

REDUCING THE BURDEN OF PREMATURITY - THE OBSTETRIC PERSPECTIVE

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INTRODUCTION DEFINITION AND PREVALENCE

‘Preterm or Premature Birth’ is defined as birth occurring before completion of 37 weeks or 259 days since the first day of the last menstrual period of the mother.¹ Every year, an estimated 15 million babies (more than one in ten births) are born preterm worldwide, and this number is rising.² In Sri Lanka, approximately 24,500 babies are born prematurely each year.³ Efforts by obstetricians and neonatologists have led to significant advances in reducing preterm birth and improving outcomes.

THE BURDEN OF PRETERM BIRTH

Prematurity has been the leading cause of neonatal mortality worldwide for at least a decade and has now become the second leading cause of childhood mortality up to five years of age.²

The global neonatal mortality rate (per 1000 live births) has come down from 18.3 in 2016 to 17 in 2019. When comparing the statistics in Sri Lanka for the years 2016 and 2019, the neonatal mortality rate (per 1000 live births) has gone up from 5.8 (2016) to 7 (2019)⁴. Similarly, the infant mortality rate (per 1000 live births) in Sri Lanka was 8.2 in 2016 and increased to 10.1 in 2019.⁴ Around 75% of deaths of children below 5 years occur during the first four weeks (28 days) of life. Of these, more than one-third are due to preterm births⁴, making it the leading cause of neonatal death in Sri Lanka as well.

The preterm babies comprise a large portion of the admissions to the neonatal intensive care units. Those who survive are at increased risk of life-long disabilities including cerebral palsy, intellectual and learning disabilities, chronic broncho-pulmonary disease, and vision and hearing impairment. Fifty percent of long-term neurological morbidity in high-income nations is linked directly to preterm delivery. In addition, preterm birth poses a threat to maternal mental health with evidence of higher risk for post-partum depression.⁵ These complications exert a huge impact on the affected families and the healthcare and educational systems of a country.

Prolonging pregnancies even for a few weeks significantly reduces risks for the new-born, since gestational age is the essential determinant of most perinatal outcomes.⁶

RISK FACTORS, PREDICTORS AND OUTCOMES

Preterm birth is a syndrome with a variety of causes. It can be basically categorized according to the gestational age.²

Extremely preterm (less than 28 weeks)

Very preterm (28 to 32 weeks)

Moderate preterm (32 to 34 weeks)

Late preterm (34 to 37 weeks)⁷

For a better understanding of risk factors and management, preterm birth can also be classified with the clinical subtype:

Spontaneous preterm birth (SPB)

Provider-initiated preterm birth (PIPB)

The pathophysiological mechanisms that underlie preterm labour are poorly understood but it is suggested that a host of multiple factors trigger the

pathogenic processes leading to a final common pathway for the initiation of uterine contractions that will lead to SPB.⁶ Unmodifiable risk factors for SPB include a shortened cervix less than 25mm before 28weeks (Risk rate is 6.19 for the length of 26mm or less) and a history of preterm delivery (1.5 to 2 fold risk of subsequent preterm delivery).⁸ Age at pregnancy and pregnancy spacing, multiple pregnancies, infection, underlying maternal chronic medical conditions, level of maternal nutrition and lifestyle, maternal psychological health, and genetics are also recognized as contributors.

PIPB is defined as induction of labour or elective caesarean birth before completion of 37 weeks of gestation for maternal or foetal indications. Increasingly high numbers of PIPB are seen among middle and high income countries but seen less in the countries with the highest burden of PTB.⁷

There is not a single or combined screening method for preterm birth with high sensitivity which will truly identify the women at risk for preterm birth while also with high specificity to prevent unnecessary interventions and high treatment costs.

The maternal history, health condition, and socio-demographic factors need to be taken into consideration. The measurement of cervical length is the most cost-effective method that is used in clinical practice. Bedside tests have also been developed for detecting markers like foetal fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), interleukin-6, and placental alpha-macroglobulin-1.

The major clinical outcomes that are important to preterm infants are survival and normal long-term neurodevelopment.(Figure 1)

PREVENTION OF PRETERM BIRTH

Interventions aimed at preventing preterm birth can be classified as primary, secondary, or tertiary prevention. Primary prevention involves the provision of interventions before and between pregnancies which enhance the mother’s health and reduce risks of her or the baby succumbing to preventable adverse pregnancy conditions.⁶ The main aim of primary prevention is to identify and improve women’s health or pregnancy outcomes through various interventions.

