnesium sulfate, calcium channel blockers, β-mimetics and atosiban were the tocolytics included in the analysis. When compared with placebo, prostaglandin inhibitors had the highest probability of delaying delivery by 48 hours (OR 5.39, 95% CI 2.14–12.34). There was no tocolytic that was significantly superior to placebo in reducing neonatal respiratory distress syndrome or neonatal mortality. Compared with placebo, the tocolytics that had the highest maternal adverse effects were β-mimetics (OR 22.68, 95% CI 7.51–73.67) and magnesium sulfate (OR 8.15, 95% CI 2.47–27.70). Prostaglandin inhibitors and calcium channel blockers were ranked in the top three medication classes for maternal and fetal outcomes and side effects. [2]

| QUESTION 2 | **Among pregnant women with preterm labor, how effective is nifedipine in improving perinatal outcomes compared to other tocolytics?** |
|---|---|
| **RECOMMENDATIONS** | Nifedipine is superior to β-2-adrenergic-receptor agonists and magnesium sulfate for tocolysis in women with preterm labor and can be used as the agent of first choice for tocolysis.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

A systematic review and meta-analysis conducted by Conde-Agudelo et al. [3] in 2011 evaluated the results of twenty-six randomized controlled trials that included 2179 women. The results showed that nifedipine was associated with a significant reduction in the risk of delivery within 7 days of the onset of treatment and before 34 weeks' gestation compared with β-2-adrenergic-receptor agonists. It also has significantly fewer maternal adverse events. Neonatal adverse outcomes such as respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, and admission to the NICU were also reduced. Comparing magnesium sulfate and nifedipine, both were shown to have the same tocolytic efficacy. As a maintenance tocolysis, nifedipine was not effective in prolonging gestation or improving neonatal outcomes when compared with no treatment.

Table 1 shows that nifedipine was associated with a significant increase in pregnancy prolongation compared with magnesium sulfate, atosiban, and nitric oxide donors.

**TABLE 1. ACUTE TOCOLYSIS: NIFEDIPINE COMPARED WITH MAGNESIUM SULFATE, ATOSIBAN, AND NITRIC OXIDE DONORS**

| Outcome | Number of Trials | Number of Events/Total number or Total Number | | Relative Risk Or mean difference (95% CI) | $I^2$ (%) |
|---|---|---|---|---|---|
| | | Nifedipine | Placebo / No Treatment | | |
| **Pregnancy outcomes** | | | | | |
| Preterm birth <34 weeks' gestation | 1 [52] | 12/37 | 9/37 | 1.33 (0.64-2.78) | NA |
| Preterm birth <37 weeks' gestation | 3 [52-54] | 59/107 | 69/108 | 0.87 (0.69-1.08) | 32 |
| Pregnancy prolongation, d | 3 [52-54] | 107 | 108 | 6.3 (1.2-11.4) | 22 |
| Gestational age at birth, wks | 3 [52-54] | 107 | 108 | 0.7 (-0.7 to 2.1) | 66 |
| At least 1 episode of recurrent preterm labor | 2 [52,53] | 16/69 | 20/68 | 1.19 (0.19-7.30) | 66 |
| More than 1 episode of recurrent preterm labor | 2 [53,54] | 21/70 | 18/71 | 1.21 (0.72-2.03) | 15 |
| **Perinatal and neonatal outcomes** | | | | | |
| Birthweight, g | 3 [52-54] | 125 | 120 | -29.4 (-209.1 to 150.4) | 0 |
| Respiratory distress syndrome | 2 [52,53] | 7/77 | 9/77 | 0.78 (0.31-1.98) | 0 |
| Necrotizing enterocolitis | 2 [52,53] | 2/77 | 1/77 | 1.67 (0.23-12.33) | 0 |
| Intraventricular hemorrhage | 2 [52,53] | 2/77 | 3/77 | 0.71 (0.14-3.54) | 30 |
| Neonatal sepsis | 1 [53] | 2/40 | 1/40 | 2.00 (0.19-21.18) | NA |
| Neonatal death | 1 [53] | 0/40 | 2/40 | 0.20 (0.01-4.04) | NA |
| Admission to NICU | 2 [52,53] | 22/77 | 19/77 | 1.16 (0.68-1.96) | 0 |
| NICU stay, d | 3 [52-54] | 125 | 120 | -0.3 (-2.1 to 1.4) | 0 |
| Preterm birth <34 weeks' gestation among women enrolled at <32 weeks' gestation | 1 [52] | 8/25 | 8/24 | 0.96 (0.43-2.15) | NA |
| Preterm birth <37 weeks' gestation among women enrolled at <32 weeks' gestation | 2 [52,54] | 35/50 | 38/52 | 0.93 (0.72-1.20) | 0 |
| Pregnancy prolongation among women enrolled at <32 weeks' gestation, d | 3 [52-54] | 66 | 75 | 11.0 (-2.1 to 24.2) | 73 |
| Gestational age at birth among women enrolled at <32 weeks' gestation | 2 [52,54] | 50 | 52 | 0.2 (-1.2 to 1.6) | 0 |
| Birthweight among women enrolled at <32 weeks' gestation | 1 [52] | 25 | 24 | 122.0 (-308.0 to 552.0) | NA |
| Admission to NICU among women enrolled at <32 weeks' gestation | 1 [52] | 5/25 | 6/24 | 0.80 (0.28-2.88) | NA |

CI, confidence interval; NA, not applicable; NICU, neonatal intensive care unit

Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: a systematic review and metaanalysis. Am J Obstet Gynecol 2011; 204:134.e1-20. Table 6, Maintenance tocolysis: nifedipine compared with placebo/no treatment.

**QUESTION 3** **Among patients with arrested threatened preterm labor, is the use of maintenance tocolysis using nifedipine effective in further prolonging pregnancy and improving neonatal outcomes?**

**RECOMMENDATION** The effect of nifedipine in prolonging pregnancy is equal to the effect of other treatments (placebo, progesterone or atosiban) and its use for long-term tocolysis is not associated with improved perinatal outcome; therefore, it should not be recommended for routine practice for this purpose.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

***Meta-Analysis for Pregnancy Prolongation***

Stated below are the results of a meta-analysis of ten journal articles that evaluated the effect of nifedipine on pregnancy prolongation. As observed from the study of Parry[4], the longest pregnancy prolongation among those treated with nifedipine estimated at 46.8 days with an estimated mean difference equal to -4.0 days. Half of the studies favor nifedipine in prolonging pregnancy (mean difference, MD>0). Among these 10 studies, the highest contribution to pooled mean difference came from the study of vanVliet in 2016[5] while the lowest contribution came from the study of Parry published in 2014. A high percentage (92.40%) of the total variation among estimates can be attributed to the heterogeneity of the studies rather than chance. On the average, the mean difference estimates vary from the true effect size by as much as 36.68 (Tau). These measures imply that studies included in the analysis vary in possibly many aspects such as sampling variation and differences of the target population. Ultimately, heterogeneity test found that variation in mean difference was noted to be significant, leading to the conclusion that the studies included were heterogeneous.

Overall, the mean pregnancy prolongation among nifedipine-treated women was 26.01 days (Table 2). This was lower than the mean pregnancy prolongation of 27.54 days observed among women who were given other treatments. The pooled mean difference was estimated to be -1.53, indicating that the pregnancy prolongation in women treated with nwas lower than the pregnancy prolongation in control women. However, this pooled mean difference was not

statistically significant (p-value=0.485), implying that the effect of nifedipine to prolong pregnancy was equal to the effect of other treatments such as placebo, progesterone or atosiban (Table 3).

**TABLE 2: AVERAGE PREGNANCY PROLONGATION**

| Study | Average Pregnancy Prolongation (days) | | Mean Difference | 95% CI | | % Weight |
|---|---|---|---|---|---|---|
| | Nifedipine | Other | | | | |
| Kamat 2014 | 16.6 | 40.1 | -23.5 | -28.60 | -18.40 | 10.96 |
| Carr 1999 | 37.0 | 32.8 | 4.2 | -5.90 | 14.30 | 7.53 |
| Sayin 2004 | 26.7 | 16.1 | 10.6 | 3.19 | 18.01 | 9.35 |
| Lyell 2008 | 33.5 | 32.6 | 0.9 | -8.92 | 10.72 | 7.71 |
| Roos 2013 | 30.0 | 32.0 | -2.0 | -4.54 | 0.54 | 12.42 |
| Parry 2014 | 46.8 | 50.8 | -4.0 | -19.89 | 11.89 | 4.65 |
| Haghighi 2017 | 23.7 | 28.6 | -4.9 | -9.79 | -0.01 | 11.10 |
| Songthamwat 2018 | 24.9 | 26.0 | -1.1 | -6.44 | 4.34 | 10.77 |
| vanVliet 2016 (a) | 7.0 | 4.0 | 3.0 | 1.34 | 4.66 | 12.74 |
| vanVliet 2016 (b) | 33.0 | 30.0 | 3.0 | 1.44 | 4.56 | 12.77 |
| **Pooled** | **26.01** | **27.54** | **-1.53** | **-5.80** | **2.75** | **100.00** |

CI, confidence interval

**TABLE 3. POOLED MEAN DIFFERENCE**

| | | |
|---|---|---|
| **Heterogeneity Test** | I-squared = 92.40%<br>Tau = 36.68 | p-value =<0.0001 |
| **Significance Test for Pooled Mean Difference** | | p-value = 0.485 |

The forest plot in Figure 1 illustrates the effect size of nifedipine compared to other treatments. It clearly shows that studies are divided in suggesting which treatment arm worked better. It can be seen from the plot that the estimate from the study of Roos [6] is the closest to the estimated true effect size (pooled MD) and the estimate is also precise. Hence, a high weight was assigned to this study (12.42%).

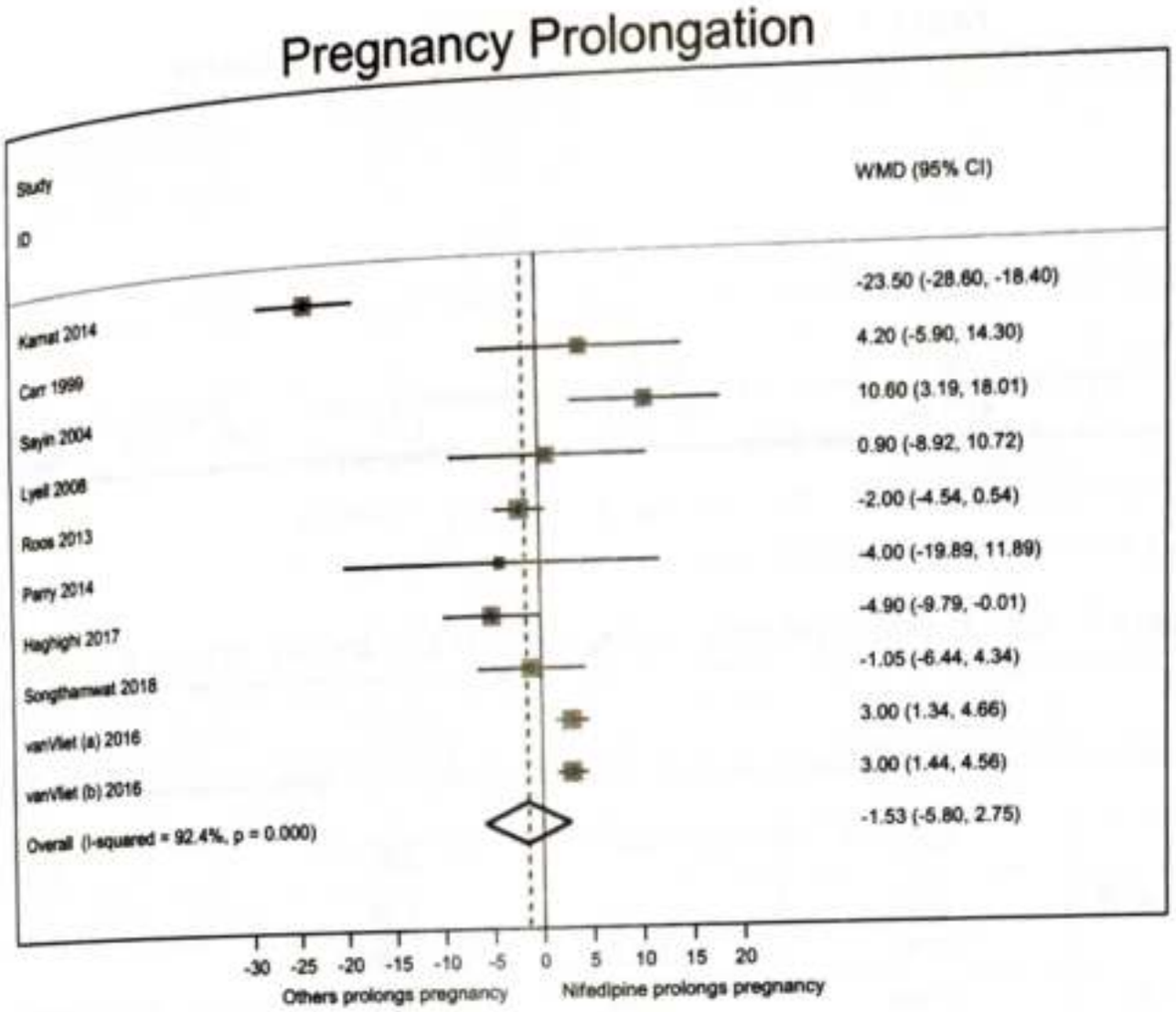


**FIGURE 1. FOREST PLOT OF PREGNANCY PROLONGATION**

In the study of van Vliet et al. entitled "Nifedipine Maintenance Tocolysis and Perinatal Outcome: An Individual Participant Data Meta-Analysis",[5] six randomized controlled trials (RCT) encompassing 787 patients (n=390 for nifedipine; n=397 for placebo/no treatment) were evaluated. The meta-analysis concluded that **maintenance tocolysis is not associated with improved perinatal outcome and is therefore not recommended for routine practice.**

The study further noted that there was no difference between the groups in terms of the incidence of perinatal death (risk ratio, RR 1.36; 95% confidence interval, 95% CI 0.35–5.33), intraventricular haemorrhage (IVH) ≥ grade II (RR 0.65; 95% CI 0.16–2.67), necrotizing enterocolitis (NEC) (RR 1.15; 95% CI 0.50–2.65), infant respiratory distress syndrome (IRDS) (RR 0.98; 95% CI 0.51–1.85), and prolongation of pregnancy (hazard ratio, HR 0.74; 95% CI 0.55–1.01).[5] Overall, the effect of nifedipine on the risk of neonatal death (Table 4), respiratory distress syndrome (Table 5), intraventricular hemorrhage (Table 6) and necrotizing enterocolitis (Table 7) is equal to the effect of other treatments such as placebo, progesterone or atosiban based on the pooled odds ratio (OR) from the meta-analysis of RCTs by Conde,[3] vanVliet,[5] Tan,[7] Songthmwat [8] and Salim.[9]

**TABLE 8. PRIMARY OUTCOMES ACCORDING TO TREATMENT [11]**

| Outcome | Nifedipine-SC group (n=121) | Nifedipine-only group (n=118) | P-value | Odds ratio (95% CI) |
|---|---|---|---|---|
| Delivery within 24 hours of admission | 6 (5.0) | 8 (6.8) | 0.55* | 1.39 (0.47–4.15) |
| Delivery within 48 hours of admission | 8 (6.6) | 11 (9.3) | 0.44* | 1.45 (0.56–3.75) |
| Delivery within 72 hours of admission | 8 (6.6) | 18 (15.3) | 0.032* | 2.54 (1.06–6.10) |
| Cases remain undelivered during hospitalization | 99 (81.8) | 81 (68.6) | 0.018* | 0.49 (0.27–0.89) |
| Delivery after discharge (≤7 days from admission) | 11 (9.1) | 24 (20.3) | 0.014* | 2.55 (1.18–5.49) |
| Latency (time in days from randomization until delivery) | 29 (1-76) | 7 (1-68) | 0.002+ | - |

SC, sildenafil citrate
Data expressed as: number (%) or median (range)
Statistical tests: * chi-square test; + Mann-Whitney test

***Maher MA, Sayyed TM, El-khadry SW. Combination of Sildenafil citrate with nifedipine appears to be superior in the management of threatened preterm labor compared to nifedipine alone: A Randomised Trial. 2018 Unedited edition. doi: 10.1111/1471-0528.15503***

Current reviews show that:

- A combination of sildenafil citrate with nifedipine appears to be superior in the management of threatened preterm labor compared to nifedipine alone.[11] This was also seen in two in-vitro studies that used myometrial samples obtained during cesarean section from preterm and term deliveries. The studies showed that more inhibition of contractility was produced when combination therapy with atosiban plus nifedipine [12] and other combination of tocolytics including nifedipine, ritrodrine, nitroglycerine and atosiban were used. [13,14,15] A greater inhibitory effect on contractility was produced when combined therapy was employed than using each drug alone.
    - The dosage used in the studies are as follows:
      Nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 6–8 hours at the same time as vaginal administration of sildenafil citrate (25 mg at 8-hourly intervals) [11]

## TABLE 9. SECONDARY MATERNAL AND OFFSPRING OUTCOMES ACCORDING TO TREATMENT

| Outcome | Nifedipine-SC group (n=121) | Nifedipine-only group (n=118) | P-value | Odds ratio (95% CI) |
|---|---|---|---|---|
| Prelabour rupture of membranes | 22 (18.2) | 18 (15.3) | 0.54* | 0.81 (0.41–1.60) |
| Harm to mother from intervention | 0 | 0 | -- | -- |
| Maternal infection | 1 (0.8) | 0 | 0.032* | -- |
| Maternal mortality | 0 | 0 | -- | -- |
| Admission to NICU | 38 (31.4) | 52 (44.1) | 0.043* | 1.72 (1.01–2.92) |
| Gestational age at delivery | | | | |
| Extremely preterm (<28 weeks) | 6 (5.0) | 11 (7.6) | 0.39* | 1.58 (0.55–4.60) |
| Very preterm (28 to <32 weeks) | 25 (20.7) | 45 (38.1) | 0.003* | 2.37 (1.33–4.21) |
| Moderate to late preterm (32 to <37 weeks) | 56 (46.3) | 44 (37.3) | 0.16* | 0.69 (0.41–1.16) |
| Neonatal birth weight (g) | 1900 (600-3100) | 1500 (650-3700) | 0.018+ | -- |
| Respiratory morbidity | 35 (28.9) | 51 (43.2) | 0.021* | 1.87 (1.09–3.19) |
| Gastrointestinal morbidity | 6 (5.0) | 9 (7.6) | 0.039* | 1.58 (0.54–4.95) |
| Early neurodevelopmental morbidity (within 1 month of delivery) | 16 (13.2) | 11 (9.3) | 0.34* | 0.68 (0.29–1.52) |
| Neonatal infection | 15 (12.4) | 16 (13.6) | 0.79* | 1.11 (0.52–2.36) |
| Perinatal death | 7 (5.8) | 12 (10.2) | 0.21* | 1.8 (0.70–4.86) |
| Harm to offspring from intervention | 0 | 0 | -- | -- |

SC, sildenafil citrate; NICU, neonatal intensive care unit
Data expressed as: number (%) or median (range).
Statistical tests: * chi-square test; + Mann-Whitney test

*Maher MA, Sayyed TM, El-khadry SW. Combination of Sildenafil citrate with nifedipine appears to be superior in the management of threatened preterm labor compared to nifedipine alone: A Randomised Trial. 2018 Unedited edition. doi: 10.1111/1471-0528.15503*

- Combination therapy with nifedipine and indomethacin was more effective than monotherapy with either of these two medications for inhibiting preterm labor, delaying delivery, and prolongation of the duration of pregnancy.[16]
    - The dosage used in the studies are as follows:
        - Indomethacin 100 mg rectally and to inhibit contractions after 2 hours, 25 mg of oral indomethacin was administered every 4 hours. The maximum daily dosage of indomethacin was 200 mg/day and the maximum duration of administration was 48 hours.
        - Nifedipine 20mg was administered orally and was repeated again after 90 minutes. In case of inhibiting contractions for 2 hours, 20mg of oral nifedipine was continued every 4 hours for 48 hours, with a maximum dose of 180 mg per day.[16]

## TABLE 10. OUTCOMES IN THREE GROUPS

| Variables | Indomethacin (n=36) | Nifedipine (n=36) | Nifedipine and Indomethacin (n=41) | P-value |
|---|---|---|---|---|
| Inhibiting contractions for 2 hours *n* (%) n=50 | 36 (72.0%) | 36 (72.0%) | 41 (82.0%) | .002* |
| Inhibiting contractions for 48 hours *n* (%) | 30 (83.3%) | 31 (86.1%) | 39 (95.1%) | .053 |
| Inhibiting contractions for 7 days *n* (%) | 26 (72.2%) | 28 (77.7%) | 37 (90.2%) | .021* |
| Gestational age at birth (weeks) m ± sd | 33.20 ± 3.69 | 33.87 ± 3.05 | 35.82 ± 4.03 | .001 |
| No. of pregnancies more than 37 weeks *n* (%) | 9 (25.0%) | 9 (25.0%) | 24 (58.5%) | .001 |
| Neonatal weight (gr) m ± sd | 2349.64 ± 716.68 | 2578.33 ± 564.88 | 2890.00 ± 910.18 | .028 |
| Apgar score minute 1 m ± sd | 7.00 ± 1.70 | 7.22 ± 1.74 | 7.93 ± 1.69 | .615 |
| Apgar score minute 5 m ± sd | 8.56 ± 1.40 | 8.89 ± 1.41 | 9.29 ± 1.16 | .189 |
| NICU admission n (%) | 15 (41.7%) | 17 (47.2%) | 15 (36.6%) | .648 |
| NICU time m ± sd | 0.40 ± 0.49 | 0.39 ± 0.49 | 0.98 ± 3.87 | .271 |

* Significant

## TABLE 11. NIFEDIPINE AND ITS MECHANISM OF ACTION, DOSAGE, MATERNAL AND FETAL SIDE EFFECTS AND CONTRAINDICATIONS

| Tocolytic Agent | Mechanism of Action | Dose | Fetal Side Effects | Maternal Side Effects | Contraindication |
|---|---|---|---|---|---|
| Calcium Channel Blockers Nifedipine [17] | Inhibits calcium-dependent myosin light-chain kinase phosphorylation leading to myometrial relaxation [17] | 30 mg loading dose then 10-20 mg orally every 4-6 hours [18] | None | Nausea, headache, flushing, dizziness, and palpitations [19] | Hypersensitivity to the drug, hypotension, or preload-dependent cardiac lesions [20] |

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Chapter 13

# Betamimetics

Kristine Therese R. Elises-Molon, MD, FPOGS, FPSMFM, FPSUOG

Betamimetics or beta-adrenergic agents are another group of tocolytics that has been widely used in the past, especially in resource-poor countries. This group of drugs includes isoxsuprine, terbutaline, ritodrine, and salbutamol. Their mechanism of action in tocolysis involves activation of adenyl cyclase to form increased cellular levels of cyclic adenosine 3',5'monophosphate (cAMP). This in turn decreases myosin light-chain kinase activity, both by phosphorylation of the myosin light-chain kinase itself, and by reducing intracellular calcium through increasing calcium uptake by the sarcoplasmic reticulum.[1] The resultant effect is a reduction in myometrial contractility.[2]

***Maternal Side Effects***

Because betamimetics stimulate beta-adrenergic receptors, their administration is significantly associated with unpleasant side effects such as headaches, nervousness, palpitations, anxiety, chest pain, dyspnea, palpitations, tremor, nausea, vomiting, nasal stuffiness and a range of biochemical disruptions such as hyperglycemia and hypokalemia.[1,3] Pulmonary edema may also be encountered, although its incidence in association with betamimetic therapy is about approximately 1 in 400.[4] These adverse effects often lead to cessation of treatment in some women.