The main aim of secondary prevention involves interventions directed towards early detection of

pregnant women at risk of preterm labour and helping them to prolong their pregnancy to term. Tertiary prevention mainly aims to minimize complications of prematurity.

Antenatal therapies with insufficient evidence of benefit include screening and treatment of asymptomatic women for lower genital tract infection, treatment for periodontal disease, bed rest and relaxation or stress reduction.

PRECONCEPTION CARE

The WHO report ‘Born Too Soon’ emphasizes on several preconception care measures to prevent premature birth. Promoting family planning to minimize teenage pregnancy and better interpregnancy spacing, lifestyle modification with cessation of smoking, healthy food and

| IMPACT | | FREQUENCY IN SURVIVORS: |
|---|--|--|
| PHYSICAL EFFECTS | Visual impairment Blindness /myopia Hypermetropia and myopia | One fourth of extremely preterm affected |
| | Hearing impairment | Up to about 10% of extremely preterm |
| | Chronic lung disease of Prematurity (From reduced exercise tolerance to requirement for home oxygen) | Up to 40% of extremely preterm |
| | Long term cardio vascular disorders and NCDs such as hypertension, reduced lung function, asthma, growth failure in infancy accelerated weight gain in adolescence | Full extent of burden still not known |
| NEURO-DEVELOPMENTAL/ BEHAVIORAL EFFECTS | Mild Disorders of executive Functioning Specific learning impairment, dyslexia, reduced Academic achievement | |
| | Moderate to severe Global development delay/ cerebral palsy | Depend on gestational age and quality of care |
| | • Psychiatric/behavioral sequelae: attention deficit hyperactivity disorder, increased anxiety and depression | |
| ECONOMIC AND SOCIETAL EFFECTS | • Impact on health service Intergenerational Psychosocial, emotional and economic, Cost of care, risk of preterm birth in offspring | Varying with medical risk factor, disability, socioeconomic Status |

Figure 1: Long-term impact of preterm birth on survivors²

micronutrient supplementation, and optimization of pre-pregnancy weight are the cost-effective strategies. Education for girls and women, economic empowerment, screening for mental and medical health conditions, pre-conception surgical interventions to normalize uterine anomalies, partner education to reduce domestic violence are also essential in building a healthy environment for future mothers. Prevention, screening, and management of sexually transmitted diseases (eg: HIV, Syphilis) and teenage HPV vaccination should be taken care of at the community level.²

ANTENATAL CARE

Enhanced antenatal care for the prevention of PTB focuses on the management of pregnancies with potential risk. The mother should be educated regarding early warning signs, possible complications of the pregnancy, healthy behaviour, and the necessity of regular antenatal care visits. Health care providers must be competent in identifying pregnancies with a higher risk for PTB and the requirement for multidisciplinary care.

REDUCING MULTIPLE PREGNANCIES

The rate of PTB is about 10% in twin pregnancies compared to the 1-2% in singletons.⁹ Mothers with multiple foetuses require close monitoring and cervical length assessment. Regulation of assisted reproductive techniques (ART), such as adopting the single embryo transfer policy by the Human Fertilization and Embryology Act in the UK¹⁰ would pave the way to reduce multiple pregnancies. Although there are no such regulations in Sri Lanka at the present, with the advances of technology similar laws and acts would be a necessity.

REDUCING MATERNAL INFECTIONS

Maternal infections generally play a significant role in the pathogenesis of preterm labour. It is reported that 80% of women presenting with preterm labour before 30 weeks had evidence of amniotic fluid infection.¹¹ Persistent or recurrent intrauterine infections probably explain many repetitive spontaneous preterm births. Various studies and trials revealed conflicting results on the benefit of prophylactic antibiotics¹² and some suggest benefit of reducing infections is only applicable to women with a previous history of preterm labour and positive screen for bacterial vaginosis.

OPTIMIZING TREATMENT OF MEDICAL DISORDERS

Complications of medical disorders are a common cause of iatrogenic preterm labour. Optimization of antenatal care with the use of medications and behavioural therapy may reduce the need for early delivery. High-risk pregnancies associated with diabetes mellitus, hypertension, autoimmune, reno-vascular, connective tissue and endocrine disorders are best managed in dedicated clinics in which additional treatment and monitoring can be provided to reduce the risk of complications.⁶

CERVICAL LENGTH SCREENING AND CERCLAGE

Generally, preterm delivery is highly unlikely where the cervical length is greater than 3 cm and highly likely when it is less than 1.5 - 2.0 cm. The RR of preterm delivery increases with decreasing cervical length⁸. Universal screening for cervical length is controversial due to concerns about its

cost-effectiveness and the availability of quality imaging for all patients.