***Fetal Side Effects***

Betamimetics cross the placenta and may trigger fetal tachycardia, hypoglycemia and hyperinsulinism upon delivery.[1]

***Contraindications***

Betamimetics are specifically contraindicated in the following clinical scenarios: poorly controlled diabetes, hyperthyroidism, arrhythmia, and heart failure.[2]

This chapter will focus on the effectiveness of betamimetics in the a) prevention of preterm labor; b) treatment of preterm labor, and 3) maintenance tocolysis after initial control of preterm labor. It also aims to highlight isoxsuprine, which is a betamimetic more commonly used in the local setting.

# I. BETAMIMETICS IN THE PREVENTION OF PRETERM LABOR

## A. Use in Singleton Gestation

| QUESTION 1 | **Among pregnant women with SINGLETON gestation at high risk for preterm labor and delivery, is the use of PROPHYLACTIC oral beta-adrenergic agents effective in preventing preterm labor?** |
|---|---|

**RECOMMENDATION** The existing data are insufficient to support or refute the use of prophylactic oral betamimetics for preventing preterm birth in women with a singleton gestation at high risk of preterm labor.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

### SUMMARY OF EVIDENCE

- In 2011, Whitworth and Quenby[5] published a systematic review that compared oral isoxsuprine to placebo in preventing preterm birth. The review included only one randomized controlled trial (RCT) involving only 64 women with a singleton gestation at high risk of preterm delivery and who did not show signs of preterm labor at the time of initiation of therapy. The following were the results:
    - Isoxsuprine did not reduce the rate of perinatal mortality (risk ratio [RR] 4.74; 95% confidence interval [CI] 0.50–45.00).
    - There was no effect on the reduction of spontaneous onset of preterm labor (RR 1.07; 95% CI 0.14–8.09) and preterm birth <37 weeks gestation (RR 1.07; 95% CI 0.14–8.09).
    - No differences were found for infant outcomes such as birth weight <2,500 grams (RR 1.74; 95% CI 0.44–6.87) or neonatal death (RR 4.74, 95% CI 0.50–45.00).
    - No report was made regarding the effects of isoxsuprine on respiratory distress syndrome (RDS), intracranial hemorrhage, retinopathy of prematurity (ROP), or necrotizing enterocolitis (NEC).
- **The results of this trial should be taken with caution since the sample size was insufficient to make adequately powered recommendations.**

## B. Use in Twin Gestation

**QUESTION 2** **Among pregnant women with TWIN gestation at high risk for preterm labor and delivery, is the use of PROPHYLACTIC oral beta-adrenergic agents effective in preventing preterm labor?**

**RECOMMENDATION** The existing data are insufficient to support or refute the use of prophylactic oral betamimetics for preventing preterm birth in women with a twin gestation at high risk of preterm labor.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

### SUMMARY OF EVIDENCE

Multifetal gestations are at a particular risk for preterm labor and delivery. Thus, appropriate research is necessary to find the tocolytic agent or intervention that may be valuable in these cases.

Another systematic review published in 2015 in the Cochrane Library[6] looked into the efficacy and safety of prophylactic oral betamimetics in the prevention of preterm labor and birth among women with ***twin*** pregnancies.

- The review included five studies (344 twin pregnant women) that compared oral betamimetics with placebo.
- The types of betamimetic agents used were different across studies. These included salbutamol, fenoterol, isoxsuprine, ritodrine and terbutaline. Only one study was reviewed per tocolytic agent.
- The following were the results:
  - The use of oral beta-adrenergic drugs for tocolysis resulted in a statistically significant reduction in the incidence of preterm labor (two trials, 194 twin pregnancies, RR 0.37; 95% CI 0.17–0.78). The studies that reported on this outcome used salbutamol and terbutaline.
  - Neonates in the betamimetics group had a lower incidence of RDS compared to those in the placebo group (two trials, 388 neonates, RR 0.30; 95% CI 0.12–0.77) but the difference was not significant when the analysis was adjusted to account for the non-independence of twins.

- Three trials (452 neonates, tocolytics used: salbutamol, isoxsuprine and ritodrine) reported that betamimetics do not have an effect in reducing neonatal mortality.

- The review cited the following limitations:
  - The types and doses of betamimetics used in the trials varied. Considering that each of the trials also had a small number of subjects, the quality of evidence is therefore markedly lowered.
  - The outcomes reported were incomplete and the definition of each outcome differed among trials.
- The review therefore concluded that **there are inadequate data to support or refute the use of prophylactic oral betamimetics for preventing preterm birth in women with a twin pregnancy at high risk of preterm labor.**

## II. BETAMIMETICS IN THE TREATMENT OF PRETERM LABOR

| | |
|---|---|
| **QUESTION 3** | **Among pregnant women in preterm labor and with singleton gestation, is the use of beta-adrenergic agents, compared with no tocolytic agent, effective in TREATING the acute phase of preterm labor and reducing adverse newborn outcomes?** |
| **RECOMMENDATION** | Betamimetics may be given to women in preterm labor and with singleton gestation to allow transfer to a tertiary center and complete antenatal corticosteroids, but serious adverse effects of beta-adrenergic stimulation should be considered.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

### SUMMARY OF EVIDENCE

- In 2014, a Cochrane systematic review [1] included twelve RCTs that compared 1) betamimetics to placebo and 2) other betamimetics to ritodrine.
  - It was found that the use of betamimetics significantly lowered the number of women giving birth within 48 hours of treatment (RR 0.68; 95% CI 0.53–0.88; 10 trials, 1209 women) and within seven days (RR 0.80; 95% CI 0.65–0.98; five trials, 911 women).

- The delay in the timing of birth did not demonstrate any improvements in neonatal outcomes such as reduction in perinatal death (RR 0.84; 95% CI 0.46–1.55, 11 trials, 1332 infants), respiratory distress syndrome (RR 0.87; 95% CI 0.71–1.08, eight trials, 1239 infants), or cerebral palsy (RR 0.19; 95% CI 0.02–1.63, one trial, 246 infants), but it must be noted that most women who were included in the trials were 32 weeks' gestation or more. Had the inclusion criteria of the studies been limited to earlier gestational ages, and the sample sizes been greater, the pregnancy prolongation brought about by betamimetics probably would have made a difference in the clinical outcome.
- It should also be mentioned that all trials included in the systematic review were conducted in hospitals that likely had capable neonatal intensive care facilities. Had the studies included women in preterm labor who needed transfer to a distant tertiary center, then the delay in the timing of delivery probably would have translated into different clinical outcomes.
- There are no sufficient data to support that one betamimetic drug is superior to another.
- The review demonstrated considerably increased maternal adverse effects with the use of betamimetics compared to placebo. These included palpitations, tremors, headache, hypokalemia, hyperglycemia, nausea or vomiting, nasal stuffiness. More serious maternal outcomes such as maternal deaths, cardiac arrest, respiratory arrest, and admission to intensive care unit were not reported. Three trials reported maternal pulmonary edema. These adverse effects were primarily related to the beta-adrenergic stimulation produced by these agents and oftentimes result in the cessation of use of this particular group of tocolytics.

- In 2011, the U.S. Food and Drug Administration (FDA)[7] issued a public warning that *injectable* terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48–72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. They further stated that oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns.
  - The FDA report was based on a review of post-marketing reports of maternal death and serious cardiovascular adverse events submitted to the Adverse Event Reporting System (AERS) from 1976 to 2009.

They identified 16 maternal deaths associated with outpatient use of terbutaline administered by subcutaneous pump or oral terbutaline alone or in combination with subcutaneous or intravenous terbutaline. Furthermore, they identified 12 maternal cases of serious cardiovascular events such as cardiac arrhythmias, myocardial infarction, pulmonary edema, hypertension, and tachycardia from 1998 to 2009.

- FDA[7] stated that although it may be deemed clinically appropriate based on the health care professional's judgment to administer terbutaline by injection in urgent and individual obstetrical situations in a hospital setting, such as in the management of tetanic uterine contractions or tachysystole with an abnormal fetal heart rate pattern,[8] the prolonged use of this drug to prevent recurrent preterm labor can result in maternal heart problems and death.[7] **Injectable terbutaline may be used only in an inpatient, monitored setting but should not be used beyond 48 to 72 hours. Oral terbutaline should not be used at all to treat or prevent preterm labor**[9]

- The usual subcutaneous terbutaline dose is 0.25 mg (250 μg) every 20 to 30 minutes for up to four doses or until tocolysis is achieved. Once contractions are controlled, 0.25 mg (250 μg) may be administered subcutaneously every three to four hours until the uterus is quiescent for 24 hours.[8,10]

## III. BETAMIMETICS FOR MAINTENANCE THERAPY AFTER THREATENED PRETERM LABOR

| | |
|---|---|
| **QUESTION 4** | **Among pregnant women with singleton gestation and arrested preterm labor, is the use of beta-adrenergic agents, compared with no tocolytic agent, effective for MAINTENANCE tocolysis?** |
| **RECOMMENDATION** | Maintenance treatment nor repeated acute tocolysis with betamimetics should not be undertaken.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

**SUMMARY OF EVIDENCE**

- In 2012, a Cochrane systematic review[8] included 13 RCTs that included 1,551 women who have had at least one episode of threatened preterm labor that settled without preterm birth. Five trials compared terbutaline versus placebo; another five used ritodrine versus placebo. One trial that involved 71 pregnant women compared terbutaline with indomethacin; two compared terbutaline with oral magnesium.
    - In this review, the betamimetics ritodrine and terbutaline did not show any reduction in the rate of preterm birth (8 trials) or admission to the neonatal intensive care unit (2 trials), when compared with placebo, no treatment or other tocolytic drugs. No difference was observed in perinatal mortality. Likewise, no difference was reported for the outcomes of preterm birth within 24 hours, 48 hours or one week, or maternal readmission to hospital.
    - Although the trials were relatively small, the results were relatively consistent between trials and the various comparisons.

The review concluded that evidence **does not support the use of oral betamimetics for maintenance therapy after threatened preterm labor.**

## IV. ISOXSUPRINE ON SPOTLIGHT

While betamimetics have been the focus of several studies in the past, most trials involved the drugs terbutaline or ritodrine. Isoxsuprine, which is the first beta-adrenergic drug used to inhibit preterm labor in 1961,[9] is another promising betamimetic as it is readily available in the local setting.

| | |
|---|---|
| **QUESTION 5** | **Among pregnant women at high risk for preterm labor and delivery, is the use of isoxsuprine, compared with no tocolytic agent, effective for acute tocolysis or maintenance tocolysis?** |
| **RECOMMENDATION** | More adequately powered studies are needed to support the use of isoxsuprine in acute or maintenance tocolysis.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Weak* |

## SUMMARY OF EVIDENCE

- In 2011, a systematic review by Giorgino and Egan [3] presented evidence that isoxsuprine hydrochloride administered acutely (intravenous administration) and as maintenance therapy (intramuscular or oral administration) is effective in the prolongation of pregnancy among women at risk of preterm delivery.

Two analyses were conducted. The first analysis reviewed two double-blind trials to compare isoxsuprine versus placebo. The second analysis evaluated data from 25 studies, 20 of which reported data on women at risk for abortion and/or premature delivery, while 5 studies reported women at risk for abortion only. Isoxsuprine was administered acutely (intravenous route) followed by maintenance therapy (intramuscular or oral route) in 13 studies (52%), maintenance therapy alone in 9 studies (36 %) or acute therapy alone in 3 studies (12%).

The following were the results:

- The first analysis demonstrated prolongation of pregnancy among patients at risk of preterm labor. Patients in the isoxsuprine arm reached full term in 89.5% of cases compared to 29.4% of patients in the placebo group ($p<0.001$).

- The secondary analysis of individual patient data showed a beneficial effect of isoxsuprine in prolonging pregnancy in 54.5% of women at risk of abortion. Although no pregnancy prolongation was demonstrated in a high proportion of patients at risk of abortion (44.8%), a gradual time-dependent increase in delay of pregnancy was observed thereafter in these patients who received isoxsuprine medication (37.1% of patients delayed until > 28 weeks). In contrast, 82.3% of all patients at risk of premature delivery showed a delay in pregnancy, of which 62.1% were between 4–12 weeks.

- Pooled individual and general data demonstrated a beneficial effect of isoxsuprine in 77.3% of cases at risk of abortion and 89% for risk of premature delivery, along with evidence of favorable tolerability.

- The study by Giorgino mentioned the following isoxsuprine regimen used in most studies:

  *For inhibition of acute phase of preterm labor:*

  Isoxsuprine administered by intravenous (IV) infusion at a rate of 0.2–0.5 mg/min until contractions have ceased

  *For maintenance therapy:*

  Isoxsuprine administered intramuscularly (IM) or per orem (PO) every 3–8 hours until labor occurs.

  *For threatened abortion:*

  Isoxsuprine 30mg/pill 1–3 pills per day every 3–8 hours

  *For preterm labor prevention or prophylaxis*

  Isoxsuprine 1–2 pills per day, starting at the second month of pregnancy and continuing for 1 or more months

- In 2015, Alavi et al.[13] conducted an RCT among 70 pregnant patients between 27 to 34 weeks gestation to assess the effect of maintenance therapy with oral isoxsuprine for the prevention of preterm labor.
  - The results showed that 14 (40%) women in the isoxsuprine arm and 12 patients (34.29%) in the control arm delivered preterm. The study did not show any significant difference between the two groups (P=0.621).

- A more recent prospective, single-center, non-comparative study, published this year by Jaju,[12] assessed the short- and long-term safety and effectiveness of isoxsuprine as a tocolytic agent. The following dosages were used for the acute and maintenance therapy of preterm labor:

  *For inhibition of acute phase of preterm labor:*

  Isoxsuprine intravenous (IV) infusion of 40-mg until uterine quiescence, *followed by*

  *For maintenance therapy:*

  Isoxsuprine intramuscular (IM) injection of 10 mg every 4 hours for the first 24 hours, *then* maintained with retard 40-mg sustained release capsule (two times a day) till the time of delivery or 37 weeks AOG

  - The primary outcome was the percentage of patients achieving successful tocolysis in the first 24 hours, first with IV and then with IM administration of isoxsuprine, followed by isoxsuprine capsule PO

in the subsequent 24 hours as maintenance therapy. Tocolysis was considered successful if the uterine quiescence was maintained for at least 48 hours.

- The results showed that all the patients in the study achieved successful tocolysis in the first 24 hours after parenteral administration of isoxsuprine (IV followed by IM administration) and right through the maintenance therapy during the subsequent 24 hours.
- Pregnancy was prolonged by a mean of 58.5 days, which was more than sufficient time for administration of corticosteroids and transfer to more capable neonatal intensive care facilities.

- **A search for existing scientific literature did not yield any single recommendation regarding the appropriate dosing of isoxsuprine for the treatment of preterm labor.** This is perhaps due to the fact that most trials on betamimetics looked into ritodrine and terbutaline as tocolytic agents.

In summary, while betamimetics seem to be effective in achieving tocolysis during the acute phase of preterm labor, the unpleasant side effects that result from beta-adrenergic stimulation may limit their use in the clinical setting and should be put into consideration. As for the use of these agents in maintenance tocolysis and prevention of preterm birth, more adequately powered studies are necessary.

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Chapter 14

# Oxytocin Receptor Antagonist

Edeliza Elvambuena-Amorin, MD, FPOGS, FPSMFM, FPSUOG
Joseph Carl M. Macalintal, MD

## QUESTION 1 Is Atosiban as effective and efficacious as Nifedipine in the prolongation of pregnancy for 48 hours among women in preterm labor?

**RECOMMENDATION** Atosiban is as effective and efficacious as Nifedipine in the prolongation of pregnancy for 48 hours among women in preterm labor.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

Four randomized controlled trials were published comparing Atosiban with Nifedipine in terms of efficacy in prolonging pregnancy for 48 hours, with conflicting results. In the study of Salim et al.[1], Nifedipine was significantly more efficacious than Atosiban (RR 1.32, 95% CI 1.01–1.73). Kashanian et al.[2] concluded that there is a trend towards Nifedipine being more efficacious than Atosiban (RR 1.10, 95% CI 0.87–1.38). On the other hand, a trend towards Atosiban being more efficacious than Nifedipine in prolonging pregnancy for 48 hours was noted in the studies by Al Omari et al.[3] and Van Vliet et al.[4] (RR 0.95, 95% CI 0.67–1.36; and RR 0.97, CI 0.86–1.09, respectively).

In terms of effectiveness in prolonging pregnancy for 48 hours, the study by Al Omari et al.[3] and Salim et al.[1] both showed no significant difference between Atosiban and Nifedipine (RR 0.92, 95% CI 0.72–1.18; and RR 0.93, 95% CI 0.83–1.05, respectively).

In the systematic review and meta-analysis by Ali et al.[5] of the above studies comparing the efficacy of Atosiban with Nifedipine, the authors concluded that there is no significant difference between the two in terms of effectiveness (RR 0.93, 95% CI 0.84–1.03), and efficacy (RR 1.06, 95% CI 0.92–1.22) in prolonging pregnancy for 48 hours.

**QUESTION 2** **Is Atosiban as effective and efficacious as Nifedipine in the prolongation of pregnancy for 7 days among women in preterm labor?**

**RECOMMENDATION** Atosiban is as effective and efficacious as Nifedipine in the prolongation of pregnancy for 7 days among women in preterm labor.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

In terms of efficacy in prolonging pregnancy for 7 days, five randomized controlled trials[1,2,3,4,6] have been published, showing that there is no significant difference between Atosiban and Nifedipine. The meta-analysis by Ali et al.[5] of these studies validated their findings (RR 1.04, 95% CI 0.89–1.21).

Two randomized controlled trials[1,3] looked into the effectiveness of Atosiban and Nifedipine in prolonging pregnancy for 7 days. These two trials, despite showing no significant difference, demonstrated conflicting trends. The study by Al Omari et al.[3] showed a trend towards Nifedipine being more effective (RR 1.05, 95% CI 0.77–1.42), whereas the study by Salim et al.[1] showed a trend towards Atosiban being more effective (RR 0.88, 95% CI 0. –1.02). Pooled data from these two trials were included in the meta-analysis by Ali et al.,[5] which showed no significant difference between Atosiban and Nifedipine in terms of effectiveness in prolonging pregnancy for 7 days (RR 0.91, 95% CI 0.79–1.05).

**QUESTION 3** **Is Atosiban better than Nifedipine in terms of maternal side-effects?**

**RECOMMENDATION** Atosiban is associated with fewer maternal side-effects than Nifedipine.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

In the meta-analysis of Ali et al.[5], the most notable result to emerge from the pooled data is that women in the Atosiban group had numerically fewer side-effects than did those in the Nifedipine group; this difference was statistically significant for headache (RR 0.47, 95% CI 0.22–0.99)[1,2,3,6] and tachycardia (RR 0.20, 95% CI 0.05–0.74),[1,2,3] but did not differ for palpitation (RR 0.37, 95% CI 0.10–1.33),[1,2,3,6] hypotension (RR 0.30, 95% CI 0.08–1.19),[1,2,3,4,6] vomiting (RR 1.55, 95% CI 0.28–8.64),[1,3] and nausea (RR 2.44, 95% CI 0.13–46.73).[1,3]

| QUESTION 4 | Is Atosiban comparable to Nifedipine in terms of neonatal side effects? |
|---|---|

**RECOMMENDATION** There are no significant differences between women given Atosiban and women given Nifedipine in terms of neonatal side effects.