RCOG recommends prophylactic cervical cerclage, if the cervical length is 25mm or less detected by the cervical assessment of a transvaginal ultrasound scan carried out between 16 and 24 weeks of gestation for who have had either preterm prelabour rupture of membranes (P-PROM) in a previous pregnancy or a history of cervical trauma. If prophylactic cerclage is used, a plan for its removal must be ensured¹³.

PROGESTERONE PROPHYLAXIS

Antenatal progesterone therapy is one of the most effective measures in reducing the risk of preterm delivery, neonatal morbidity, and mortality in women with single gestation with a history of spontaneous preterm delivery. Progesterone is secreted by corpus luteum for the maintenance of early pregnancy until when the placenta takes over this function approximately between 7-9 weeks. Progesterone appears to help maintain uterine quiescence by inhibiting myometrial contraction through the modulation of cytokine production and inhibiting the expression of contraction associated protein genes within the myometrium. In a randomized controlled study, treatment with vaginal progesterone showed less frequency of spontaneous delivery before 34 weeks of gestation in the progesterone group than in the placebo group (19.2% vs. 34.4%)¹⁴. Progesterone is not beneficial in multiple gestation pregnancies. Prophylactic vaginal progesterone is considered for women who have either a history of spontaneous preterm birth (up to 34+0 weeks of pregnancy) or mid-trimester loss (from 16+0 weeks of pregnancy onwards) or results from a transvaginal ultrasound scan carried out between

16+0 and 24+0 weeks of pregnancy that show a cervical length of 25 mm or less. When using vaginal progesterone, treatment to be commenced between 16+0 and 24+0 weeks of pregnancy and continued until at least 34 weeks¹³.

CERVICAL PESSARY

The main aim of inserting a pessary is to produce a more acute cervical angle relative to the uterus, thereby preventing the direct pressure over the cervix and foetal membranes at the level of the internal cervical opening. Utilization of cervical pessary for the prevention of preterm labour is a recent phenomenon and more evidence to assess its potential clinical efficacy is required. Despite the conflicting results provided by the clinical trials, they are good alternatives to cerclage and progesterone supplementation, especially for developing countries. It is also suggested that the use of cervical pessary is superior to the expectant management for the prevention of preterm labour in women with a singleton pregnancy with a short cervix¹⁵.

CERVICAL CERCLAGE OR PROGESTERONE?

A metanalysis in 2018 including five trials each comparing vaginal progesterone vs placebo and cerclage vs no cerclage revealed that vaginal progesterone and cervical cerclage are equally effective for the prevention of PTB <35 weeks of gestation, in women with singleton pregnancies, previous PTB and short cervix. There was a significant reduction in perinatal morbidity and mortality as well¹⁶. The treatment of choice will be determined by the preference of the physician and the patient, adverse effects, and the cost-effectiveness.

EVALUATION OF PATIENTS WITH PRETERM LABOUR

Preterm labour is diagnosed when a mother with less than 37 completed weeks of the gestational period has regular uterine contractions that are followed by progressive cervical dilation and effacement. It is essential to determine if the patient is in true labour or if the delivery is imminent. Less than 10% of women with a clinical diagnosis of preterm labour will deliver within seven days of initial presentation¹⁷.

A distinction between the clinical presentation of both preterm labour (PTL) and preterm pre-labour rupture of membranes (P-PROM) could be difficult and vary. The diagnosis that is often made based on the clinical findings could be unreliable, thus many studies have suggested the use of transvaginal ultrasound cervical length assessment (CL), oncofoetal fibronectin test (offFN), the Actim Partus test, Amnisure, and Nitrazine in improving the diagnosis.

It is of utmost importance to conduct an initial assessment of women with preterm contractions to find out the likelihood of the patient delivering prematurely. A comprehensive algorithm to follow for preterm labour assessment is also available for further reference at <http://www.marchofdimes.org/pdf/nevada/nv-Preterm-Labor-Assessment-Toolkit.pdf>¹⁸.

The diagnosis of P-PROM is made by observing the pooling of amniotic fluid by a sterile speculum examination. If the pooling is not observed, the NICE guidelines (2020) advise performing phosphorylated insulin like growth factor binding protein 1 test (PIGFBP-1; used in Actim Partus test) or placental alpha macroglobulin I test (PAMG-1; Amnisure test) of vaginal fluid. It is suggested not

use Nitrazine test to diagnose P-PROM¹³.

Diagnosis of preterm labour for women with intact membranes should follow the clinical assessment which includes clinical history taking and sterile speculum examination. If it is suggestive of preterm labour and she is 29+6 weeks or less, a treatment plan for preterm labour is to be followed. If she is 30 weeks or more, the likelihood of birth within 48 hours is determined with transvaginal ultrasound measurement of cervical length or foetal fibronectin test¹³.

A risk prediction tool (combining quantitative foetal fibronectin, cervical length, and past obstetric history) for both symptomatic and high-risk asymptomatic women has been developed to provide an individualized estimate of preterm delivery¹⁹.

Up-to-date algorithm for diagnosis and management of preterm labour is also available for further reference²⁰.

MANAGEMENT OF PRETERM LABOUR

Management of preterm labour begins with a comprehensive history, examination, and investigations, collaboratively aimed at determining the diagnosis and excluding the fetomaternal complications that require imminent delivery. Despite great medical advances in managing prematurity, finding the best strategy to minimize the preterm birth rate and to improve neonatal outcomes is still debatable. Exclusion of the conditions associated with expedited delivery allows adjunct tests (such as cervical length measurement, foetal fibronectin) to be utilized and to initiate targeted use of therapies to improve neonatal outcomes²⁰.

Treatment modalities for the management of preterm labour include; antenatal corticosteroid therapy, cervical cerclage, tocolysis, antibiotics, administration of magnesium sulphate, use of cervical pessary, and foetal monitoring. The current dilemma related to management perspective is not in deciding the best treatment modality but determining which is better for the patient and the physician with less adverse events and best cost-effectiveness.

ANTENATAL CORTICOSTEROID THERAPY

The use of corticosteroids is associated with a significant reduction in neonatal morbidity and mortality. It is associated with enhanced foetal lung maturation, reduction in respiratory distress syndrome, necrotizing enterocolitis, intraventricular haemorrhage, and neonatal ICU admissions¹⁷. It is recommended to offer maternal corticosteroids to women between 24 and 33 weeks of pregnancy and to consider for women between 34 and 35 weeks who are in suspected or diagnosed or established preterm labour. The optimal benefit of corticosteroid therapy is said to be achieved between 24 – 34 weeks of gestation, but the results of the Epicure study have shown reduced neonatal mortality and improved neurodevelopment with deliveries between 22 – 24 weeks as well⁶.

The RCOG Green Top guidelines state, ‘Although there are limited data to support the use of antenatal corticosteroids in multiple pregnancy, the overall improvement in outcomes in singleton foetuses would suggest that steroids could be beneficial in multiple pregnancy’²¹. Repeated doses of corticosteroids are not encouraged since

there is a concern regarding an increased risk of cerebral palsy. According to the RCOG guidelines ‘Antenatal corticosteroid use reduces neonatal death within the first 24 hours and therefore should still be given even if delivery is expected within this time’²¹ as a rescue therapy.

Betamethasone 12 mg given intramuscularly in two doses or dexamethasone 6 mg given intramuscularly in four doses are the steroids of choice to enhance lung maturation²¹.

RESCUE CERVICAL CERCLAGE

In a study conducted in women with prolapse of the amniotic sac during live pregnancies between the 17+0 and 26+0 weeks of gestation, the following results were noted. With emergency cerclage, the pregnancy was prolonged by 41 days with an outcome of 72% live births as opposed to the pregnancy prolongation of 3 days and only 25% of live births resulting with the conservative therapy (including bed rest, tocolysis, and antibiotics)²².

It is recommended to consider rescue cerclage for women between 16 and 27+6 weeks of pregnancy with a dilated cervix and exposed, unruptured foetal membranes, while contraindicated when there are signs of infection, active vaginal bleeding, or uterine contractions¹³.

TOCOLYSIS

Tocolytic agents are medicines that are given to women in preterm labour to prolong pregnancy for at least 48 hours to enable administration of antenatal corticosteroids, magnesium sulphate, or

buy more time for maternal transport to a tertiary care facility.

Tocolytics in common use include calcium channel blockers (Nifedipine), oxytocin receptor antagonists (Atosiban), and cyclooxygenase inhibitors (Indomethacin). Betamimetics (Eg: Ritodrine) associated with severe maternal side effects are no longer recommended.