*Quality of Evidence: Very Low*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Pooled data from the meta-analysis of Ali et. al revealed no significant differences between the Atosiban group and the Nifedipine group regarding the development of neonatal side-effects of respiratory distress syndrome (RR 0.79, 95% CI 0.27–2.34),[1,3] bradycardia (RR 0.98, 95% CI 0.10–9.85),[1,3] sepsis (RR 0.98, 95% CI 0.60–1.60),[1,3,4] apnea (RR 1.19, 95% CI 69–2.04),[1,3,4] necrotizing enterocolitis (RR 1.75, 95% CI 0.11–29.02) [1,3] and hemorrhagic disease (RR 0.79, 95% CI 0.26–2.41).[1,3,4]

| QUESTION 5 | How long should Atosiban be used in the inhibition of preterm labor? |
|---|---|

**RECOMMENDATION** The duration of treatment is up to 15 to 45 hours (from the bolus injection to low-dose subsequent infusion). Treatment schedule should not exceed 330 mg and retreatment can be done to a maximum of 4 times. (*Ungraded Recommendation)*

| QUESTION 6 | What is the recommended dosing regimen of Atosiban as a tocolytic agent? |
|---|---|
| **RECOMMENDATION** | The regimen of Atosiban as a short-term intravenous therapy (bolus injection) begins with an initial bolus of 6.75 mg administered over 1 minute, followed immediately by an infusion of 300 ug/min for 3 hours (high-dose loading infusion), then 100 ug/min for up to 15 to 45 hours (low-dose subsequent infusion). *(Ungraded Recommendation)* |

| QUESTION 7 | Should Atosiban be used as maintenance therapy for preventing preterm birth after threatened preterm labor? |
|---|---|
| **RECOMMENDATION** | There is insufficient evidence to support the use of oxytocin receptor antagonist as maintenance therapy after an episode of preterm labor.<br><br>*Quality of Evidence: Low*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

A Cochrane review identified only one good quality multicenter controlled trial which showed that subcutaneously administered Atosiban as maintenance therapy did not reduce the incidence of preterm birth or improve neonatal outcomes when compared with placebo treatment. The trial randomized 513 women in whom preterm labor (with intact membranes and limited cervical dilatation) ceased following intravenous treatment with Atosiban. When compared with placebo, Atosiban did not reduce preterm birth before 37 weeks (RR 0.89; 95% CI 0.71-1.12), 32 weeks (RR 0.85; 95% CI 0.47-1.55), or 28 weeks (RR 0.75; 95% CI 0.28-2.01).[7]

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Chapter 15

# Magnesium Sulfate for Neuroprotection

Zarinah G. Gonzaga, MD, FPOGS, FPSUOG, FPSMFM

The exact mechanism by which magnesium ions helps in preventing preterm labor is believed to be related to its calcium antagonist effect. Magnesium ions in relatively high concentrations are known to inhibit extracellular calcium ion entry, intracellular calcium release, cytosolic calcium oscillations, and phasic contractions of myometrial smooth muscle. The effect of magnesium sulfate in inhibiting myometrial contractions in humans is consistent with these intracellular and extracellular mechanisms. In addition, it also hyperpolarizes the plasma membrane and inhibits myosin light chain kinase activity by competing with intracellular calcium. The net effect of these actions of magnesium sulfate is the reduction in myometrial contractility.[1, 2]

The customary protocol for magnesium sulfate (MgSO4) administration in preterm labor is to give a loading dose of 4 to 6 grams magnesium sulfate in 10% to 20% solution (60mL of 10% magnesium sulfate in 5% dextrose in 0.9% normal saline) given over 30 minutes. This is then followed by a maintenance infusion of 2g/hour (40 grams of magnesium sulfate added to 1L of 5% dextrose in 0.9% normal saline or Ringer lactate, at 50mL/hour). The intravenous rate is increased by 1g/hour until the contractions are noted to occur at fewer than once in 10 minutes, or until a maximum of 4g/hour is reached.[3] Once contractions have stopped, or are occurring fewer than once in every 10 to 15 minutes, the infusion may be discontinued without titrating down the infusion rate.[4]

| QUESTION 1 | Should magnesium sulfate be used as primary therapy for preterm labor? |
|---|---|
| **RECOMMENDATION** | Available evidence does not support the use of magnesium sulfate as primary therapy to arrest preterm labor.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

### 1. *Quality of the Evidence*

To date, only one systematic review on the effectiveness of magnesium sulfate as a tocolytic agent has been published.[5] This review of 37 randomized controlled trials (RCTs) involving a total of 3,571 women provided evidence that magnesium sulfate was not effective in reducing the risk of birth within 48 hours of treatment compared to no tocolytic drug (relative risk, [RR], 0.56, 95% confidence interval [CI], 0.27–1.14, 3 trials, 182 participants), betamimetic therapy (RR, 1.09; 95% CI, 0.72–1.65, 7 trials, 503 participants), calcium channel blockers (RR, 1.19; 95% CI, 0.86–1.65, 5 trials, 588 participants), COX inhibitors (RR, 1.08; 95% CI, 0.91–1.27, 2 trials, 318 participants), and prostaglandin inhibitors (RR, 0.93; 95% CI, 0.71–1.22], 2 trials, 221 participants), or in preventing birth <37 weeks compared to no alternative tocolytic drug (RR, 0.52; 95% CI, 0.46–0.83, 1 trial, 65 participants), betamimetic drugs (RR, 1.03; 95% CI, 0.77–1.39, 6 trials 473 participants), calcium channel blockers (RR, 1.06; 95% CI 0.87–1.29], 3 trials, 362 participants), and prostaglandin inhibitors (RR, 1.83; 95% CI, 0.58–5.81, 1 trial, 88 participants). In addition, there was no significant difference found in neonatal outcomes with magnesium sulfate compared with no alternative tocolytic (RR, 2.34; 95% CI, 0.78–7.01, 3 trials, 284 participants), betamimetics (RR, 0.92; 95% CI, 0.20–4.12, 5 trials, 344 participants), calcium channel blockers (RR, 1.02; 95 CI, 0.37–2.83, 5 trials, 675 participants, COX inhibitors (RR, 8.19; 95% CI, 0.45–150.22, 2 trials, 314 participants), and prostaglandin inhibitors (RR, 0.77; 95% CI, 0.27–2.21, 3 trials, 355 participants). No serious maternal outcomes were reported in all groups.

The risk of bias of the studies included in this systematic review was graded moderate to high risk of bias. There was insufficient detail to make a judgment on allocation concealment in 27 of 37 trials. Blinding of outcome assessors was mentioned in only 1 trial while none of the remaining 36 specifically mentioned blinded assessment of outcomes. Only 11 of 37 trials were judged to be free of selective reporting bias.

Overall, the group is moderately confident in the effect estimate from this systematic review.

## 2. Balance Between Clinical Benefits and Harms

Evidence from randomized trials[6] assessing magnesium sulfate versus placebo or no treatment showed high rates of minor maternal adverse effects without an increase in major maternal complications. The absolute risk of having any adverse effect of treatment was 38% (2,521 of 6642) for women with exposure to antenatal magnesium sulfate compared to 8.5% (567 of 6680) for women not exposed to magnesium sulfate. The most frequently reported adverse effects include warmth or flushing, sweating and arm discomfort or problems at the intravenous site.

Magnesium sulfate was also associated with modest adverse effect on the fetal heart rate patterns.[7] This included a statistically significant decrease in the baseline fetal heart rate (mean difference [MD] -6.19bpm, 95% CI, -13.46 to 1.07) although all the fetal heart rates (FHR) remained within the normal range. There was also an observed small reduction in the FHR variability (mean of -0.99bpm, 95% CI -1.91 to -0.80) and a decrease in the number and frequency of FHR accelerations by not more than 5 to 10 beats per minute (bpm) without an increase in the deceleration patterns. In addition, case reports and data from retrospective studies support an association between prolonged (more than 5 to 7 days) maternal administration of magnesium sulfate with neonatal hypocalcemia and skeletal abnormalities.[8]

Taking into account that there is no proof of a beneficial effect on important outcomes in preterm birth and evidence of an association with adverse maternal and fetal side effects, the recommendation against the intervention is strengthened.

## 3. Values, Preferences, and Burden of Patients

Shared decision making between the healthcare provider and the patient before initiating tocolytic therapy is very important. Information to patient should include explaining the purpose of the interventions and what can be expected.

The route of administration of magnesium sulfate is also a major factor affecting patient preference since it is given intravenously.

## 4. Costs

No formal cost-effectiveness study was available.

**QUESTION 2** **Should magnesium sulfate be used as maintenance therapy after threatened preterm labor?**

**RECOMMENDATION** There is insufficient evidence to support the use of magnesium sulfate as maintenance therapy after an episode of threatened preterm labor.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

### 1. *Quality of the Evidence*

To date, there is only one systematic review that assessed whether magnesium maintenance therapy is effective in preventing preterm birth after an initial episode of preterm labor has been arrested. This review consisted of four trials of 422 women and showed no statistically significant differences in the incidence of preterm birth or perinatal mortality when maintenance therapy with magnesium sulfate was compared with placebo or no treatment, or compared to other alternative therapies, specifically ritodrine or terbutaline. Based on this review, there is not enough evidence to show any difference between maintenance therapy with magnesium sulfate compared with either placebo or no treatment, or alternative therapies in preventing preterm birth after an episode of threatened preterm labor.

Of the four trials in this review, only one was rated of reasonable quality for randomization, allocation concealment, blinding of outcomes assessment and free of selective reporting. In addition, the trials were too small to exclude either important benefits or harms from maintenance therapy with magnesium sulfate. Overall, the group has limited confidence in the effect estimate. Further research is likely to have an important impact on and may change the estimate.

## 2. Balance Between Clinical Benefits and Harms

Prolonged use of magnesium sulfate injections may be associated with adverse effects such as bone malformations in exposed babies. For this reason, the U.S. Food and Drug Administration (FDA) recommends against prolonged use of magnesium sulfate as a tocolytic agent.[8]

## 3. Values, Preferences, and Burden of Patients

The intravenous route of administration is likely to affect patient preference.

## 4. Costs

No formal cost-effectiveness study was available.

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Chapter 16

# Role of Antenatal Steroids in Preterm Labor and Delivery

Leah Socorro N. Rivera, MD, FPOGS, FPSMFM, FPSUOG
Jacqueline Perote-Pedroso, MD, FPOGS, FPSUOG

Liggins in 1969 studied the effect of dexamethasone on premature parturition in fetal sheep. They found that there was inflation in the lung of lambs at gestations at which they would be considered airless. It was hypothesized that dexamethasone promoted the production of surfactant. This revolutionized the management of preterm labor and delivery, decreasing neonatal mortality and morbidity.

## DEFINITION OF TERMS

- **RESCUE COURSES** – one more full course of antenatal steroids in women previously given one dose of antenatal corticosteroids if undelivered after two weeks from the initial course and age of gestation is <34 weeks
- **RESCUE DOSE** – one 12-mg dose of betamethasone given 7 days after an initial two doses of betamethasone 12 mg, 24 hours apart
- **INCOMPLETE COURSES** – one 12-mg dose of betamethasone given before delivery with no prior course of antenatal steroids
- **MULTIPLE COURSES** – betamethasone 24 mg in divided doses every 7 days until 34 weeks
- **NEONATAL MORTALITY** – death of the neonate within 28 days of life
- **MATERNAL DEATH** – death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.

**QUESTION 1** **Should antenatal corticosteroids be given to patients with preterm labor to reduce neonatal mortality and morbidity?**

**RECOMMENDATION** Antenatal steroids should be given to patients in preterm labor to reduce the incidence of respiratory distress syndrome, cerebroventricular hemorrhage, necrotizing enterocolitis and neonatal death.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

In a meta-analysis published in 2017[1] which included 28 randomized controlled trials (RCT), it was shown that antenatal steroids significantly reduced respiratory distress syndrome (RDS) (relative risk [RR], 0.66; 95% confidence interval [CI] 0.56–0.77), neonatal death (RR 0.69; 95% CI 0.59–0.81), cerebroventricular hemorrhage (RR 0.55 95% CI 0.40–0.76), necrotizing enterocolitis (RR 0.50; 95% CI 0.32–0.78), and systemic infection within the first 48 hours in treated infants (RR 0.60; 95% CI 0.66–1.04) without increasing the chances of having small-for-gestational-age infants (RR 1.11; 95% CI 0.96–1.28).

In the same meta-analysis, the incidence of maternal death (RR 0.98; 95% CI 0.06–15.50) and chorioamnionitis (RR 0.83; 95% CI 0.66–1.06) were not affected by the steroids. However, endometritis (RR 1.20 95% CI 0.87–1.63) seemed to increase in incidence in the steroid-treated group although this was not statistically significant (P value=0.26).

**QUESTION 2** **When should steroids be given in patients with preterm labor?**

**RECOMMENDATION** Antenatal steroids should be given to patients at risk for preterm labor and delivery between 26 and 34 weeks age of gestation (AOG). Administration may also be considered in patients at risk for preterm delivery beyond 34 weeks to 36 6/7 weeks provided these patients were not previously given a previous course of antenatal steroids.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

A meta-analysis by Roberts,[1] which included both patients with preterm prelabor rupture of membranes (PPROM) and with intact membranes, showed that antenatal corticosteroids would be of benefit in reducing perinatal/neonatal mortality, intraventricular hemorrhage and respiratory distress syndrome if steroids are first given at less than 35 weeks AOG.

This review included studies according to the gestational age at which pregnant women entered trials to receive their first dose of corticosteroids and have classified it into two, slightly overlapping subgroups: 1) women less than, and including, 35 weeks and 0 days and 2) women greater than, and including, 34 weeks and 0 days. Twenty (20) studies contributed data to the younger gestational age group and six studies contributed data to the older gestational age group.

Steroids given at less than 35 weeks showed a decrease in the incidence of perinatal death rate (RR 0.71; 95% CI 0.58–0.87), neonatal death rate (RR 0.67 95% CI; 0.57–0.69), respiratory distress syndrome (RDS) (RR 0.65; 95% CI 0.58–0.73) and intraventricular hemorrhage (IVH) (RR 0.54; 95% CI 0.42–0.68). Furthermore, when steroids were given to pregnant women more than 34 weeks age of gestation, respiratory distress syndrome was also significantly decreased (RR 0.71; 95% CI 0.56–0.91) but there was heterogeneity in the population included in this analysis. Perinatal death rate (RR 1.03; 95% CI 0.29–3.67), neonatal death rate (RR 0.83; 95% CI 0.22–3.07) and fetal death rate (RR 1.62; 95% CI 0.28–9.37) were not decreased significantly. The incidence of IVH seemed to be increased for patients who received steroids after 34 weeks (RR 4.91; 95% CI 0.24–102.09) but more studies need to be included to be able to have statistical significance.

According to the latest guideline released by the American College of Obstetricians and Gynecologists (ACOG)[3] released in August 2017, a single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk for preterm delivery within 7 days, including those with ruptured membranes and multiple gestation. Steroids may also be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation. This is irrespective of membrane rupture status and regardless of fetal number. Administration of betamethasone may be considered in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk for preterm birth within 7 days, and who have not received a previous course of antenatal steroids.

**PRACTICAL RECOMMENDATION:**

In clinical practice in the Philippines, it is recommended that antenatal steroids be given for patients in preterm labor and at risk for preterm delivery at 26 to 36 6/7 weeks age of gestation. It is also in conjunction with the capability of the newborn services units in the different hospitals.

| QUESTION 3 | **What is the better antenatal corticosteroid to use in patients in preterm labor?** |
|---|---|
| **RECOMMENDATION** | No high quality evidence exists to support superiority of one antenatal steroid over the other in preventing neonatal morbidity in patients at risk for preterm delivery.<br><br>*Quality of Evidence: High*<br>*Strength of Recommendation: Strong* |

**SUMMARY OF EVIDENCE**

In a meta-analysis by Brownfoot [2] which included 12 studies conducted among patients at risk for preterm labor and delivery, it was shown that dexamethasone is more effective in preventing intraventicular hemorrhage (RR 0.44, 95% CI 0.21–0.92). Vasopressor use was decreased in dexamethasone-treated infants (RR 0.44; 95% CI; 0.17–1.11) but this was not statistically significant (P=0.081).

No statistically significant differences were seen between those exposed to betamethasone or dexamethasone for other primary outcomes: respiratory distress syndrome (RDS) (RR 1.06; 95% CI 0.88–1.27), neonatal death (RR 1.41; 95% CI 0.54–3.67), bronchopulmonary dysplasia (RR 2.50; 95% CI 0.10–61.34), periventricular leukomalacia (RR 0.83; 95% CI 0.23–3.03), necrotizing enterocolitis (RR 1.29; 95% CI 0.38–4.4) and neonatal sepsis (RR 1.30; 95% CI 0.78–2.19).

## QUESTION 4 Should rescue courses be given to patients with preterm labor?

**RECOMMENDATION** A single rescue course is recommended for patients less than 34 0/7 weeks who are still at risk for preterm delivery within 7 days, and whose first course of steroids was given 14 days prior.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

A multicenter trial published in 2009[3] included 437 pregnant patients with singleton gestation at 26 to 34 weeks AOG who previously received one course of antenatal steroids but remained undelivered after 14 days. The patients were randomized to receive another single rescue course of steroids consisting of two 12-mg dose of Betamethasone. Among patients given the rescue course, the risk of having respiratory distress syndrome was reduced (odds ratio [OR], 0.45; 95% CI 0.27–0.75). The need for mechanical ventilator (OR, 0.56; 95% CI 0.33–0.92) was also reduced significantly.

## QUESTION 5 Should incomplete courses be given to patients with preterm labor?

**RECOMMENDATION** At present, incomplete courses are not recommended because of evidence of possible harm to the fetus. More studies are needed to evaluate the effect of incomplete courses of steroids in the incidence of neonatal morbidity and mortality.

*Quality of Evidence: Very Low*
*Strength of Recommendation: Weak*

### SUMMARY OF EVIDENCE

Two retrospective cohort studies by Costa[6] and Elimian[7] included women in preterm labor with intact membranes, PPROM and medically indicated delivery between 23–34 weeks. Incomplete course of antenatal steroids was defined as

one 12-mg dose of betamethasone given before delivery with no prior course of antenatal steroids. These studies showed that an incomplete course of steroids increased the risk of RDS (RR 2.08; 95% CI 1.69–2.55) and decreased the risk of sepsis (RR 0.48; 95% CI 0.36–0.63). It was also shown that the rates of intraventricular hemorrhage (RR 0.87; 95% CI 0.67–1.13), necrotizing enterocolitis (RR 0.80; 95% CI 0.39–1.63), and need for vasopressors (RR 0.77; 95% CI 0.49–1.23) were also reduced although these were not statistically significant. Neonatal death was only reported in the study by Eliaman [7] after adjusting for gestational age using logistic regression to be reduced in the incomplete course group (OR, 0.31; 95% CI 0.11–0.86; P=0.02).

## QUESTION 6 Should multiple courses be given to patients with preterm labor?

**RECOMMENDATION** Multiple courses of steroids should not be given in patients with preterm labor.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

Crowther et al.[8] showed that multiple courses of steroids significantly decreased the risk of RDS (RR 0.83; 95% CI 0.75–0.91). Perinatal death (RR 0.94; 95% CI 0.71–1.23), intraventricular hemorrhage (RR 0.94; 95% CI 0.75–1.18), periventricular leukomalacia (RR 0.77; 95% CI 0.43–1.37), necrotizing enterocolitis (RR 0.78; 95% CI 0.65–0.95) and proven infection in the NICU (RR 1.00; 95% CI 0.83–1.2) were not reduced by giving multiple courses of steroids. The risk of small-for-gestational-age (SGA) baby (RR 1.18; 95% CI 0.97–1.43) as well as the development of chorioamnionitis (RR 1.16; 95% CI 0.92–1.46) and puerperal sepsis (RR 1.15; 95% CI 0.83–1.60) were increased in patients given multiple courses although these were not found to be statistically significant.

**QUESTION 7** **Do antenatal corticosteroids have short-term and long-term adverse effects on the infant and the mother?**

**RECOMMENDATION** Antenatal corticosteroids given as a single course appear to have no significant adverse long-term effects on the infant and mother. However, it can increase the risk of glucose intolerance for patients given multiple doses.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

### 1. EFFECT ON INFANT OUTCOME

**Hypothalamus-Pituitary-Adrenal (HPA) Axis**

Determination of fetal cortisol in the cord blood and amniotic fluid showed acute suppression in response to the injection of antenatal steroids.[9-11] This suppression of endogenous fetal / neonatal cortisol production appeared to last until the immediate postnatal period among preterm infants then returned to normal levels after.

One study has evaluated the consequences of antenatal steroids treatment on adult HPA axis functioning. Morning cortisol levels at 30 years of age were 7% higher, among individuals given antenatal steroids as compared to the control group. However, this increase was not significant after consideration of factors including sex, birth weight, gestational age at birth, trial type, body-mass index, and use of oral contraceptives.[12] Even in the presence of multiple confounding variables, there is still a possibility that prenatal steroids treatment may exert long-term consequences on the functioning of the HPA axis in humans.

### 2. EFFECT ON CHILDHOOD OUTCOME

**Placebo versus one course of steroids**

In a Cochrane meta-analysis [1], no statistically significant differences were seen between those exposed to antenatal corticosteroids and controls for childhood weight (fixed weighted mean difference [FWMD] 0.30 kg, 95% CI -0.39 to 1.00

kg, two studies, 333 children), height (FWMD 1.02 cm, 95% CI -0.26 to 2.29 cm, two studies, 334 children), head circumference (FWMD 0.27 cm, 95% CI -0.08 to 0.63 cm, two studies, 328 children), lung function (vital capacity FWMD -1.68 % predicted, 95% CI -5.12 to 1.75 % predicted, two studies, 150 children), systolic blood pressure (FWMD -1.60 mmHg, 95% CI -4.06 to 0.86 mmHg, one study, 223 children), visual impairment (RR 0.55; 95% CI 0.24–1.23, two studies, 166 children), hearing impairment (RR 0.64, 95% CI 0.04–9.87, two studies, 166 children), behavioral/learning difficulties (RR 0.86; 95% CI 0.35–2.09, one study, 90 children) or intellectual impairment (RR 0.86; 95% CI 0.44–1.69, three studies, 778 children).

**Multiple Courses Versus Single Course**

Head circumference small-for-age (RR 1.10; 95% CI 0.77–1.56), total childhood mortality (RR 1.06; 95% CI 0.80–1.41) and cerebral palsy (RR 1.03; 95% CI 0.71–1.50) were increased in children previously given multiple courses of steroids in a study by Crowther;[8] however, results were not statistically significant.

## 3. EFFECT ON MATERNAL OUTCOME

A single course of antenatal steroids was found to increase the risk for development of glucose intolerance in the mother (RR 2.71; 95% CI 1.14–6.46) but did not appear to increase the risk of chorioamnionitis (RR 0.91; 95% CI 0.7–1.18), puerperal sepsis (RR 1.35; 95% CI 0.93–1.95), hypertension (RR 1.00; 95% CI 0.36–2.76) nor maternal mortality (RR 0.98; 95% CI 0.06–15.50).[1]

On the other hand, in a study by Crowther,[8] it was found that multiple courses of antenatal steroids compared with single course did not affect the manner of delivery, development of postpartum hemorrhage nor maternal hypertension. In contrast to single course of steroids, multiple courses seemed to increase the risk of glucose intolerance (RR 1.31; 95% CI 0.89–1.93) although the data was not statistically significant. This may be due to the fact that there is only one study to date that studied the effect of multiple courses of steroids in maternal blood sugar control.

**QUESTION 8** **Among pregnant women with multifetal gestation at risk for preterm delivery within 7 days, should antenatal corticosteroids be administered to improve neonatal outcomes?**

**RECOMMENDATION** **MULTIFETAL PREGNANCY**

Patients with multifetal gestation should be offered antenatal steroids if they are at risk for preterm delivery.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

In a Cochrane meta-analysis published in 2017,[1] no statistically significant differences were found in women with multifetal pregnancy who were given a course of antenatal steroids in terms of risk reduction of neonatal death (RR 0.79; 95% CI 0.39–1.61), respiratory distress syndrome (RR 0.85; 95% CI 0.6–1.2), cerebroventricular hemorrhage (RR 0.39; 95% CI 0.07–2.06), chorioamnionitis (RR 0.43; 95% CI 0.04–4.49) and birth weight (FWMD 82.36 g, 95% CI –146.23 to 310.95 g). The lack of beneficial effect of the antenatal steroids on reduction of neonatal mortality and morbidity in multifetal pregnancy may be because the optimal dose and pharmacokinetics of the drug are not clearly understood. Therson et al. [13] showed that multifetal pregnancy attenuates the effects of antenatal steroids. The Royal College of Obstetricians and Gynaecologists (RCOG) recommended the use of antenatal steroids in multifetal pregnancy despite the limited data because of the proven beneficial effects it has for singleton pregnancies.[14]

**RECOMMENDATION** **HYPERTENSIVE DISORDERS**

Antenatal corticosteroids should be administered to hypertensive pregnant women at risk for preterm delivery within 7 days.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

Infants born to pregnancies complicated by hypertension syndromes and treated with corticosteroids had significantly reduced risk of neonatal death (RR 0.50, 95% CI 0.29–0.87), RDS (RR 0.50, 95% CI 0.35–0.72), and cerebroventricular hemorrhage (RR 0.38, 95% CI 0.17–0.87). No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for combined fetal and neonatal death (RR 0.83, 95% CI 0.57–1.20), birth weight (FWMD -131.72 grams, 95% CI -319.68 to 56.24 grams), chorioamnionitis (RR 2.36, 95% CI 0.36–15.73) or puerperal sepsis (RR 0.68, 95% CI 0.30–1.52).[1]

**RECOMMENDATION**

**GESTATIONAL DIABETES MELLITUS**

Antenatal corticosteroids should be administered to pregnant women with gestational diabetes mellitus and at risk for preterm delivery within 7 days.

*Quality of Evidence: Good clinical practice (GPP)*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

The National Institute for Health and Care Excellence (NICE) 2015 guidelines on management of gestational diabetes mellitus in pregnancy reiterated that diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation. Women with impaired glucose tolerance or diabetes who are receiving fetal steroids should have additional insulin according to an agreed protocol and be closely monitored.[15]

Women with either insulin-dependent diabetes or gestational diabetes were not entered into randomized controlled trials (RCTs) of antenatal corticosteroid therapy. There is therefore no evidence from RCTs that antenatal corticosteroid therapy is either safe or effective in these circumstances.

**RECOMMENDATION** **INTRAUTERINE GROWTH RESTRICTION**

Antenatal steroid may be given in patients with growth restricted fetuses between 26 to 34 weeks age of gestation.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

In a case study published by Schapp et al.,[14] 124 preterm infants between 26 to 32 weeks age of gestation and with growth restriction secondary to placental insufficiency were divided into steroid group and placebo. The neonates in the steroid group had decreased risk of RDS, intracerebral hemorrhage and neonatal mortality although the numbers were not statistically significant. Long-term follow-up of these neonates showed that survival without disability or handicap at 2 years was better in the corticosteroid group (OR 3.2; 95% CI 1.1–11.2). While more growth problems were noted in the steroid group, no difference was noted in the behavior of neonates randomized to the placebo or steroid group. Therefore, the benefits of steroid therapy appear to outweigh the possible adverse effects. More high quality studies are needed to determine the effect of antenatal steroid on the outcome of these neonates.

**RECOMMENDATION** **INTRAAMNIOTIC INFECTION OR CHORIOAMNIONITIS**

Administration of corticosteroids should not delay the need for delivery in a patient with histological and clinically diagnosed chorioamnionitis.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

In a meta-analysis of nine observational studies,[11] the use of antenatal steroids appeared to be safe and was shown to reduce adverse neonatal outcomes following preterm birth associated with chorioamnionitis, whether histologically or clinically diagnosed.

While the evidence among cases of clinically apparent chorioamnionitis was less robust and more susceptible to bias, the data among histologically diagnosed chorioamnionitis showed significant reductions in mortality, respiratory distress syndrome and all degrees of intraventricular hemorrhage. In patients with clinically diagnosed chorioamnionitis, steroid therapy was correlated with reductions only in intraventricular hemorrhage and periventricular leukomalacia.

The Liggins[17] institute in 2015 did a subgroup analysis of women with chorioamnionitis included in Robert's[6] recent meta-analysis. This study included four trials with a small proportion of women with chorioamnionitis which ranged from 2% to 33%. They studied whether a single course of steroids will decrease neonatal morbidity and mortality. It was reported that there was no difference between the risk of intrapartum maternal pyrexia (RR 1.00; 95% CI 0.15–6.87) and puerperal sepsis (RR 2.65; 95% CI 1.18–5.91). For the infant outcomes, however, there was note of a significant reduction in the risk of perinatal death (RR 0.48; 95% CI 0.32–0.72), neonatal death (RR 0.48; 95% CI 0.34–0.68) and respiratory distress syndrome (RR 0.67; 95% CI 0.53–0.84).

It should be emphasized that caution be used in interpreting the evidence of the two studies. The studies did not mention the temporal relationship between the administration of the steroids and the onset of chorioamnionitis which may make application of the findings of the studies less useful. This amount of evidence is low-grade and cannot be used to form a clinical recommendation.

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Chapter 17

# Magnesium Sulfate for Neuroprotection

Marie Catheleen P. Santiago, MD, FPOGS, FPSUOG, FPSMFM

## DEFINITION OF TERMS

- **CEREBRAL PALSY** – 30% or more delay in gross motor developmental milestones (e.g. inability to sit without arm support by 9.5 months or walk by 17 months of corrected age); aberration in muscle tone (e.g. scissoring), 4+ or absent deep-tendon reflexes, or movement abnormality (e.g. posturing or gait asymmetry); or persistence of primitive reflexes or absence of protective reflexes[1]

- **GROSS MOTOR DYSFUNCTION** - walking with minimal restriction such as toe walking or asymmetrical gait, or not walking independently, the last group being considered to have substantial gross motor dysfunction [2]

- **INTELLECTUAL IMPAIRMENT** - score of < 85 on the Mental Development Index of the Bayley Scale of Infant Development[3]

| QUESTION 1 | **Should magnesium sulfate (versus no magnesium sulfate) be given for patients at risk for preterm delivery for prevention of cerebral palsy, gross motor dysfunction, and intellectual impairment?** |
|---|---|
| **RECOMMENDATION** | Magnesium sulfate should be administered to women at risk of delivery before 33 weeks age of gestation for fetal neuroprotection.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

In the studies reviewed, magnesium sulfate was either given for fetal neuroprotection or withheld among patients at risk of preterm delivery in general.

There are 3 randomized controlled, double-blinded trials that followed up infants up to 2 years of age, born to mothers either given or not given magnesium sulfate for the prevention of cerebral palsy, gross motor dysfunction and cognitive impairment.

Crowther et al. (ACTOMgSO4 trial) in 2003 studied 1,062 women with babies less than 30 weeks gestation and in whom birth was anticipated within 24 hours. Women were randomly allocated to either intravenous magnesium sulfate (N=535 women, 629 live babies) or an identical volume of saline placebo (N=527 women, 626 live babies). The magnesium sulfate dose that was administered was 4 g given over 20 minutes, followed by 1 g/hour for up to 24 hours or until birth, whichever came first. There were no repeat courses of treatment. The primary endpoints of the study were total pediatric mortality up to a corrected age of two years; cerebral palsy at two years' corrected age; and the combined adverse outcome of death or cerebral palsy at 2-year follow-up.[2]

In the study of Marret et al. (PreMag trial) in 2006, a total of 573 women whose birth was planned or expected within 24 hours with singleton, twin or triplet less than 33 weeks' gestation were enrolled. Women were randomly allocated to either intravenous magnesium sulfate of 4 g or an equal volume of isotonic saline placebo over 30 minutes. There were no repeat courses of treatment.[4]

Rouse et al. (BEAM trial) in 2008 enrolled women 2,241 women who were at least 24 weeks gestation but less than 32 weeks at high risk of spontaneous birth due to ruptured membranes at 22 to 31 weeks gestation, or advanced preterm labor with dilatation 4–8 cm and intact membranes; or if an indicated preterm birth was anticipated with 24 hours. They were "randomized in a double-blind fashion" to either intravenous magnesium sulfate (N=1096 women, 1188 babies) or identical-appearing placebo (N=1145 women, 1256 babies). The magnesium sulfate dose was 6 g over 20 to 30 minutes, followed by a maintenance infusion of 2 g/hour. If delivery had not occurred after 12 hours and was no longer considered imminent, the infusion was discontinued and resumed when delivery threatened. If at least 6 hours had transpired, another loading dose was given. Retreatment was withheld if: pre-eclampsia/eclampsia developed; maternal or fetal condition deteriorated so re-treatment would be detrimental; or if the gestational age had reached 34 weeks. The primary outcome was the composite of (1) stillbirth or infant death by one year of age, or (2) moderate or severe cerebral palsy as assessed at or beyond two years' corrected age.[1]

The studies show that there is moderate evidence supporting the neuroprotective effects of magnesium sulfate on the fetus when given to mothers at risk for delivery before 33 weeks age of gestation. The three studies revealed that the occurrence of cerebral palsy (OR 0.67, 95% CI 0.52–0.87) and

intellectual impairment (OR1.02, 95% CI 0.83–1.25) was reduced when magnesium sulfate was given. Two studies showed that gross motor dysfunction was lower in those given magnesium sulfate (OR 0.68, 95% CI 0.49 to 0.95).

| QUESTION 2 | At what age of gestation (AOG) should magnesium sulfate be given for fetal neuroprotection? |
|---|---|

**RECOMMENDATION** Magnesium sulfate should be given to women at risk for imminent delivery from 24 to 33 weeks AOG.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Women at risk of delivery at the limits of viability are counseled about management strategies. If the family decides in favor of neonatal interventions at this gestational age, magnesium sulfate is administered for neuroprotection. None of the trials mentioned above included pregnancies <24 weeks AOG.[1,2,4,5]

The upper limit of gestational age has not been well-studied.[6] The majority of data has been derived from pregnancies <33 weeks.[1,2,4,5]

| QUESTION 3 | What is the dosage of magnesium sulfate for neuroprotection? |
|---|---|

**RECOMMENDATION** Magnesium sulfate is administered at 4 g intravenous loading dose over 20 minutes and a maintenance dose of 1 g/ hour, at a maximum of 24 hours.

The duration of magnesium sulfate is limited to a maximum of 24 hours, even if delivery has not transpired, since this is the maximum duration of therapy in the cited studies.[2,5]

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

There is heterogeneity in the dosage of magnesium sulfate given for neuroprotection. This recommended regimen is likely to have more beneficial side effect and safety profile than higher-dose regimen.[1,2,4,5]

## QUESTION 4 — Can magnesium sulfate for neuroprotection be used in combination with calcium channel blockers for tocolysis?

**RECOMMENDATION**

The concomitant use of calcium channel blocker and magnesium sulfate could act synergistically to suppress muscular contractility, with possible respiratory depression.[6,7] Their use together should be done with caution.

There are no studies that reviewed the effects of concomitant use of magnesium sulfate and calcium channel blockers on uterine contractility and possible uterine atony.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

Maternal side effects are increased with concomitant use of magnesium sulfate and calcium channel blockers. Magnesium markedly inhibits acetylcholine release and its use with calcium channel blockers could theoretically interfere with neurotransmitter release and muscle contractility.[7] However, the data on their combined use is sparse; thus, no standard approach has been established.[6]

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Chapter 18

# Intrapartal Surveillance and Delivery

Jocelyn Cenizal-Bambalan, MD, FPOGS, FPSMFM, FPSUOG
Joanna Pauline Chua Ursua, MD, FPOGS, FPSMFM, FPSUOG
Ma. Cresilda Paz B. Salamilao-Sabularce, MD, DPOGS

## I. ELECTRONIC FETAL HEART RATE MONITORING VERSUS INTERMITTENT AUSCULTATION IN PRETERM GESTATIONS

| QUESTION 1 | **Is electronic fetal heart rate (FHR) monitoring better than intermittent auscultation in monitoring preterm fetuses?** |
|---|---|

**RECOMMENDATION**

There is no significant difference in the prevalence of low five-minute Apgar scores, intrapartum acidosis, intracranial hemorrhage, or frequency of cesarean section between using electronic FHR monitoring versus intermittent auscultation on preterm fetuses.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

The most common methods of fetal heart rate (FHR) monitoring are **continuous electronic FHR monitoring (EFM)** and **intermittent auscultation**. EFM can be done with an external cardiotocography monitor or an internal (scalp) lead in which FHR variability and changes from the baseline heart rate can be assessed. On the other hand, intermittent auscultation consists of auscultating FHR with either a stethoscope or a Doppler probe for 30 seconds immediately following a contraction. This monitoring must be performed every 30 minutes during stage I of labor and every 15 minutes during stage II.[3]

The American College of Obstetricians and Gynecologists (ACOG) published a practice bulletin on intrapartum monitoring for term gestations in 2009 but the decision to monitor the preterm fetus remains vague. There is paucity of recommendations based on scientific evidence for monitoring preterm fetuses during labor.[1]

As the fetal central nervous system develop and mature with increasing gestational age, fetal heart rate patterns change. The development and maturation of the fetal central nervous system with increasing gestational ages reflect varying FHR patterns. Thus, the definition of a normal FHR pattern in the preterm remains a challenge.

A multi-centered randomized trial compared the use of electronic FHR monitoring versus intermittent auscultation on 246 preterm singleton pregnancies with fetal weights of 700–1750 g and concluded that there were no significant differences in the prevalence of low five-minute Apgar scores, intrapartum acidosis, intracranial hemorrhage, or frequency of cesarean section (P greater than .10) between the two groups. Perinatal or infant death was associated with 14% of pregnancies with electronic FHR monitoring and 15% with auscultation.[7]

Analysis of data from randomized trials comparing these two techniques show no difference in the rate of intrapartum fetal death rate (approximately 0.5 per 1,000 births with either approach) and no difference in Apgar scores and NICU admissions. Neither approach has resulted in a reduction in cerebral palsy or incidence of infant neurologic impairment. However, several advantages of EFM have been demonstrated, including a reduction in neonatal seizures and better prediction of fetal acidemia at birth. The decision to do EFM monitoring in the preterm fetus requires discussion between the obstetrician and neonatologist considering as well the likelihood of severe morbidity of the preterm fetus.[7]

## II. INTERPRETING INTRAPARTUM CARDIOTOCOGRAM AT DIFFERENT GESTATIONS AND TIMING OF INTERVENTION

**QUESTION 2** **Among preterm fetuses at different gestations, how should EFM be interpreted?**

### *24 to 26 Weeks Gestation*

**RECOMMENDATION** Use of EFM necessitates full understanding of the physiology of the fetal autonomic nervous system of this gestational age group. Clinical correlation and cautious interpretation of tracings is warranted.

Baseline FHR in this age group of fetuses is likely to remain at the higher end of normal (between 150–160 beats per minute) due to the unopposed effect of the sympathetic nervous system. Although the baseline FHR is expected to be higher, any rate greater than 160 should be still considered to be tachycardic and possible causes should be investigated such as administration of tocolytics (terbutaline) or chorioamnionitis in cases of preterm prelabor rupture of membranes.[7]

Interpretation of baseline variability and cycling is difficult at this age of gestation because FHR variability may be reduced as a result of impaired development of the parasympathetic component of the autonomic nervous system. Clinical correlation with review of medications is warranted. Medications such as pethidine, magnesium sulfate and even steroids have been associated with reduced fetal heart rate variability. Since variability is an indicator of fetal acid-base balance and absent variability is predictive of cerebral asphyxia, instances where variability is persistently reduced without explanation should be viewed with caution.[1]

Accelerations at this gestation may not be present or may be less frequent with lower amplitude, with a rise of 10 beats from the baseline rather than 15 beats. Therefore, time limits for non-stress testing may be extended up to 90 minutes.[5] Normal accelerations are usually noted after 25 weeks gestation.

Mild FHR variable decelerations are common at this gestation. In the presence of good variability and accelerations, these decelerations should not be considered as indicative of hypoxia, and interventions should be avoided based on this parameter alone.[1,5]

## *26 to 28 Weeks Gestation*

**RECOMMENDATION** Use of EFM necessitates full understanding of the physiology of the fetal autonomic nervous system of this gestational age group. Clinical correlation and cautious interpretation of tracings is warranted.

FHR tracings within this age group show many similarities to the 24–26 weeks cohort. After 27 weeks, the frequency of variable decelerations is markedly reduced and variability begins to rise to normal levels. The frequency of accelerations is also likely to increase.

Interpretation of tracings within this age group still warrants caution. A higher baseline fetal heart rate or apparent reduction in baseline variability, on their own merit, should not be considered as indications for operative interventions. However, a combination of abnormalities or an observed deterioration in the features of the CTG should arouse suspicion of possible hypoxia and acidosis. Timing of intervention should not be based on the tracings alone.

Survival in this group is significantly higher than those between 24–26 weeks. Most tertiary institutions in the Philippines have high survival rates for this age bracket. Since approximately half of those babies who survive may develop long-term neurological or developmental defects, the continuous use of EFM may aid in fetal monitoring during labor.[1]

## 28 to 32 Weeks Gestation

**RECOMMENDATION** Since baseline FHR and variability are comparable to the term fetus, EFM fetal monitoring is recommended for this gestational age group. Clinical correlation and cautious interpretation of tracings is warranted.

Baseline FHR in this cohort decreases from the upper limits to normal range. Baseline variability of greater than 5 beats per minute (bpm) begins to develop. Accelerations become more evident but may not necessarily achieve the 15 beats per minute rise from baseline lasting 15 seconds that is seen in term fetuses. Variable decelarative patterns reduce in number and eventually disappear. The presence of late decelerations likely represents uteroplacental insuffiency. Since acidosis may develop more quickly in the preterm or growth-restricted fetus, one should therefore have a lower threshold for intervention.

Survival dramatically increases beyond 28 weeks as the fetal organs and neurological axis matures. Although the National Institute for Health and Care Excellence (NICE) guidelines on EFM cannot be directly applied to this age group, baseline FHR and variability are often comparable to the term fetus. Hence fetal monitoring is recommended in this gestational group.[1]

## 32 to 34 Weeks Gestation

**RECOMMENDATION** Continuous EFM in this group is recommended. Features of CTG classification into non-reassuring and reassuring according to NICE guidelines and to the three-tier classification system may be applied in this gestational age group.[1]

Baseline FHR and variability are comparable to the term fetus in this cohort and accelerations with amplitude of greater than 15 beats from the baseline are an indicator of fetal well-being. Variable and late decelerations can be classified according to NICE guidelines and appropriate intervention should be taken.

Since the preterm fetus has lower compensatory mechanisms to intrapartum insults and acidosis may develop more quickly, EFM monitoring may be used in identifying intrapartum hypoxia guiding proper timing of intervention.

## SUMMARY

Interpreting EFM tracings in preterm fetuses necessitate an understanding of the physiology of fetal heart rate and the development of the fetal cardiovascular and neurological systems. The ability of preterm fetuses to combat hypoxia may be less than that of a term fetus. Recognition of acidosis in the preterm fetus is vital to fetal survival and outcome. Women with gestations between 24–26 weeks should be counseled on the use of EFM as survival in the group is largely determined by fetal maturity than the mode of delivery.

## III. ADDITIONAL TESTS OF FETAL WELL-BEING IN MONITORING A PRETERM FETUS

| QUESTION 3 | What additional tests of fetal well-being are available for the preterm fetus? |
|---|---|

**RECOMMENDATION** Adjuvants to EFM are fetal scalp blood sampling, fetal pulse oximetry and fetal electrocardiogram (ECG) (ST Analyzer or STAN). These tests have limited use in the preterm fetus and need further research.

Fetal blood sampling involves sampling a small amount of blood from the fetal scalp to measure pH or lactate. This poses potential complications to the preterm fetus which has reduced scalp thickness, immature coagulation system and a wider separation of skull bones.

Fetal pulse oximetry optically measures oxygen concentration in fetal hemoglobin from the fetal head. This method demonstrated no reduction in

operative delivery rates and adverse neonatal outcome and is therefore considered obsolete.

Fetal ECG or STAN, detects fetal ST elevations which reflects glycogenolysis during hypoxic stress. The preterm fetal myocardium has less stored glycogen and increased water content, hence, ST analyzer is not recommended prior to 36 weeks gestation.[1]

## IV. MODE OF DELIVERY OF PRETERM GESTATIONS

| QUESTION 4 | **Is planned immediate cesarean delivery compared to planned vaginal delivery more superior in terms of decreasing neonatal morbidity among preterm babies?** |
|---|---|

**RECOMMENDATION** There is not enough evidence to evaluate the use of a policy of planned immediate cesarean delivery for preterm babies.[2,9]

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

Werner and Savitz et al. studied 2,885 singleton, liveborn vertex neonates between 25 to 34 weeks gestation, their mode of delivery and associated morbidities and concluded that there was no significant difference in intraventricular hemorrhage, subdural hemorrhage, seizure, or sepsis between those delivered via cesarean section and vaginal delivery.[9]

An analysis by Alfirevic, et al., in 2012, involving six studies, concluded that there was no significant difference between planned immediate cesarean section and planned vaginal delivery with respect to birth injury to infant (risk ratio (RR) 0.56, 95%, confidence interval (CI) 0.05–5.62; one trial, 38 women) or birth asphyxia (RR 1.63, 95% CI 0.84–3.14; one trial, 12 women). The

difference between the two groups with regard to perinatal deaths was not significant (0.29, 95% CI 0.07–1.14; three trials, 89 women).[2]

There was also no difference between the cesarean or vaginal delivery groups in terms of markers of possible birth asphyxia (RR 1.63, 95% CI 0.84–3.14; one trial, 12 women) or Apgar score less than seven at five minutes (RR 0.83, 95% CI 0.43–1.60; four trials, 115 women) and no difference in attempts at breastfeeding (RR 1.40, 95% 0.11–17.45; one trial, 12 women).

There was also no difference in neonatal fitting / seizures (RR 0.22, 95% CI 0.01–4.32; three trials, 77 women), hypoxic ischemic encephalopathy (RR 4.00, 95% CI 0.20 to 82.01; one trial, 12 women) or respiratory distress syndrome (RR 0.55, 95% CI 0.27–1.10; three trials, 103 women).

On the maternal side, there was no significant difference between the two groups with regard to postpartum hemorrhage. There was a significant advantage for women in the vaginal delivery group with respect to maternal puerperal pyrexia (RR 2.98, 95% CI 1.18–7.53; three trials, 89 women) and other maternal infection (RR 2.63, 95% CI 1.02–6.78; three trials, 103 women), but no significant differences in wound infection (RR 1.16, 95% CI 0.18–7.70; three trials, 103 women), maternal stay more than 10 days (RR 1.27, 95% CI 0.35–4.65; three trials, 78 women) or the need for blood transfusion.[2]

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Chapter 19

# Preterm Labor in Special Circumstances

Maria Geraldine Assumption Gavina N. Castillo-Torralba, MD,
FPOGS, FPSMFM, FPSUOG

## I. NON-OBSTETRIC ABDOMINAL SURGERY DURING PREGNANCY AND PRETERM DELIVERY

**QUESTION 1** **Among patients who will undergo non-obstetric abdominal operation during pregnancy, is tocolysis needed to prevent preterm labor?**

**RECOMMENDATION** There is no proven benefit in the routine administration of prophylactic preoperative tocolysis to prevent preterm labor in cases of non-obstetric abdominal operation during pregnancy.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

### SUMMARY OF EVIDENCE

Abdominal surgery performed in the antenatal period for non-obstetric reasons occurs in approximately 2% of pregnant women.[1,2] The most common operation in such cases is appendectomy followed by cholecystectomy. There are limited data to base recommendations since it is difficult to conduct randomized trials in these conditions. Manipulation of the uterus during surgery for these procedures, especially during the third trimester, may cause uterine contractions that may lead to preterm labor and delivery. This is the reason for the common practice of administering intravenous tocolytics prior to the scheduled operation. However, there is no proven benefit to prophylactic tocolytics prior, during or after surgery in any age of gestation for appendectomy and cholecystectomy.[3] Tocolysis will be indicated in these cases only if uterine contractions occur.[3] Retrospective studies are limited and conflicting on this topic. Allen et al. conducted a retrospective study (period of 17 years) of pregnant patients who had an abdominal operation at one institution.[4] The most common postoperative complication in this study was

premature labor, which occurred in 19 patients (21%).[4] In 16 of these patients, early tocolytics was started without fetal loss.[4] In contrast to the retrospective study of Hunt et al., tocolysis with intravenous magnesium sulfate had no definite effect on the incidence of preterm delivery among the 57 pregnant patients who underwent non-obstetric abdominal surgery.[5] More studies are needed to assess the indications and limitations of tocolytics for non-obstetric abdominal surgery during pregnancy.

## QUESTION 2

**Among patients who will undergo non-obstetric abdominal surgery during pregnancy, is laparoscopy associated with a higher rate of preterm delivery compared to exploratory laparotomy?**

**RECOMMENDATION** Laparoscopic appendectomy or cholecystectomy during pregnancy is associated with a higher preterm birth rate compared with open exploratory laparotomy. However, it is not clear if this increase resulted from the procedure itself or from other factors related to the disease requiring surgery.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

Many studies report advantages of laparoscopy over laparotomy for non-obstetric abdominal surgery during pregnancy. These include decrease in fetal respiratory depression because there is lesser need for maternal postoperative analgesics, fewer wound infections and less manipulation of the uterus to obtain better visualization.[6-8] Additional advantages of laparoscopy include a shorter hospital stay and decrease risk of thromboembolic events.[9] However, uterine perforation is a major complication of laparoscopy during pregnancy which is likely to occur when the trocar is introduced into the abdominal cavity[10]. There are no RCTs comparing laparoscopy versus open exploratory laparotomy for appendectomy or cholecystectomy during pregnancy. The risk of preterm birth is higher after laparoscopic appendectomy according to one meta-analysis (RR 1.44, 95% CI 0.78–1.76), but significantly lower according to another meta-analysis (2.1% vs. 8.1%, p<0.0001).[11] For cholecystectomy, laparoscopy was associated with a higher preterm birth rate (6 in 89 cases, versus 2 in 69 cases).[11] However, it is difficult to determine in these reports the other

contributory factors (e.g. type of anesthesia or the disease itself) as the actual cause of preterm labor aside from the surgical approach done.

## II. PLACENTA PREVIA

| | |
|---|---|
| **QUESTION 3** | **Should tocolytics be administered to control preterm labor in patients with placenta previa who are bleeding?** |
| **RECOMMENDATION** | The routine use of tocolytics in the management of patients with bleeding placenta previa is not recommended because of the lack of proven benefits and the known risk of possible adverse effects.<br><br>*Quality of Evidence: Moderate to Low*<br>*Strength of Recommendation: Weak* |

### SUMMARY OF EVIDENCE

Placenta previa is an obstetric complication presenting as painless vaginal bleeding in the third trimester because of the abnormal location of the placenta near or covering the internal cervical os. Bleeding in cases of placenta previa may also be triggered by uterine contractions, which may promote placental separation. This has prompted the use of tocolytics to control the preterm labor and therefore to stop the acute bleeding episode with the goal of preventing preterm birth of the fetus. Preterm labor in patients with placenta previa is managed depending on the age of gestation, severity of bleeding and the status of the mother and the fetus. An actively bleeding placenta previa is a potential obstetric emergency. However, if both the patient and the preterm fetus are stable and there is no persistent active bleeding, management favors close observation. There is controversy regarding the role of tocolytics in the setting of hemorrhage due to placenta previa. Tocolytics have been reported to be useful in selected stable cases of previa to prolong the pregnancy to enable further fetal growth and maturation. Limited use of tocolytics even in the setting of bleeding placenta previa is usually done to complete antenatal corticosteroids.[12]

The latest systematic review of Morfaw published in 2018[13] evaluated the use of tocolytics in pregnant patients with symptomatic bleeding placenta previa. It

showed no significant effect on prolongation of pregnancy and other maternal and neonatal outcomes. In this review, there was no significant difference in pregnancy prolongation with the use of tocolytics in cases of bleeding placenta previa (mean difference [MD] 11.51 days; 95% CI, – 1.75, 24.76; 3 trials, 253 participants; low certainty evidence). Tocolytic agents had no significant effect on gestational age at delivery (MD 0.33 weeks [95% CI – 1.53, 2.19]: 2 trials, 169 participants, moderate certainty evidence), birth weight (MD 0.12 kg [95% CI – 0.26, 0.5 kg]: 2 trials, 169 participants, moderate certainty evidence), risk of premature delivery (risk ratio [RR] 1.04; 95% CI 0.56, 1.94): 2 trials, 169 participants, low certainty evidence), risk of repeat vaginal bleeding (RR 1.05 [95% CI 0.73, 1.51]: 2 trials, 169 participants, moderate certainty evidence). Tocolytics had no significant effect on the risk of perinatal death (risk difference [RD]: 0.00 [95% CI – 0.04, 0.03]: 2 trials, 169 women; low certainty evidence), number of days of maternal hospitalization (MD 0.60 days [95% CI – 0.79, 1.99]: 1 trial, 109 women; low certainty evidence), risk of fetal admissions into neonatology (RR 1.30 [95% CI 0.80, 2.12]: 1 trial, 109 participants, low certainty evidence) and on the duration of stay in neonatology units (MD 0.70 days [95% CI -5.26, 6.66]: 1 trial, 109 participants, low certainty evidence). [13] The cautious use of tocolytics in cases of bleeding placenta previa as recommended by the Royal College of Obstetricians and Gynaecologists (RCOG) should be reconsidered.[12] There is not enough evidence to recommend routine tocolytic use for this indication.

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Chapter 20

# Periviable Birth: An Obstetrical Perspective

Leslie R. Rigor, MD, FPOGS, FPSMFM, FPSUOG

Approximately 0.5% of all births occur before the third trimester. Majority of neonatal deaths and more than 40% of infant deaths result from these very early deliveries. Families and health care teams are confronted with complex and ethically challenging decisions when delivery is anticipated near the limit of viability. ***Periviable birth*** is delivery occurring from 20 0/7 weeks to 25 6/7 weeks of gestations.

Accurate pregnancy dating is of great importance in the periviable period. The best estimate of age of gestation (AOG) should be used for counseling and decision-making.

Obstetric interventions considered in pregnant women at risk of periviable delivery include treatments to delay delivery and efforts to improve newborn outcome should delivery be inevitable. Specific circumstances dictate the treatment / interventions.

## I. ANTENATAL CORTICOSTEROIDS (ACS)

| QUESTION 1 | **Among pregnant women at high risk of threatened and periviable birth, is antenatal corticosteroid therapy compared with no therapy, effective in reducing adverse newborn outcome?** |
|---|---|

**RECOMMENDATIONS**

- Antenatal corticosteroid therapy is recommended for gestational ages 24 0/7 to 25 6/7 weeks.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- Antenatal corticosteroid therapy may be considered in gestational ages 23 0/7 to 23 6/7 weeks.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Weak*

- Antenatal corticosteroid therapy is not recommended for gestational ages 20 0/7 weeks to 21 6/7 weeks and 22 0/7 weeks to 22 6/7 weeks.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

### A. Antenatal Corticosteroids Versus Placebo or No Treatment (22 to 25 weeks Age of Gestation) [1]

This is a prospective multicenter cohort study of 10,541 infants born at 22 to 25 weeks AOG in the USA. The primary outcomes were effect on death or childhood neurodevelopment impairment. The results showed:

- Hospital deaths were significantly lower in exposed infant born at 23 weeks (adjusted odds ratio [aOR] 0.49; 95% confidence interval [CI] 6.39–0.61), 24 weeks (aOR 0.64; 95% CI 0.54–0.76) and 25 weeks (aOR 0.57; 95% CI 0.48–0.69).
- No effect on infants born at 22 weeks as far as hospital deaths is concerned (OR 0.61; 95% CI 0.3–1.07); this may be due to smaller size included in this group.
- Long-term morbidity after 18 to 22 months follow-up
    - Intact survival was higher in steroid exposed infants (35.8% vs. 18.5%, aOR 1.66; 95% CI 1.46–1.90)
    - Death or neurodevelopmental impairment was also significantly less frequent in preterm babies born at 23 to 25 weeks AOG but not those born at 22 weeks.
- The study failed to demonstrate any reduction in chronic lung diseases or bronchopulmonary dysplasia.
- Subgroup analyses demonstrated that the effect was significant in all subgroups except small-for-gestational age (SGA) infants and mother with hypertension and pre-eclampsia.

### B. Antenatal Corticosteroids for Neonates Born Before 25 weeks – A Systematic Review & Meta-analysis

A meta-analysis published by Deshmukh[2] in 2017 assessed neonatal outcomes after antenatal corticosteroid administration. Eight (8) high-quality non-randomized controlled trials (RCT) were reviewed. No RCTs were included. The

meta-analysis concluded that exposure to antenatal corticosteroids is associated with a decrease in mortality and intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) in neonates born before 25 weeks (moderate to low quality evidence). The following were the results:

- Decrease in mortality among infants given steroids
  (N = 10,109; OR 0.47 (0.39–0.56) p< 0.00001)
  Level of Evidence: Moderate
- Decrease in severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) in neonates born <25 weeks but given steroids
  (N = 5,084; OR 0.71 (0.61 – 0.82) p< 0.00001)
  Level of Evidence: Low
- No significant difference in chronic lung disease
  (N = 4,649; OR 1.19 (0.85 – 1.65) p>0.31)
  Level of Evidence: Low
- No significant difference in necrotizing enterocolitis (NEC)
  (N=5,403; OR 0.95 (0.76 – 1.19) p≥0.65)
  Level of Evidence: Low
- Mortality was comparable in neonates born at 22, 23 or 24 weeks

C. **Large Cohort Study – Neonates Network of Japan**[3]

The study reviewed 11,607 preterm births from 87 tertiary care center (those delivering in the periviable period). The results showed:

- Antenatal corticosteroids significantly improved fetal survival and reduced the frequency of severe intraventricular hemorrhage
- Although ACS treatment was effective in decreasing respiratory distress syndrome, surfactant use, and duration of O2 use in preterm infants born between 24 and 29 weeks of gestation, it was not as effective in the 22- to 23-week group.
- ACS treatment was extremely effective at decreasing both IVH and severe IVH in preterm infants at the gestational age of 24 to 29 weeks but not in infants born at <24 weeks of gestation.
- There were no improvements in chronic lung disease, patent ductus arteriosus and necrotizing enterocolitis

## D. Effect of Antenatal Corticosteroids Given Prior to 26 Weeks Age of Gestation – A Systematic Review of Randomized Controlled Trials

In 2011, Onland et al. [4] performed a systematic review to determine the effects of administration of corticosteroids to women at risk of preterm birth <26 weeks AOG. Nine randomized trials were included. Interestingly, this meta-analysis revealed no significant reduction of neonatal mortality and morbidity in the corticosteroid group as compared with nonintervention. This is in stark contrast to the results of most studies in the existing literature that support the beneficial effects of corticosteroids on improving neonatal outcomes.

Onland's article further discussed that their conclusion should be interpreted with caution, as the apparent lack of beneficial effect of steroids on the neonatal outcome may be because the analyses are underpowered. The trials included in their review included a small population compared with existing literature.

## II. TOCOLYTICS FOR PRETERM LABOR TO ALLOW CORTICOSTEROID ADMINISTRATION

| | |
|---|---|
| **QUESTION 2** | **Among pregnant women at risk of threatened and imminent periviable birth, is the use of tocolytic agents compared with no tocolytic agents, effective in delaying preterm birth to allow for antenatal corticosteroid administration and reducing adverse newborn outcome? If so, which population of pregnant women should be offered tocolytics considering gestational age at presentation or birth interval between presentation and anticipated birth?**<br><br>**Which population of pregnant women should not be offered tocolytics?** |
| **RECOMMENDATIONS** | • Tocolytic therapy is recommended for gestational ages 24 0/7 to 25 6/7 weeks.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

- Tocolytic therapy may be considered in gestational ages 23 0/7 to 23 6/7 weeks.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Weak*

- Tocolytic therapy is not recommended for gestational ages 20 0/7 weeks to 21 6/7 weeks and 22 0/7 weeks to 22 6/7 weeks.

  *Quality of Evidence: High*
  *Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

- No studies on women with preterm labor or preterm prelabor rupture of membranes at 20–25 weeks of gestation
- Compared with placebo, tocolytics are not associated with a reduction in neonatal mortality (Level of evidence 2, moderate quality)
- All tocolytic treatment should be prescribed for 48 hour (Grade B, moderate quality)
- There is no scientific evidence to propose tocolysis with advanced dilatation (Grade C) or prescribe tocolysis after 34 weeks.
- There is no evidence to define a gestational age lower limit for tocolysis (Professional Conference)
- Tocolysis is not recommended before 24 weeks but may be considered based on individual circumstances at 23 weeks.

## III. MAGNESIUM SULFATE FOR FETAL NEUROPROTECTION

| QUESTION 3 | **Among pregnant women at risk for threatened or imminent periviable birth, is magnesium sulfate therapy, compared with no therapy, effective for neuroprotection?** |
|---|---|

**RECOMMENDATIONS**

- The use of magnesium sulfate for fetal neuroprotection is recommended for women at risk for threatened and periviable birth at

gestational ages 24 0/7 to 24 6/7 weeks and 25 0/7 to 25 6/7 weeks.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

- The use of magnesium sulfate for fetal neuroprotection may be considered in women at risk for threatened and periviable birth at gestational ages 23 0/7 to 23 6/7 weeks.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Weak*

- The use of magnesium sulfate for fetal neuroprotection is not recommended for gestational ages 20 0/7 weeks to 21 6/7 weeks and 22 0/7 weeks to 22 6/7 weeks

  *Quality of Evidence: High*
  *Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

In 2008, Rouse [5] conducted a multicenter trial that involved 2,241 women at imminent risk for delivery before 32 weeks. The women were randomized to receive either magnesium sulfate or placebo. The primary outcome was the total stillbirths or infant death by 1 year or moderate to severe cerebral palsy (CP) at or beyond 2 years.

- The study showed that there was no significant decrease in the primary outcome
- There was note of decrease in moderate to severe CP in the magnesium sulfate group
- In a secondary analysis, moderate or severe CP occurred significantly less frequently with magnesium sulfate (4.2% vs. 7.3%, P: 0.004)

Doyle,[6,7] in a Cochrane systematic review published in 2009, analyzed the results of five trials involving 6145 babies. The following were the results:

- Prenatal administration of magnesium sulfate reduced the occurrence of CP when given with neuroprotection intent (relative risk [RR] 0.71; 95% confidence interval [CI] 0.55–0.91).
- Magnesium sulfate reduced the total occurrence of death and CP (Summary RR 0.86; 95% CI, 0.74–0.98).
- There was no effect on fetal and infant death (Summary RR 0.95; 95% CI 0.80–1.12).

The PREMAG trial [8] was a randomized controlled trial that included 564 gravid women (688 infants) before 33 weeks gestation with planned or expected delivery within 24 hours. Women were randomized to magnesium sulfate or placebo. The primary outcome was infant death or severe white matter injury.

- No significant difference in total infant death or severe white matter injury or both between the two groups.
- No statistically significant reduction in CP or death or both
- Demonstrated significant reductions in death or "gross motor dysfunction" or both and death or "motor or cognitive dysfunction" or both with magnesium sulfate

In a multicenter placebo-controlled trial published in 2003 by Crowther,[9] 1,062 women (1,255 infants) in whom delivery was planned or expected within 24 hours at less than 30 weeks AOG were assigned to receive either magnesium sulfate or placebo. The primary outcome was infant death or CP or both by 2 years corrected age.

- No significant reductions in infant deaths or CP or both seen with magnesium sulfate treatment.
- On secondary analysis, there was note of significantly less frequent "substantial gross motor dysfunction".

In 2009, Conde-Agudelo and Romero [10] conducted a systematic review and meta-analysis of six RCTs involving 4,796 women and 5,357 infants to evaluate whether administration of magnesium sulfate among women at risk of preterm delivery before 34 weeks AOG may lower the risk of cerebral palsy in the infants.

- Magnesium sulfate afforded significant reduction in the risk of cerebral palsy (RR 0.69; 95% CI 0.55–0.88), moderate or severe cerebral palsy (RR 0.64; 95% CI 0.44–0.92), and substantial gross motor dysfunction (RR 0.60; 95% CI 0.43–0.83).
- There was no overall difference in the risk of total pediatric mortality (RR 1.01; 95% CI 0.89–1.14).

In 2015, the World Health Organization (WHO) [11] published a guideline entitled "WHO Recommendations on Interventions to Improve Preterm Birth

Outcomes". In this article, they enumerated the effects of administration of magnesium sulfate versus no active treatment for fetal neuroprotection.

- Magnesium sulfate vs. no active treatment (all women and babies)
    1. Maternal morbidity and death
        a. No significant differences on maternal mortality or serious morbidity
        b. No significant differences for rates of postpartum hemorrhage, cesarean births or length of maternal hospital stay
    2. Infant outcome
        a. No significant difference for overall infant mortality
        b. No significant differences with regard to intraventricular hemorrhage (IVH) periventricular leukomalacia, major or any neurological impairment, blindness, deafness, developmental delay, or intellectual impairment.
        c. No significant differences for neonatal convulsions, neonatal hypotonia, or requirement for ongoing respiratory support (although there was a trend towards reduced risk in magnesium sulfate group)
        d. Infants exposed to magnesium sulfate were at reduced risk (39%) of substantial gross motor dysfunction (RR 0.61; 95% CI, 0.44-0.85, 5 studies 6,039 infants).
        e. Risk of cerebral palsy (CP) was significantly reduced (by 30%) in the magnesium sulfate group (RR 0.70; 95% CI 0.55-0.89)

- Magnesium sulfate vs. placebo or no treatment (gestational age at administration)
    - Evidence on magnesium sulfate use at < 30 weeks as opposed to < 34 weeks was not clear
    - CP was reduced in women in magnesium sulfate group at < 34 weeks (RR 0.69, 0.54-0.88; 4 studies, 5,192 women), but not in women randomized at < 30 weeks (RR 0.86, 0.56-1.31; 2 studies 1537 women) although the point estimate favored a reduction in CP with magnesium sulfate use in the population.

- Magnesium sulfate vs. placebo or no treatment (with the intention to prevent preterm birth-related neurologic complications)
    - No significant differences for overall pediatric mortality, fetal death or infant death.

- Composite outcome of death or CP was significantly reduced in the treated group (RR 0.85, 95% CI 0.74–0.98; 4 studies, 4446 infants). The reduction in risk of moderate/severe cerebral palsy in the treated group remained consistent (RR 0.64, 95% CI, 0.44-0.92; 3 studies, 4,837 infants).
- For composite outcome of death or gross motor dysfunction, a trend was observed towards reduction in the magnesium sulfate group (RR 0.84, 95% CI, 0.71-1.00; 3 studies, 4,387 infants).

## IV. INTRAPARTUM ANTIBIOTICS FOR GROUP B STREPTOCOCCI PROPHYLAXIS

| QUESTION 4 | **Among patients in preterm labor, is intrapartum Group B Streptococci (GBS) prophylaxis versus placebo, beneficial in improving neonatal outcomes?** |
|---|---|

**RECOMMENDATIONS**

- Intrapartum GBS prophylaxis is recommended for gestational ages 24 0/7 weeks to 24 6/7 weeks and 25 0/7 weeks to 25 6/7 weeks

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- Intrapartum GBS prophylaxis should be considered at 23 0/7 to 23 6/7 weeks gestational age.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Weak*

- Intrapartum GBS prophylaxis is not recommended for gestational age 20 0/7 weeks to 21 6/7 weeks and 22 0/7 weeks to 22 6/7 weeks.

  *Quality of Evidence: High*
  *Strength of Recommendation: Strong*

**RECOMMENDATION**

Intrapartum prophylaxis or Group B Streptococci (GBS) is indicated in the following clinical situations:

- Previous infant with invasive GBS diseases
- GBS bacteriuria during any trimester of the pregnancy
- (+) GBS vaginal-rectal screening cultures in late gestation during current pregnancy
- Unknown GBS status and any of the following:
  - Delivery at < 37 weeks gestation
  - Ruptured membranes ≥ 18 hours
  - Intrapartum temp ≥ 100.4 F (≥39.0 °C)
  - Intrapartum nucleic acid amplification test positive for GBS

## V. ANTIBIOTICS TO PROLONG LATENCY DURING EXPECTANT MANAGEMENT OF PRETERM PRELABOR RUPTURE OF MEMBRANES, IF DELIVERY IS NOT CONSIDERED IMMINENT

**QUESTION 5**

Among pregnant patients with preterm prelabor rupture of membranes (PPROM) whose delivery is not imminent, is routine antibiotic prophylaxis, compared with no antibiotic prophylaxis, effective in improving maternal and newborn outcomes?

**RECOMMENDATIONS**

- The use of antibiotics to prolong latency is recommended for gestational ages 24 0/7 weeks to 24 6/7 weeks and 25 0/7 weeks to 25 6/7 weeks

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- The use of antibiotics to prolong latency may be considered at 23 0/7 to 23 6/7 weeks gestational age.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Weak*

- The use of antibiotics to prolong latency may be considered at gestational ages 20 0/7 weeks to 21 6/7 weeks and 22 0/7 weeks to 22 6/7 weeks.

  *Quality of Evidence: Low*
  *Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

- A Cochrane systematic review published by Kenyon [12] in 2013 analyzed 22 trials that involved a total of 6,872 women and babies. It showed that the use of antibiotics following preterm rupture of membranes showed statistically significant reduction in
  - chorioamnionitis (Average risk ratio [RR] 0.66; 95% CI 0.46–0.96)
  - number of babies born within 48 hours (Average RR 0.71; 95% CI 0.58–0.87) and 7 days of randomization ( Average RR 0.79; 95% CI 0.71–0.89)
  - neonatal infection (RR 0.67; 95% CI 0.52–0.85)
  - oxygen therapy (RR 0.88; 95% CI 0.81–0.96)
  - abnormal cerebral ultrasound prior to discharge (RR 0.81; 95% CI 0.68–0.98)

  Co-amoxiclav was associated with increased incidence of necrotizing enterocolitis (RR 4.7; 95% CI 1.57–14.23)
- The ORACLE Children Study (Kenyon) [13] stated the routine prescription of antibiotics to women with PPROM is associated with prolongation of pregnancy and improvements in a number of short term neonatal morbidities. There was no significant effect on perinatal morbidity.
- Maternal-Fetal Medicine Units Network Multicenter trial demonstrated reduction in neonatal morbidity and mortality. A decrease in respiratory distress syndrome (RDS), NEC, IVH and early-onset sepsis was also noted. [14, 15]
- Most trials described a statistically significant prolongation of latency period but generally did not show an improvement of neonatal outcome

## VI. CESAREAN DELIVERY FOR FETAL INDICATION

**QUESTION 6** **Among pregnant women at risk of threatened and periviable birth, is caesarean delivery for fetal indications able to improve neonatal outcome compared to vaginal delivery?**

**RECOMMENDATIONS**

- Cesarean section for fetal indication to prolong latency is recommended for gestational ages 25 0/7 weeks to 25 6/7 weeks.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- Cesarean section for fetal indication should be considered at 24 0/7 to 24 6/7 weeks gestation.

  *Quality of Evidence: High*
  *Strength of Recommendation: Strong*

- Cesarean section for fetal indication should be considered at 23 0/7 to 23 6/7 weeks gestation.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- Cesarean section for fetal indication is not recommended at 20 0/7 to 21 6/7 weeks and 22 0/7 and 22 6/7 weeks.

  *Quality of Evidence: High*
  *Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

- In a systematic review and meta-analysis conducted by Hannaford [16] in 2017, the authors evaluated survival after periviable birth based on the mode of delivery. Included in the review were women with singleton

pregnancies from 22 0/7 to 24 6/7 weeks, where neonatal resuscitation was desired. Anomalous fetuses were excluded. The following were the results:

- Six (6) studies, which covered 1990-2013, were included in the final analysis.
- Of the 2,564 deliveries, 1,115 delivered vaginally and 1,433 by cesarean section (CS). The CS rate was 56% while vaginal delivery rate was 44%.
- Over-all mortality rate was not significantly different with CS compared with vaginal delivery (vaginal delivery 41% vs. CS 63% [pooled RR 0.97; 95% CI 0.66–1.41])
- Evidence from this study did not suggest a survival benefit of CS during the periviable period.

- In 2012, Alfirevic et al. [17] assessed the effects of planned immediate cesarean delivery versus planned vaginal birth for women in preterm labor. The systematic review, which was published in Cochrane, included four studies (116 women) for data analysis. The following were the results:
  - No significant difference with respect to birth injury to infant (RR 0.56; 95% CI 0.05–5.62) or birth asphyxia (RR 1.63; 95% CI 0.84–3.14)
  - No significant differences in perinatal deaths (RR 0.29; 95% CI 0.07–1.14)
  - No difference in APGAR score of <7 at 5 minutes (RR 1.63; 95% CI 0.84–3.14)
  - There were 7 cases of major maternal postpartum complications in the cesarean delivery group
  - Less maternal pyrexia in the vaginal delivery group (RR 2.98, 95% CI 1.18-7.53; three trials, 89 women) and other maternal infection (RR 2.63, 95% CI 1.02-6.78; three trials, 103 women) but no significant difference in wound infection (RR 1.16, 95% CI 0.18-7.70; three trials, 103 women)

- A systematic review [18] that looked into the effects of elective cesarean section versus expectant management as the mode of delivery of small babies was published in 2001. Six RCTs were included, 3 involved fetuses with cephalic presentation and 3 in breech presentation. The studies involved a total of 122 subjects.
  - There were 8 neonatal deaths reported in the review. Of these, 2 underwent CS and 6 underwent expectant management. The difference was not statistically significant.
  - There were 8 women who suffered major complications after CS.

- Elective CS may have some benefits for babies, but this has to be weighed against the increased risks to the mother with complications related to surgery.
- The systematic review concluded that there is not enough evidence to evaluate the use of a policy for elective caesarean delivery for small babies.

- A retrospective study that evaluated neonatal outcomes with respect to mode of delivery was presented during the American College of Obstetricians and Gynecologists (ACOG) 59th Annual Meeting held in 2010.[19] The researchers compared outcomes that included neonatal deaths, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), respiratory distress syndrome, and clinical sepsis in 52 infants delivered by cesarean section and 74 delivered vaginally. The study concluded that the mode of delivery does not provide any significant advantage in decreasing infant morbidity and mortality.
- Published literature for CS in the periviable period is limited by lack of data adequate enough to reflect causes, interventions and contribution of current practices on outcomes.
- RCTs of adequate size have not been performed.
- Current available data do not consistently support routine CS to improve perinatal mortality rates or neurologic outcomes for early preterm infants.
- Data suggesting improved outcomes with CS for malpresentation are limited.
- CS in the periviable period results in greater maternal morbidity both immediately and post-operatively for future pregnancies.

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Chapter 21

# Periviable Birth: A Neonatal Perspective

Belen Amparo E. Velasco, MD, MHSA, FPPS, FPSNbM

Globally, an estimated 14.8 million babies are born preterm yearly. 96.5% percent of these preterm babies are from developing countries. The countries of Bangladesh, China, India, Indonesia and Nigeria accounted for 6.6 million (44.6%) of preterm births in 2014. 5.2% of these preterm babies were extremely premature (less than 28 weeks). Based on predictions from 183 countries, this translates to a worldwide preterm birth rate of 10.6% (range of 5 to 18%).[1,2]

As of 2014, the estimated preterm birth rate in the Philippines is 13.27%.[3] In terms of number of preterm births, the Philippines ranked eighth among 184 countries. This is worrisome because of reports that one million of these preterm succumb each year due to complications of prematurity.[2,4] Developing countries, including the Philippines, lack data addressing the birth of the periviable infant. In the 1940s, a 24-week gestation or a 500 gram-baby is presumed to die and is only afforded comfort care.[5,6]

The question now is where we are at present in the Philippines. Who are the infants at age of viability in the Philippine setting? How do they fare with the limited resources in most of our birthing facilities? Determining the age of viability in the Philippines is challenging but is desirable so that our clinicians can render appropriate measures for these infants who can or cannot survive with a fair quality of life.

The main objective is to come up with recommendations on the standard of care for periviable infants in the Philippines.

Specific objectives include:

1. To determine the standard of care of periviable infants in high-income countries (HIC) and low to middle-income countries (LMIC) based on existing meta-analysis and systematic reviews.
2. To determine the survival rate of the periviable infant (the extremely premature and very premature infants) in Neonatal Intensive Care Units (NICU) in the Philippines
3. To determine the NICU practices in the Philippines on care of the periviable infants.
4. To update policy makers of civil societies like the Philippine Society of Newborn Medicine (PSNbM) and of the government in formulating

more feasible and practical guidelines appropriate for the Filipino periviable infant.

## DEFINITION OF PERIVIABLE BIRTH (LIMIT OF VIABILITY)

In 2017, the American College of Obstetricians and Gynecologists (ACOG), Society for Maternal-Fetal Medicine (SMFM), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) and the Perinatal Pediatrics Section of the American Academy of Pediatrics (AAP) jointly issued an updated consensus regarding periviability from **20 weeks to 26 weeks** at about 500 grams and provided recommendations regarding 'individualized compassionate care.'[8-16] The Eunice Kennedy Shriver NICHD NRN Outcome Data Calculator for a 24-week infant weighing 500 grams would show a survival rate of 45% (50% if ventilated) and survival without profound neurologic impairment of 33% (37% if ventilated).[12]

The viability limit in Japan 'based on medical data is currently at 22 completed weeks (from 24 weeks)' while the 'social consensus is about 24 to 28 weeks gestation.'[17] In Hong Kong, the minimum age of viability is 21 to 22 weeks gestation; with sporadic reports of survivors at 21 to 22 weeksgestation.[4, 15,18] Park reviewed viability in South Korea at 23 to 26 weeks gestation.[19] In Nigeria, a lower middle-income country with the third highest number of preterm births and neonatal deaths, the legal age of viability is 28 weeks although there are already survivors with 24 to 28 weeks gestation.[20,21,22]

Glass in 2018[23] referred to viability as the 'gestational age during which time there is **50% chance of survival,**' with or without medical intervention. With great variation due to differences in technological and human resources, the standard viability limit **for high-income countries (HIC)** is **22 to 24 weeks weighing 500 grams** and **for low- to middle-income countries (LMIC)** is **28 weeks and weighing 800 grams.**[24] The World Health Organization (WHO) has reduced the limit to 24 weeks among developing countries, recognizing the immense improvement of their NICU technology and manpower. In recent years, the United Kingdom and the United States followed Japan in reducing the limit to 22 weeks and 20 weeks, respectively.[22]

The **'gray zone'** of infant viability, where the outcome was described as very unpredictable, aptly referred to babies 'delivered between 23 0/7 and 24 6/7 weeks gestation and with a birth weight of 500 to 599 grams in several countries in Europe and North America.[25,26,27] No gray zone has been described for LMICs.

**QUESTION 1** **What is the standard of care recommended for infants 22 to 28 weeks gestation — comfort care or full resuscitation (intubation, ventilation, inotropic support, surfactant) worldwide?**

**RECOMMENDATION** For infants with confirmed <23 weeks gestation and/or birth weight <400 grams, non-initiation of resuscitation is ethical. Palliative comfort care (NCC) is strongly recommended.

*Quality of Evidence: High*
*Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

Presuming the baby is born alive, assessed at 22 weeks with weight of 390 grams, singleton, female, and received antenatal steroids, the probability of survival based on the NICHD NRN Outcome Data Calculator is only 5% and, if ventilated, 17%.[11] Palliative comfort care is best for this baby.

Compassionate, palliative comfort care (NCC) refers to 'non-intervention' or non-resuscitation' of the newborn at the delivery room (DR) with provision of warmth, human touch and, ethically, pain medications. All born babies are dried and swaddled in warm clothing. The family members, particularly the mother, if feasible, are encouraged to cuddle their baby. After about 30 minutes of stay in the DR, the baby may be brought to the NICU for provision of comfort to the baby. This will also give 'respectful support' to the family after antenatal conference with them. NCC is indicated[74] in newborns with the following conditions with poor prognosis: babies born extremely prematurely (<23 weeks), babies with lethal congenital anomalies (trisomy 13 or 18, anencephaly), and babies where parents decided for palliative care (like in cases of severe asphyxia). The decision to provide NCC is primarily based on medical factors (such as medical condition at birth, major congenital anomalies, probability of death or future disability)[74-79] although socio-demographic (economic status of the family, technical and resources of the hospital) and religious influences are considered.[74,75] Arzuaga in 2014[77] noted that the most important factor in decision-making for the neonatal team is 'parental wish.'

Garten (2019)[80] delineated the psychological and physical distress of the dying infant which should be addressed with the combination of non-pharmacologic

and pharmacologic measures. Non-pharmacological strategies include behavioral (swaddling and tucking) and physical (kangaroo care, non-nutritive sucking) approach. Sucrose may be given per orem for analgesia. In the absence of vascular access, opioids and benzodiazepines may be given in the simplest, safest, and least unpleasant way through the oral, intranasal and rectal route at a dose of 0.1 to 0.2 mg/kg every 3 to 4 hours. Morphine may be given at a dose of 0.05 to 0.1mg/kg every 3 to 6 hours intravenous or subcutaneous. Midazolam may be given as an alternative at a dose of 0.05 to 0.1mg/kg every 2 to 4 hours intravenous or subcutaneous. Oral analgesics (paracetamol) are not proven efficacious.

Durrmeyer (2017)[81] reported that the administration of comfort medicine was often done in infants with gasping ($p<0.001$). Gasping is a physiologic brainstem reflex due to asphyxia, characterized by a severe brain injury with a flat electroencephalogram (EEG) tracing. His study, with administration of comfort medicines in 35/73 babies, recommended more studies on their use.[81]

Cummings (2015)[82] affirmed that NCC should be the course of action in decisions not to resuscitate the newborn. He underscored the need to encourage families to 'spend time' with the 'dying' baby and to extend religious, psychosocial, cultural and compassionate support.

Guimaraes (2012)[83] described the end-of-life decision-making for the periviable infant with poor prognosis as truly 'challenging.' The medical team has to respect the 'right to life with dignity' of the baby even with physical and mental immaturity. A compassionate family-centered NCC should therefore be accorded to the babies and their families.

In 2008, Pignotti[84] presented 15 documents from obstetric and neonatology societies from various HICs like Canada, the United States, the United Kingdom, Germany, France, Singapore, Spain, Switzerland, the Netherlands, Australia and New Zealand which emphasized 'compassionate, comfort or palliative care' (NCC) which was recommended by the International Liaison Committee on Resuscitation.[85]

The discourse of Mercurio (2019)[9] and the reviews of Rysavy (2015), Guillén (2015), Stanak (2017) and Patel (2017)[11,28,39,66] cited the Comfort Care (CC) stand of HICs like Argentina, Australia, Belgium, Canada, France, Ireland, the Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, the United Kingdom and the United States. Stanak (2017)[11] and Zeitlin (2013)[16] described comfort care for the 22-week infant in Austria and other German speaking countries, based on the consensus guidelines of the Austrian Society of Pediatrics and

Adolescent Medicine and guidelines of the other German-speaking countries. Across other HICs in Asia like Taiwan,[37] Hong Kong[18] and Singapore,[86] there is an agreement for compassionate care below the age of viability as long as the gestational age is confirmed. Nguyen (2013)[86] further reported that the Singapore Ministry of Health stipulated that physicians 'should not be forced to under-treat or over-treat an infant.'

At 22 0/7 to 6/7 weeks (<23 weeks), there is 'near zero' survivor in HICs in Europe, North and South America, and Asia except in the United States, the United Kingdom, Sweden, Japan and Hong Kong. Since countries and scientific organizations base their official guidelines (GLs) on their country's survival rates per gestational age, there is no country that recommends active care for the <22 weekers, except Japan, Sweden and the United States.

Wyckoff (2015)[13] underscored the statement of the American Heart Association (AHA) recommending ONLY comfort care and NOT aggressive resuscitation to babies with less than 22 weeks gestation.[13]

The Philippines, a lower middle-income country,[87] is grouped with El Salvador, India, Indonesia, Nicaragua, Nigeria and Suriname. Whereas Nigeria, for example, still has the legal age of fetal viability at 28 weeks, there were clamors to redefine this especially with good survivors of infants 24 to 28 weeks.[20,21] Similar to 'scaling up' of the NICU II to Level III done in Ghana, India, and Nicaragua, Suriname[88] had statistically significant reduction of mortality among its low birth weight babies though not of its very low birth weight (VLBW) infants. The incidence of late-onset sepsis (38.8%) and necrotizing enterocolitis (NEC) (12.5%), however, remained unchanged. Full resuscitation is done on the VLBW and less than 28-week infants.

The Philippines, as defined in the Standards of Newborn Care 2017 and the Administrative Manual 2019 of the Philippine Society of Newborn Society,[89,90] recommends non-initiation of resuscitation for <23 weeks gestation and <400 grams. The Society adopted the set guidelines of the AHA and the AAP which recommended that resuscitation should be withheld <23 weeks, that is, family-centered comfort care to babies with 22 weeks gestation.

In 2016, the AAP Neonatal Resuscitation Programme[91] redefined its guidelines because of better survival observed in Japan, Sweden, the United Kingdom and the United States. It recommended that resuscitation should be withheld down to <22 weeks. Currently, the United Kingdom and the United States followed Japan in reducing the limit to 22 weeks and 20 weeks, respectively.[21]

## RECOMMENDATIONS

- For infants born in the gray zone or 23 0/7 to 24 6/7 weeks gestation (borderline viability), three options are adopted with greater involvement of the parents. These options are:
    1. No recommended intervention (NR)
    2. Individualized care (IC)
    3. Parental wish (PW)

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- Where parental wish is unknown or uncertain, initiation of life-sustaining treatment (LST) is carried out until further discussion with family.

  *Quality of Evidence: Low*
  *Strength of Recommendation: Strong*

- Where the gestational age is uncertain and not confirmed, initiation of life-sustaining treatment (LST) is appropriate until such time the clinical situation dictates that the treatment be continued or not or parental request is signified.

  *Quality of Evidence: Low*
  *Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Decision-making at this time is cumbersome and complicated. Charafeddine (2014)[92] reported the regard of physicians for babies ≤25 weeks and ≤800 grams as 'non-viable.' Thorough analysis of the infant is vital — his prenatal history, genetic factors, age of gestation, birth weight, clinical condition upon delivery and response to resuscitative measures — which should be extensively discussed with the parents. In this zone, the parental wish usually takes the upper hand.[19, 20]

At 23 weeks gestation, the countries of Australia, France, the Netherlands, Poland, Portugal and Switzerland still recommended palliative comfort care. Guillén (2015), Hawlik (2017) and Stanak (2017) identified the different interventions (no recommended intervention, individualized care or parental wish) of the other HICs in Europe (Austria, Ireland, Italy, Sweden, the United Kingdom), North and South America (Argentina, Canada, the United States) and Asia-Oceania (Australia, Japan, New Zealand, Singapore).[11,38,39]

A 2010 European survey of Gallagher[93] reviewed national guidelines of resuscitation for infants born at 22 to 25 weeks GA and found 'little consensus' on how care is managed.

**RECOMMENDATIONS**

- In infants beyond the age of viability, 25 weeks and/or 500 grams weight for the Level III/IV NICU in the Philippines, and 28 weeks and/or 1000 grams weight for the Level II NICU in the Philippines, pro-active care is obligatory. In the Philippine setting, full resuscitation is initiated depending on the status of the infant and availability of the technological equipment (mechanical ventilator / Continuous positive airway pressure [CPAP]), medicines (surfactant, inotropes) and personnel (competent neonatal team) in level III NICUs.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- Institute the following measures, as warranted.
  1. Provide thermoregulation using either incubator or radiant warmer
  2. Start oxygen at 30% when there is no oxygen blender
  3. Provide positive pressure ventilation: hook to nasal CPAP or mechanical ventilator as needed

  *Quality of Evidence: Low*
  *Strength of Recommendation: Strong*

- If the heart rate remains zero after ten minutes of effective resuscitation, life-saving treatment is best stopped.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- The decision to continue or discontinue resuscitative measures depends on the prior conference between the neonatologist and the parents and the response of the infant to the LST.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- In the event of a pregnant mother in a NICU II center about to deliver a ≤32 weeks baby or a mother pregnant in a Level I facility with a ≤35 weeks baby, maternal transport to a higher level of care is recommended.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

- For infants with major congenital anomalies (anencephaly, hydrops fetalis, trisomy 18) not compatible with life (with almost certain death or severe morbidity) life-saving treatment is not given.

  *Quality of Evidence: Moderate*
  *Strength of Recommendation: Strong*

**SUMMARY OF EVIDENCE**

Proactive perinatal care means provision of a 'high intensity of care' that includes intubation, chest compression, inotropic support, and admission to the NICU for mechanical ventilation and surfactant.[94] In the Philippines, newborn resuscitation follows the guidelines of the Newborn Resuscitation Program of the AAP[91] and the WHO[95-97], and more recently in 2018, the Newborn

Resuscitation Philippines Plus (NRPh+) of the Philippine Society of Newborn Medicine (PSNbM).[98]

Seri (2008)[25] opined that the 25-week infants usually weighing 500 grams are developed enough to sustain the rigors of resuscitation and NICU admission. At least 50% of them survive without severe morbidity and neurologic impairment. The NICHD NRN Outcome Data Calculator shows a likelihood of survival of 58% and, if ventilated, 62%.[12]

In Sweden, Japan, Germany, the United Kingdom and the United States, full resuscitation is commonly administered from 22 weeks gestational age. According to Guillén (2015)[39], Stanak (2017)[11], Patel (2017)[66] and Mercurio (2019)[9], there is an agreement among highly developed countries to initiate active care in infants ≥25 weeks. The study of Goodman (2002)[67] compared hospitals in Sweden, those rendering a high-intensity of active treatment at 22 to 24 weeks of gestation (activity score 96 to 100) against those offering a low intensity of active treatment (activity score 74 to 80). The survival rate of the former (71%) with high-intensity care is higher than that (41%) of the latter.

The Japanese Motherhood Protection Act was amended to reset the age of viability from 24 to 22 completed weeks of gestation based on the survival rate of the preterm infants (2002 to 2004) of 31% and 56% at 22 and 23 weeks gestation, respectively. Thus, full resuscitation of newborn starts at 22 weeks in Japan.[99]

Hospitals across the Philippines differ in their interventions due to hierarchal classifications of NICU levels owing to availability of technological and human resources more in Level III/IV NICUs than in Level II NICUs. A district hospital with a Level I NICU would do comfort care to a <25 week infant or even refer to a Level III NICU while a tertiary center with a Level III/IV NICU will render full resuscitation and NICU admission. The classification of NICU levels are adopted from US standards,[90] and are recently reviewed by the PSNbM for classification of the Philippine Pediatric Society (PPS) accredited hospitals.[100]

1. **Level I NICUs** (provision of basic uncomplicated neonatal care) have meager resources to do active care for infants ≤35 weeks and/or with weight ≤2,000 grams who remain physiologically unstable. These NICUs stabilize the infants, regardless of gestational age and birth weight, who are clinically ill until transfer to a higher level of care. Most would just have one or no ventilator with no readily available surfactant, inotrope and competent neonatal team.

2. **Level II NICUs** (provision of care for moderately ill infants) adopt proactive care for babies ≥32 weeks gestation and with birth weight ≥1,500 grams. However, the unavailability of enough ventilators/CPAP and surfactant restrict their capability. At most, these NICUs stabilize infants born ≤32 weeks of gestation and/or with weight ≤1,500 grams until transfer to a Level III NICU.

3. **Level III NICUs** (provision of care for serious neonatal illnesses, abnormalities and VLBW infants) provide full resuscitation to infants born ≤32 weeks of gestation and/or with weight ≤1,500 grams due to availability of technical equipments (ventilator, CPAP, arterial blood gas machine, incubator, radiant warmer), laboratory and radiologic procedures, medicines (surfactant, inotropes and blood products) and the neonatal team (neonatologist, nurse, respiratory therapist)round-the-clock. These NICUs have full access to all pediatric subspecialties.

4. **Level IV NICUs** (provision of surgical repair of major operable congenital anomalies) have access to a full range of pediatric medical and surgical subspecialties and procedures including ECMO and high frequency ventilation.

Table 1 shows the survival rate of the extremely premature (24 to 27 weeks) and the very premature (28 to 31 weeks) in Philippine NICUs. In both Level II and Level III NICUs, there was almost no survival for ≤23-week infants, except for one, primarily because only comfort care was afforded. In Level III NICUs, the survival rate ranged from 0 to 57% at 24 to 27 weeks and ranged from 41 to 100% at 28 to 31 weeks, the highest survival being in the private facilities. In Level II NICUs, the survival rate ranged from 0 to 100% at 24 to 27 weeks, and from 30 to 100% at 28 to 31 weeks. Note the 100% survival occurred in private hospitals with Level II and III NICUs.

Reality check on the unavailability of equipment hinders full resuscitation in some of these NICUs. This overview guides the neonatal teams in their respective NICUs to recommend palliative comfort care at 23 weeks during antenatal family conference or birth planning.

Inasmuch as survival rate of the extremely preterm infant (EPI) (24 to 27 weeks) was ≤57% with average survival rate of 30% and 22% in public Level III and Level II NICUs, respectively, there is a need for review of the conduct of neonatal resuscitation and monitoring of these infants less than 28 weeks. Level III NICUs may review the round-the-clock availability and functionality of resources

(equipment and NICU personnel) to fulfill the required equipment to patient and nurse to patient ratios. Level II NICUs may choose the best option for their neonatal center, whether to adopt maternal transport, transfer of stabilized infant to a higher level of care or 'scaling up' of intensive care in terms of equipment, NICU personnel and access to subspecialty services. With a survival rate of the very preterm infant (VPI) (28 to 31 weeks) averaged at 56% for Level II NICUs and 61% for Level III NICUs, the after-birth care, monitoring and recognition of morbidities need to be assessed and followed-up. Referral and follow-up of the stabilized periviable infants to a Level III/IV NICU facility constitutes best practice.

There was trending of better survival among Level III versus Level II neonatal centers. Lasswell (2010) [101] documented a significant difference in the neonatal mortality of VLBW and VPI in Level II versus Level I centers (adjusted OR 1.62, 95% CI 1.44 to 1.83).

Note the disparity in survival among private versus public hospitals, the former with better equipment to patient ratio and nurse to patient ratio. This finding agreed with the study of Chung (2011) [102] who reported that low hospital volume is a very important center-level factor resulting to increased survival among the VLBW.

**TABLE 1: SURVIVAL RATE (%) OF PERIVIABLE INFANTS IN HOSPITAL NICUs IN THE PHILIPPINES, 2018**

| Hospital | ≤23 weeks | 24 to 27 weeks | 28 to 31 weeks | Total |
|---|---|---|---|---|
| **LEVEL III NICU** | | | | |
| **Private Level III NICU** | | | | |
| Hospital A | – | – | 100 | (5/6) 83 |
| Hospital B | – | 57 | 80 | (7/11) 64 |
| **Public Level III NICU** | | | | |
| Hospital C | – | 16 | 60 | (132/265) 50 |
| Hospital D | – | 8 | 41 | (188/571) 33 |
| Hospital E | – | 0 | 57 | (27/60) 45 |
| Hospital F | – | 50 | 67 | (34/52) 65 |
| Hospital G | – | 25 | 64 | (19/32) 59 |
| Hospital H | – | 42 | 81 | (157/218) 72 |
| Hospital I | – | 18 | 56 | (162/332) 49 |
| Hospital J | 18 | 22 | 64 | (180/340) 53 |
| **LEVEL II NICU** | | | | |
| **Private Level II NICU** | | | | |
| Hospital K | – | – | 83 | (15/19) 79 |
| Hospital L | – | 50 | 100 | (2/4) 50 |
| Hospital M | – | 100 | 100 | (5/6) 83 |
| **Public Level II NICU** | | | | |
| Hospital N | – | 21 | 73 | (49/83) 59 |
| Hospital O | – | 13 | 30 | (17/81) 21 |
| Hospital P | – | – | 53 | (9/21) 43 |
| Hospital Q | – | 57 | 67 | (133/203) 66 |
| Hospital R | – | 26 | 42 | (51/127) 40 |
| Hospital S | – | 70 | 72 | (87/128) 68 |

Table 2 describes the standard of care practiced by the different NICUs in the Philippines. The NICUs render palliative comfort care (NCC) to babies ≤23 weeks and 10% of them offer pharmacologic measures (PCC) like Midazolam. Thirty-seven percent (37%) of Level II and Level III NICUs (private and public) opt to render NCC to the 24-week babies then administer proactive care to the ≥25-weekers. Sixty-three percent (63%) of the NICUs initiate proactive care (AC with or without surfactant) to ≥24-week infants. Level II NICUs, lacking adequate equipment / procedures and NICU personnel, may transfer <32-week infants once stabilized to a Level III NICU facility. The referral is best for better monitoring and evaluation by more skilled neonatal personnel / subspecialists and further studies (blood gas determination, cranial ultrasonography, echocardiography, surgical clearance, retinopathy or prematurity [ROP] clearance).

**TABLE 2: STANDARD OF CARE OF PERIVIABLE INFANTS IN HOSPITAL NICUs IN THE PHILIPPINES, 2016-2018**

| Hospital | ≤23 weeks | 24 weeks | 25 weeks | 26 weeks | 27 weeks | ≥28 weeks |
|---|---|---|---|---|---|---|
| **LEVEL III NICU** | | | | | | |
| **Private Level III NICU** | | | | | | |
| Hospital A | NCC | AC-S | AC-S | AC-S | AC-S | AC-S |
| Hospital B | NCC | PCC | AC-S | AC-S | AC-S | AC-S |
| | | | | | | |
| Hospital C | NCC | AC-S | AC-S | AC-S | AC-S | AC-S |
| Hospital D | NCC | AC-S | AC-S | AC-S | AC-S | AC-S |
| Hospital E | NCC | NCC | AC-S | AC-S | AC-S | AC-S |
| Hospital F | PCC | AC-S | AC-S | AC-S | AC-S | AC-S |
| Hospital G | NCC | AC-S | AC-S | AC-S | AC-S | AC-S |
| Hospital H | NCC | AC-S | AC-S | AC-S | AC-S | AC-S |
| Hospital I | NCC | AC-SD | AC-SD | AC-SD | AC-SD | AC-SD |
| Hospital J | NCC | AC-SD | AC-SD | AC-SD | AC-SD | AC-SD |
| | | | | | | |
| **Private Level II NICU** | | | | | | |
| Hospital K | NCC | NCC | AC-SD | AC-SD | AC-SD | AC-SD |
| Hospital L | NCC | NCC | AC-S | AC-S | AC-S | AC-S |
| Hospital M | NCC | AC | AC-SD | AC-SD | AC-SD | AC-SD |
| **Public Level II NICU** | | | | | | |
| Hospital N | NCC | V | V | V | V | AC-S |
| Hospital O | NCC | AC-SD | AC-SD | AC-SD | AC-SD | AC-SD |
| Hospital P | NCC | NCC | AC-SD | AC-SD | AC-SD | AC-SD |
| Hospital Q | NCC | NCC | AC-SD | AC-SD | AC-SD | AC-SD |
| Hospital R | NCC | AC-SD | AC-SD | AC-SD | AC-SD | AC-SD |
| Hospital S | NCC | NCC | V | AC-SD | AC-SD | AC-SD |

NCC, Comfort care; PCC, Pharmacologic comfort care; AC, Active care; S, Surfactant; SD, Depends on availability; V, Variable

In several instances, the Level III NICUs cannot accommodate the Level II NICU referrals. The best practice is the establishment of a national / regional / provincial neonatal network which are already existing in the HICs worldwide and even in our Southeast Asian neighbors (Singapore and Malaysia).[38,39,66] Another alternative is scaling-up of the Level II NICU facilities in terms of equipment and manpower similar to the development of the NICUs in Ghana, India, Nicaragua and Suriname.[88]

Level II centers may transfer pregnant mothers confirmed to deliver to a ≤32 week-infant to a Level III NICU. Similarly, hospitals with a Level I facility may transport pregnant mothers expected to deliver to a ≤35-week infant to a higher level of care. Maternal transport is an option only if the facility lacks technical and human resources and maternal/family preference is respected. Chow (2015)[103] and Jensen (2015)[104] reported transfer of high-risk pregnancies to a

tertiary facility, especially one with high-volume of VLBW infant deliveries and a Level III NICU, has better outcome, that is, increased survival and reduced morbidity.

An update of this guideline is planned in three years.

## SUMMARY OF RECOMMENDATIONS

| GESTATIONAL AGE / BIRTH WEIGHT | RECOMMENDATIONS | GRADE |
|---|---|---|
| <23 weeks and/or <400 grams | Provide palliative comfort care (Strong recommendation) | High |
| 23 0/7 to 23 6/7 weeks | Provide palliative comfort care (Strong recommendation) | Moderate |
| 24 0/7 to 24 6/7 weeks | • Should the family decide for resuscitation after counseling, initiate life-sustaining treatment and admit to NICU. (Strong recommendation) | High |
| | • Should the family decide for palliative care, support their wish. (Strong recommendation) | High |
| | • If parental wishes are unknown at the time of birth:<br>o Consider the individual circumstances / best interest of the baby: the condition at birth and the severity of morbidity and prognosis<br>o Initiate resuscitation and reassess the condition of the baby until parental wish is known<br>o Redirect to palliative care should the baby show signs of dying. (Strong recommendation) | Low |
| >25 weeks and/or >500 grams | • NICU III / IV (Strong Recommendation)<br>o Initiate life-sustaining treatment and admit to NICU<br>o If intervention becomes futile or parents decide palliative care, redirect to palliative care<br>o Provide thermoregulation in either radiant warmer or incubator<br>o Start oxygen at 30% when there is no oxygen blender<br>o Provide mechanical ventilation either by non-invasive (nCPAP or NIPPV) or invasive ventilation as needed | High<br>Low<br>Low<br>Low<br>Low |
| 25 0/7 to 32 0/7 weeks * | NICU II (Strong Recommendation)<br>o Transport the pregnant mother to a NICU III/IV center should there be insufficient technical and human resources | Low |
| 25 0/7 to 35 0/7 weeks * | NICU I (Strong Recommendation)<br>o Transport the pregnant mother to a higher level of care center should there be insufficient technical and human resources | Low |

* Based on NICU levels in PSNbM Standards of Newborn Care, 2017

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|---|---|
| Technical Working Group: | Ma. Conchitina Bandong, MD<br>Ma. Lourdes S. Imperial, MD |
| Peer Reviewers: | Emilio A. Hernandez, Jr. , MD<br>Josie Niu-Kho, MD<br>Jose B. Salazar, MD<br>Jean U. Tay, MD |
| Contributors: | Melani Adolfo, MD<br>Christine Basilia, MD<br>Charito Corpuz, MD<br>Eleanor DR Cuarte, MD<br>Fay de Ocampo, MD<br>Daisy Garcia, MD<br>Dahlia C. Go, MD<br>Nathalie Anne R. Hernaez, MD<br>Maan Ilao, MD<br>Ness R. Macasaet, MD<br>Sheila Anne Masangkay, MD<br>Aurea Alicia D. Matias, MD<br>Mary Ann Cyril Mesalucha, MD<br>Bing Otayza, MD<br>Wilfredo Santos, MD<br>Rowena Vergara, MD<br>Maria Leonora Villaruz, MD<br>Ma. Cristina VC Woo, MD |

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Chapter 22

# Government Initiatives

Mila D. Zaragoza-Ibay, MD, MBAH, FPOGS, FPSMFM, FPSUOG
Ma. Lourdes A. Salaveria-Imperial, MD, FPPS, FPSNbM

Prematurity is an increasing concern globally due to the sheer number of babies being born early, estimated at 15 million a year, or approximately 10.6% of all live births.[1] The number has been rising in the past decade, and prematurity with all its attendant complications in the small newborns has ranked as the top leading cause of death for children under 5 years old, accounting for nearly 1 million deaths or 35% of all neonatal deaths in 2010.[2] Those who are able to hurdle the challenges of prematurity and survive are not much better off, as they are expected to live with disability for the remainder of their lives. Prematurity also contributes to babies being born small for gestational age or being low birth weight (LBW), defined as birth weight of less than 2,500 grams. An estimated 15.5% or 20 million LBW infants are born annually, with almost all of them in developing countries.[1] Being LBW is also a significant factor that contributes to 60–80% of all newborn deaths. The Philippines was 8th among 15 countries that accounted for two-thirds of the world's preterm births in 2012.[3] It has been widely recognized that neonatal and infant mortality rates can be reduced by improving the care for the pregnant mother, providing safe and quality care during delivery, and improving the care of the small baby. Three-fourths of premature newborn deaths can be prevented with evidence-based, cost-effective preventive and therapeutic interventions, but these approaches have been ineffective in our country due to a lack of comprehensive guidelines and inconsistent delivery of services during preterm labor and birth.

## CARE FOR THE SMALL BABY COURSE

The Department of Health (DOH) sought to address the gaps in the care for premature and small babies when it created the Care for the Small Baby (CSB) Course in 2014. The training course was aimed at government health care workers providing maternal and newborn care. Its main objective was to improve the survival of the premature and low birth weight (LBW) newborn by providing evidence-based interventions for the care of mothers, premature and LBW newborns. The workshop provided a system of caring for the small baby in health facilities and communities that involves the principles of Essential Intrapartum and Newborn Care (EINC) integrated with Kangaroo Mother Care

(KMC). Both programs were already included in the DOH Administrative Order 2009-0025 on Adopting New Policies and Protocol on Essential Newborn Care[4] but had been previously taught as 2 separate stand-alone courses. The key interventions of both protocols that were incorporated in the CSB Course involved the following:

1. **Essential Intrapartum and Newborn Care**
    a. Prevention and management of premature birth and low birth weight
    b. The 4 Core Steps of Immediate Newborn Care
    c. Postnatal care of mother and newborn
    d. Basic newborn resuscitation
2. **Kangaroo Mother Care**
    a. **Continuous skin-to-skin contact**
    b. **Exclusive breastfeeding**
    c. **Early discharge from the hospital**
    d. **Close follow-up at the clinic**

Since the adoption of this program 5 years ago, many government health workers have been trained in all regions of the country. Recently, other organizations and facilities have sought to do their part in disseminating the CSB curriculum by conducting courses in partnership with the DOH. The Philippine Pediatric Society-Southern Tagalog Chapter (PPS-STC) has spearheaded the training of health workers in private healthcare institutions (HCI) in the CALABARZON area by holding CSB workshops conducted by their CSB trainors. The UP-Philippine General Hospital and St. Luke's Medical Center in Quezon City have likewise conducted CSB workshops to accommodate healthcare providers in private HCIs.

## PHILHEALTH Z BENEFIT PACKAGE FOR PREMATURE AND SMALL NEWBORNS

Despite having evidence-based, cost-effective interventions available, they remained largely inaccessible to majority of the population. The rising rate of prematurity combined with the exorbitant costs involved in the management of a preterm infant and its subsequent financial impact on the family did very little to reduce our child mortality rate. In 2015, the DOH and the Philippine Health Insurance Corporation (PhilHealth) sought to alleviate the inadequacy of existing government financing for services that address the prevention and management

of prematurity and its complications by the creation of a comprehensive benefit package that would ensure the following:

1. Equitable access of the poorest and most vulnerable segments of the population
2. Financial risk protection for all other member segments
3. Attainment of better and more equitable health outcomes

With assistance from UNICEF Philippines, the technical working group on the Z Benefit package for prematurity embarked on the project by defining the impact of prematurity based on the global burden of the disease, regional estimates and statistics gathered from the EINC scaling-up project and from selected government hospitals from 2010 to 2013.[5-8] The most common conditions accompanying prematurity were determined based on international and local references. The best recommendations in addressing these conditions were formulated in accordance with international and local clinical practice guidelines that were current at the time, balanced by practice recommendations from local experts. Thus, the benefit package aimed to address preventive services for the woman in premature labor, and cost-effective interventions for the small and very small baby.

The methodology used in calculating the packages utilized standard care algorithms and outcomes for 1) the very small newborn (500 g to < 1,500 g birth weight), 2) the small newborn (1500 g to < 2500 g birth weight), and for 3) women in labor at < 37 weeks age of gestation. Costing was based on values for antenatal, in-patient and pre-discharge care services obtained from a combination of 11 hospitals and 3 maternity clinics in both government and private sectors surveyed nationwide. The final packages consisted of 9 diagnosis-related groups (DRG) divided into interventions for 1) prevention of preterm delivery (4 DRGs), 2) preterms 24 weeks to < 32 weeks and very small newborns (3 DRGs), and 3) preterms 32 weeks to < 37 weeks and small newborns (2 DRGs).[9]

The packages aimed at prevention of preterm delivery covered medications and interventions in the management of severe preeclampsia and eclampsia, preterm prelabor rupture of membranes (PPROM), and vaginal bleeding. The last package covered the costs of a timely and coordinated referral and transfer of the woman at risk for premature delivery to a higher level facility.[10]

The benefit packages for the newborn whose early delivery could not be prevented covered essential interventions at birth and management of complications of prematurity that included hypothermia, anemia of prematurity, respiratory distress syndrome, sepsis, necrotizing enterocolitis, jaundice,

hemodynamically significant ductus arteriosus, apnea of prematurity, retinopathy of prematurity, intracranial hemorrhage, hearing loss, and possible metabolic disorders. The packages varied according to the diagnostic and therapeutic services indicated for the abovementioned conditions, with the highest cost assigned to the very small babies who are more critically ill and would require more intensive ventilatory support and medical management. The comprehensive care covered by the packages extends to Kangaroo Care for the growing premature and mandatory pre-discharge screening services for the surviving newborn.[10] At the completion of the project, DOH and PhilHealth released the Z Benefit Package for Premature and Small Newborns in May 2017, and in 2018 the first healthcare institution to be contracted as a provider was the Governor Celestino Gallares Memorial Hospital (GCGMH) in Tagbilaran City, Bohol.[11]

## THE WAY FORWARD

To complement the benefit package for premature newborns, the DOH began to formulate a comprehensive national policy that aimed to "address key elements on interventions to reduce the gaps in quality care for preterms and LBW newborns".[12] The objectives of the policy are the provision of evidence-based, cost-effective, and quality interventions in the prevention of preterm births and low birth weight deliveries, as well as the management of premature and low birth weight newborns wherein financial risk protection is assured. The Administrative Order (AO) entitled National Policy on the Quality of Care for Small Babies to Fast Track Neonatal Mortality Reduction: Addressing Prematurity and Low Birth Weight is being finalized and is expected to be released very soon.[12]

Since the launch of the Z benefit package in 2016, the uptake has been slow due to bottlenecks in its roll-out and implementation. Challenges encountered involved the apparent inadequacy of hospitals to deliver the services and the capacity of PhilHealth to promptly accredit applying hospitals based on the standards mandated by the benefit package. Thus, DOH, with the support of UNICEF Philippines, has announced a project to accelerate the contracting of 27 hospitals nationwide for the Z Benefit Package for Premature and Small Newborns. The 2020 project aims to build up the capacity of hospitals and their service delivery networks for compliance with the benefit package standards, and assist PhilHealth regional offices in the accreditation process in order to achieve high level of accreditation rates.

## GLOBAL ACTIONS OF THE WORLD HEALTH ORGANIZATION

The World Health Organization (WHO)[13] is working to reduce the health problems and lives lost as a result of preterm birth with the following specific actions:

- working with countries and partners to implement the Every Newborn: An action plan to end preventable deaths adopted in May 2014 in the framework of the UN Secretary-General's Global Strategy for Women's, Children's and Adolescents ; Health (2016-30);
- working with countries to strengthen the availability and quality of data on preterm births;
- providing updated analyses of global preterm birth levels and trends every 3 to 5 years;
- working with partners around the world to conduct research into the causes of preterm birth, and test effectiveness and delivery approaches for interventions to prevent preterm birth and treat babies that are born preterm;
- regularly updating clinical guidelines for the management of pregnancy and mothers with preterm labor or at risk of preterm birth, and those on the care of preterm babies, including Kangaroo Mother Care, feeding babies with low birth weight, treating infections and respiratory problems, and home-based follow-up care (WHO Recommendations on interventions to improve preterm outcomes 2015);
- developing tools to improve health workers' skills and assess the quality of care provided to mothers at risk of preterm delivery and preterm babies; and
- supporting countries to implement WHO 's antenatal care guidelines, aimed at reducing the risk of negative pregnancy outcomes, including preterm births, and ensuring a positive pregnancy experience for all women.

*"Preterm birth remains a crucial issue in child mortality and reflects the need for improved quality of maternal and newborn care. To better understand the epidemiology of preterm birth, the quality and volume of data needs to be improved, including standardization of definitions, measurement, monitoring and reporting."*

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Chapter 23

# Care of Preterm Infants

Emilio A. Hernandez, Jr., MD, MHSA, FPPS, FPSNbM

The worldwide preterm birth rate is 10.6% (range of 5 to 18%).[1,2] The estimated preterm birth rate in the Philippines is 13.27%.[3] Prematurity refers to 'birth before the completion of 37 weeks gestation, that is, until 36 6/7 weeks or before 37 0/7 weeks (before 259 days)[2,4] Preterm babies have an increased risk of complications and often require special care in a neonatal intensive care unit (NICU). Survival rates for preterm infants vary enormously and depend on the following: (1) the reason for the premature birth, (2) the gestational age at birth, (3) the birth weight, and (4) the expertise and the care of the NICU staff.

The care of the premature infant is quite complex and ever changing. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment may become necessary or appropriate.

After birth of a premature baby, the measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administration of Vitamin K are the same for infants as for those of term babies. Additional considerations for the premature care are the need for:

1. Oxygen therapy and resuscitation
2. Thermal control
3. Management of respiratory distress syndrome
4. Nutrition

This chapter will focus on these four needs of the preterm infant.

# I. OXYGEN THERAPY AND RESUSCITATION

**QUESTION 1** **Among newly born premature infants needing resuscitation at birth, what is the initial oxygen concentration to use?**

**RECOMMENDATION** The current recommendation to initiate resuscitation at the delivery room is 21% to 30% oxygen. It is also advised to use pulse oximeter and oxygen blender during resuscitation.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

When resuscitating a preterm baby, it is important to balance the desire to reach the oxygen saturation to 95–100% against avoiding exposure to excessive levels of oxygen resulting to oxygen-associated injury.[5]

The use of progressively higher concentrations of oxygen (>30%) should only be considered for newborns undergoing oxygen therapy if the heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation using 21% to 30% oxygen.

**QUESTION 2** **Among newly born premature infants needing oxygen in the delivery room, what are the target oxygen saturation levels?**

**RECOMMENDATION** The target oxygen saturation levels are as follows:

| Minute of Life | Oxygen Saturation |
|---|---|
| 1st minute | 60-65% |
| 2nd minute | 65-70% |
| 3rd minute | 70-75% |
| 4th minute | 75-80% |
| 5th minute | 80-85% |
| 10th minute | 85-95% |

The adjustment of the concentration of oxygen levels should be by 10% (FiO2=0.1) per 30 seconds and must be guided by oxygen saturation levels reached.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Current initial steps of resuscitation for both the term and the preterm babies follow the guidelines set by the Newborn Resuscitation Program of the American Academy of Pediatrics[5] and, more recently in 2018, the Newborn Resuscitation Philippines Plus (NRPh+) +.[6]

**QUESTION 3** **Among premature babies needing respiratory support soon after birth and before admission to the NICU, what ventilatory method is advised?**

**RECOMMENDATION** When stabilizing preterm babies who are spontaneously breathing but needing respiratory support, use nasal continuous positive airway pressure (CPAP) rather than intubation and positive pressure ventilation (PPV).

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Continuous positive airway pressure (CPAP) help stabilize the lungs, reduce airway resistance and increase functional residual capacity, which may prevent lung injury and respiratory distress syndrome (RDS). Recent randomized trials, such as the controlled Continuous Positive Airway Pressure or Intubation at Birth (COIN) trial and Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) show that with early CPAP, stabilization without intubation in the delivery room is feasible.[7,8]

## II. THERMAL CARE

**QUESTION 4** **Among stable preterm babies needing routine thermal care, is Kangaroo Mother Care (KMC) compared to conventional care more effective in preventing hypothermia thus lowering neonatal morbidity and mortality?**

**RECOMMENDATION** Kangaroo mother care is recommended for the routine care of newborns weighing 2000 grams or less at birth. It should be started as soon as the newborns are clinically stable.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

The definition of Kangaroo mother care (KMC) is care of preterm infants carried skin-to-skin with the mother. Its key features include early, continuous and prolonged skin- to-skin contact between the mother and the baby and exclusive breastfeeding (ideally) or feeding with breastmilk.

Evidence for this recommendation was based on facility-based studies, mainly from low- and middle-income countries.[8, 9]

There is insufficient evidence to make a recommendation to provide KMC to unstable neonates.[8]

**QUESTION 5** **Among preterm babies, is *continuous* KMC compared to conventional care more effective in preventing hypothermia thus lowering the neonatal mortality and morbidity?**

**RECOMMENDATION** Newborns weighing 2000 grams or less at birth should be provided as close to continuous Kangaroo mother care as possible.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Continuous KMC is defined as the practice of skin-to-skin care continuously throughout the day without breaking the contact between mother and baby.[8]

| QUESTION 6 | **Among preterm babies, is *intermittent* KMC compared to conventional care more effective in preventing hypothermia thus lowering the neonatal morbidity and mortality?** |
|---|---|
| **RECOMMENDATION** | Intermittent Kangaroo mother care, rather than conventional care, is recommended for newborns weighing 2000 grams or less at birth, if continuous Kangaroo mother care is not possible.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Intermittent Kangaroo mother care, rather than conventional care, is recommended for newborns weighing 2000 grams or less at birth, if continuous Kangaroo mother care is not possible.

| QUESTION 7 | **Are radiant warmers more superior to incubators in providing a thermo-neutral environment for preterm babies?** |
|---|---|
| **RECOMMENDATION** | There is insufficient evidence to support superiority of either radiant warmers or incubators over the other for the care of preterm babies. In making any choice between the two devices, the health-care providers' preferences and costs should be considered.<br><br>*Quality of Evidence: Low*<br>*Strength of Recommendation: Weak* |

## SUMMARY OF EVIDENCE

A thermo-neutral environment was considered to be environmental conditions under which a baby maintains temperature in a normal range at minimum metabolic rate.

Unstable newborns weighing 2000 grams or less at birth, or stable newborns weighing less than 2000 grams who cannot be given Kangaroo mother care, should be cared for in a thermo-neutral environment either under radiant warmers or in incubators.[10]

There is insufficient evidence to support superiority of either radiant warmers or incubators over the other for the care of preterm babies. In making any choice between the two devices, the health-care providers' preferences and costs should be considered.[10]

Radiant warmers result in increased insensible water loss compared to incubators. This needs to be taken into account when calculating daily fluid requirements.[10]

| **QUESTION 8** | **Among preterm neonates with hypothermia, are plastic bags / wraps more effective than conventional thermal care in the NICU?** |
|---|---|

**RECOMMENDATION** There is insufficient evidence on the effectiveness of plastic bags / wraps in providing thermal care for preterm newborns immediately after birth. However, during stabilization and transfer of preterm newborns to specialized neonatal care wards, wrapping in plastic bags / wraps may be considered as an alternative to prevent hypothermia.

*Quality of Evidence: Low*
*Strength of Recommendation: Weak*

## SUMMARY OF EVIDENCE

Preterm babies have a high risk of developing hypothermia and complications from cold stress.[11] While drying with warm towels, skin to skin contacts, and early breastfeeding may be sufficient to maintain normal body temperature in

some preterms, additional measures are required especially among the extreme premature infants.

Depending on baby's weight and gestation, some preterms may benefit from the use of a thermal mattress and occlusive wrap.[10]

## III. MANAGEMENT OF RESPIRATORY DISTRESS SYNDROME (RDS)

**QUESTION 9** **Among preterm newborns with respiratory distress syndrome, is continuous positive airway pressure (CPAP) therapy the first line of ventilatory support?**

**RECOMMENDATION** Continuous positive airway pressure (CPAP) should be administered in the treatment of preterm newborns with RDS.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

CPAP is used primarily for preterm infants with RDS. Most centers have used nasal CPAP soon after birth among preterms with sufficient respiratory drive. The sooner nasal CPAP therapy is started, the better the results are in prematures with RDS.[11]

Among preterm babies who are breathing spontaneously and have heart rates of at least 100 bpm, but have labored respirations or oxygen saturations below the target range, administration of CPAP rather than PPV is helpful. Using early CPAP may avoid the need for invasive ventilation.[11, 12]

There is some evidence that early use of nasal CPAP instead of invasive ventilation could lead to a small reduction in the incidence of bronchpulmonary dysplasia (BPD).[12]

| QUESTION 10 | Among preterm newborns with respiratory distress syndrome, when should CPAP be administered? |
|---|---|
| **RECOMMENDATION** | Continuous positive airway pressure (CPAP) therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made.<br><br>*Quality of Evidence: Low*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Evidence on the timing of initiation of CPAP therapy for preterm newborns with RDS was derived from a Cochrane review by Ho et al.[11] The study involved initiation of CPAP therapy immediately following the diagnosis of RDS, and these neonates required fraction of inspired oxygen (FiO2) between 0.3 and 0.7. In the comparison arm, CPAP was initiated only when RDS was worsening and babies required relatively higher FiO2 (between 0.5 and 1.0). In the study, early CPAP was defined as CPAP initiated within 5 minutes of birth, and late CPAP was that initiated at least 30 minutes after birth.[11,12]

| QUESTION 11 | Among preterm babies diagnosed with RDS, is surfactant therapy recommended? |
|---|---|
| **RECOMMENDATION** | Surfactant therapy is recommended for intubated and ventilated newborns with respiratory distress syndrome but should be administered only in health-care facilities where intubation, ventilator care, blood gas analysis, newborn nursing care and monitoring are available.<br><br>*Quality of Evidence: Moderate*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Consider administering surfactant if the preterm baby is not improving with CPAP. Prior to administration of surfactant, the baby should undergo tracheal intubation.[14]

Appropriate endotracheal tube placement should be confirmed by auscultation of bilateral breath sounds or chest x-ray prior to surfactant administration.[14]

It is preferable that surfactant be administered by an experienced physician.[14]

In some cases, the endotracheal tube may be removed immediately after administration of surfactant and the baby is hooked back to CPAP. This strategy, the INSURE (Intubation, SURfactant, Extubation), is a proven complement of nasal CPAP for the treatment of RDS.

**QUESTION 12** **Among babies in respiratory distress needing surfactant replacement therapy, is natural (animal-derived) surfactant more superior to protein-containing synthetic surfactant in reducing the incidence of neonatal mortality and morbidity?**

**RECOMMENDATION** Either animal-derived or protein-containing synthetic surfactants can be used for surfactant replacement therapy in ventilated preterm newborns with respiratory distress syndrome.

*Quality of Evidence: Moderate*
*Strength of Recommendation: Strong*

### SUMMARY OF EVIDENCE

The protein-free synthetic surfactants increase the risk of pneumothorax when compared with animal-derived surfactant. This type of synthetic surfactant is no longer commercially available.

***Protein-containing synthetic versus natural surfactants***

The systematic review by Pfister et al. [15] included two studies that compared the effects of the newer generation protein-containing surfactants with those of

natural surfactants on mortality and morbidity outcomes when used in newborns with clinical or radiological features of RDS or at risk of RDS.

A meta-analysis of randomized control trials showed that natural surfactants were faster-acting with lower incidence of pneumothorax and death.[15,16]

**QUESTION 13** **Among premature babies with RDS, can prophylactic administration of surfactant reduce the incidence of RDS?**

**RECOMMENDATION** Administration of surfactant before the onset of respiratory distress syndrome (prophylactic administration) in preterm newborns should not be done.

*Quality of Evidence: Low*
*Strength of Recommendation: Strong*

## SUMMARY OF EVIDENCE

Prophylactic surfactant refers to the administration of doses within the first 15 minutes after birth. To avoid giving an unnecessary expensive surfactant and subjecting a premature to the risks of intubation, prophylactic surfactant should be ideally be given to premies who would eventually developed RDS.[15]

There have been some reports that recommended prophylactic surfactant administration especially to extremely premature babies because the likelihood of CPAP failures among these subgroups of premature infants population is relatively high.

The benefits of prophylactic surfactant in older clinical studies appear to have disappeared in the modern era of antenatal steroids and routine use of CPAP.[15,16]

| QUESTION 14 | **Among preterm babies in respiratory distress, is early administration of surfactant comparable to rescue therapy in lowering the incidence of neonatal mortality and morbidity?** |
|---|---|
| RECOMMENDATION | In intubated preterm newborns with RDS, surfactant should be administered early (within the first 2 hours after birth) rather than waiting for the symptoms to worsen before giving rescue therapy.<br><br>*Quality of Evidence: Low*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

Early surfactant therapy is administration of surfactant among intubated premature infanst with RDS within 2 hours from delivery while *rescue* surfactant therapy refers to surfactant administration among preterms with established RDS usually at several hours of age.

Premature babies receiving early surfactant therapy (compared to resue surfactant treatment), have decreased rates of pneumothorax, pulmonary interstitial emphysema, BPD and decreased risk of neonatal mortality. [15,16]

# V. NUTRITIONAL SUPPORT OF PREMATURE BABIES

| QUESTION 15 | **When do babies need parenteral nutrition?** |
|---|---|
| RECOMMENDATION | Parenteral nutrition should be started promptly in premature babies within the first 24 hours if they cannot tolerate enteral feeding. Parenteral nutrition may be stopped once 90% enteral feeding is given.[18,19]<br><br>*Quality of Evidence: Low*<br>*Strength of Recommendation: Strong* |

## SUMMARY OF EVIDENCE

A sufficient supply of nutrients is necessary for the baby's normal growth, brain development, and to prevent the occurrence of nutrient deficits and growth failure.

Babies who cannot be fed by mouth or by a feeding tube require parenteral nutrition: [18,19]

- Immature preterm babies (most babies born before 32 weeks of gestation) during the first weeks of life
- Babies with illnesses involving disorders of swallowing or the digestion of food (e.g. due to diseases of the esophagus, stomach, and/or intestine)

Today, one strives to provide at least a small amount of enteral nutrition from the first days of life. Therefore, usually partial parenteral nutrition is provided to babies, combined with some enteral feedings. Enteral nutrition should be increased over time following a unit protocol, as tolerated by the baby, and parenteral nutrition should be decreased accordingly.

The following table illustrates nutrition guidelines that may be used in the NICU:

**TABLE 1: EARLY AGGRESSIVE NUTRITION GUIDELINES USED IN NICU**

| | |
|---|---|
| Fluids | GA <28 week; keep incubator humidified 90% for 5–7 days<br>Day 1: 60–80 ml/kg/day, gradually increase 10–20 ml/kg/day (according to the change in BW, serum Na, urine amount and circulatory status) to 120–150ml/kg/d at day 7 (including IV and feeding amount)<br>Postnatal weight loss of 5%/d to a maximum of 15% of BW is acceptable |
| Energy | The goal is 120 kcal/kg/d and protein 3.6–4.0 g/kg/d |
| Glucose | Infusion at 4–6 mg/kg/min (upper limit 10–13 mg/kg/min) to maintain BS at 50–120 |
| Protein | IV amino acid (10%) 3 g/kg/d can be started within hours after birth, increase 0.5–1 to 3.5–4 g/kg/d<br>Only glucose and AA infusion (with or without Ca gluconate) in day 1. Vitamin added in day 2 after BS becomes stable. |
| Fat | Start from days 2–3 after assessment of serum Na and in-out balance<br>Na (3–5 mEq/kg/d), Cl (3–5 mEq/kg/d), K (2–4 mEq/kg/d), Ca (1.5–2.2 mmol/kg), P (1.5–2.2 mmol/kg), Mg (0.3–0.4 mmol/kg) |
| Trace Elements | Zinc (6–8 µmol/kg/d), Copper (0.3–0.6 µmol/kg/d), Selenium (13–25 nmol/kg/d), Manganese (18–28 nmol/kg/d), Iodine (8 nmol/kg/d), Chromium (4–8 nmol/kg/d), Molybdenum (2–10 nmol/kg/d) |
| Early enteral feedings | Usually, human milk is initiated at 0.5 ml/kg (10ml/kg/d) on day 1 if possible (at least within 3–5 days) and advanced (10–20 ml/kg/d) as tolerated. The goal of feeding amount is 120–150 ml/kg/day.<br>Do not stop parenteral nutrition until enteral feeds are >90% of full. |

BS, blood sugar; GA, gestational age; IV, intravenous; NICU, neonatal intensive care unit;
*From Su BH. Optimizing nutrition in preterm infants. Pediatr Neonatol 2014; 55:5-13. Table 2, Early Aggressive Nutrition Guidelines Used IN NICU* [18]

## TABLE 2: EVIDENCE-BASED EARLY NUTRITIONAL PRACTICE FOR VLBW INFANTS: RECOMMENDATIONS AND EVIDENCE QUALITY

| Practice | Strength of Recommendation* | Evidence Quality† |
|---|---|---|
| Prompt provision of energy: | | |
| Glucose infusion providing about 6 mg/kg/min | Recommended | B |
| Increase to about 10 mg/kg/d by 7 days of age | | |
| Maintain blood sugar 50 -120 mg/dL | | |
| Prompt provision of parenteral amino acids: | | |
| Initiate 3.0 g/kg/d within hours of birth | Recommended | B |
| Advance to 4.0 g/kg/d by 0.5-1.0 g/kg/d steps | | |
| Initiate lipid emulsion within the first 24 to 30 hrs of birth | | |
| Start 0.5 to 1.0 g/kg/d | Recommended | B |
| Advance to 3.0 to 3.5 g/kg/d by 0.5 to 1.0 g/kg/d steps | | |
| Initiate trophic feedings by 5 days of age | | |
| Provide about 10 mL/kg/d (human milk if possible) | Recommended | B |
| Begin advancing to ~150 mL/kg/d by 10 to 20 mL/kg/d steps within the next several days | | |

Adapted with permission.[37]

*Strength of Recommendation: strongly recommended; recommended; option; not recommended.

†Grade of Evidence Quality: A, Well-designed, RCTs performed on appropriate populations; B, RCTs with minor limitations, overwhelmingly consistent evidence from observational studies; C, Observational studies (case-control and cohort design); D, Expert opinion (case reports, reasoning from first principles).

*Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence. Semin Perinatol 2007; 31:48-55. Table 2, Evidence-Based Early Nutritional Practice for VLBW Infants: Recommendations and Evidence Quality, page 54.* [20]

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## GRADE QUALITY OF EVIDENCE

| GRADE | SYMBOL | DEFINITION |
|---|---|---|
| High | ⊕⊕⊕⊕ | Further research is *unlikely to change* confidence in the estimate of effect. |
| Moderate | ⊕⊕⊕◯ | Further research is *likely* to have an important impact on confidence in the estimate of effect and may change the estimate. |
| Low | ⊕⊕◯◯ | Further research is *very likely* to have an important impact on confidence in the estimate of effect and is likely to change the estimate. |
| Very Low | ⊕◯◯◯ | Any estimate of effect is *very uncertain.* |

## GRADE STRENGTH OF RECOMMENDATION

| TARGET GROUP | STRONG RECOMMENDATION | WEAK RECOMMENDATION |
|---|---|---|
| Patient | Most people in the situation would want the recommended course of action and only a small proportion would not | The majority of people in the situation would want the recommended course of action, but many would not |
| Clinician | Most patients should receive the recommended course of action | Recognize that different choices will be appropriate for different patients and that there must be greater effort with helping each patient to arrive at a management decision consistent with his/her values and preferences Decision aids and shared decision making are particularly useful |
| Policy makers | The recommendation can be adopted as a policy in most situations | Policy making will require substantial debate and involvement of many stakeholders |