It is recommended to offer Nifedipine for tocolysis for women between 26 and 33 weeks of pregnancy who have an intact membrane and are in suspected preterm labour. It is suggested to offer Atosiban for tocolysis if Nifedipine is contraindicated²³.

ANTIBIOTICS

Preterm labour is associated with intrauterine bacterial infection and it is more evident before 32 weeks of gestation. Several reviews and meta-analyses conducted to determine the effectiveness of the use of prophylactic antibiotics found out that there was no benefit of its use especially, with intact membranes. It is further suggested that babies exposed to antenatal Co-amoxiclav had an increased risk of cerebral palsy¹².

It is recommended to use a combination of clinical assessment and tests (C reactive protein, white blood cell count, and measurement of foetal heart rate using cardiotocography) to diagnose intrauterine infection (chorioamnionitis) in women with P-PROM. Further, it is suggested to offer oral Erythromycin 250mg 4 times a day (or oral Penicillin) for a maximum of 10 days for women with P-PROM or until she is in established labour¹³.

MAGNESIUM SULPHATE

Administration of antenatal magnesium sulphate has been shown to decrease the occurrence and severity of cerebral palsy in infants due to its neuroprotective effect.²⁴ It is recommended to offer intravenous magnesium sulphate for women between 24 and 29 +6 weeks of pregnancy and to consider it for women between 30 and 33+6 weeks of pregnancy, who are in established preterm labour or having a planned preterm birth within 24 hours.

Magnesium sulphate is given as a 4g bolus over 15 minutes, followed by 1g per hour until the birth or for 24 hours. It is also advised to monitor clinical signs of magnesium toxicity (bradycardia, hypotension, respiratory depression, hyporeflexia, and decreased urine output) at least every 4 hours¹³.

ANTENATAL AND INTRAPARTUM FOETAL MONITORING

The monitoring options for a patient in established P-PROM include foetal heart rate monitoring, foetal scalp electrodes, and foetal scalp blood sampling.

It is recommended to offer women in established preterm labour (but with no other risk factors), a choice of foetal heart rate monitoring using either cardiotocography using external ultrasound or by intermittent auscultation. If it is not possible to monitor foetal heart rate using the above methods it is advisable to discuss with the women between 34 and 36+6 weeks of pregnancy, the possible use of a foetal scalp electrode. The possibility of using foetal scalp blood sampling between 34 and 36+6 weeks of pregnancy can be considered if the benefits are likely to outweigh the potential risks¹³.

MODE OF BIRTH AND TIMING OF CORD CLAMPING

It is recommended discussing the risks and benefits of caesarean delivery and vaginal birth with women in suspected, diagnosed, or established preterm labour and women with P-PROM. Caesarean delivery could be considered for women in suspected, diagnosed, or established preterm labour between 26 and 36+6 weeks of pregnancy with breech presentation. Clamping of the cord should be done between 30 seconds to 3 minutes following delivery with the baby positioned at or below the level of the placenta. If a preterm baby needs to be moved away from mother for resuscitation or in a significant maternal bleeding, milking of the cord is considered followed by clamping as soon as possible¹³.

PRACTICE POINTS AND RECOMMENDATIONS

01. Preterm birth is a health issue with a significant burden due to the high rate of neonatal morbidity and mortality associated with prematurity. Gestational age of delivery is the main determining factor of the foetal outcome hence prolonging pregnancies even for a few weeks reduces risks for the newborn.
02. The risk of recurrence of preterm birth mainly depends on the associated specific condition which necessitated the previous early delivery.
03. There is not a single or combined screening method with high sensitivity and specificity for early identification of preterm birth.
04. Primary prevention initiated during the period of preconception is the most effective step in reducing the incidence of preterm labour.

05. The risk of PTB is inversely related to the length of the cervix. Natural progesterone decreases the risk by 50%, in singleton pregnancies with a short cervix with statistically significant reduction in the risk of respiratory distress syndrome, low birth weight, and fewer admissions to the neonatal intensive care unit.
06. The risk estimation for preterm delivery can be improved by transvaginal cervical length assessment combine with the detection of fetal fibronectin in the cervicovaginal secretions.
07. Vaginal progesterone and cervical cerclage are equally effective for the prevention of preterm labour in women with singleton pregnancies. However, there is no adequate evidence that progesterone is effective in preventing preterm deliveries in multiple pregnancies. Therefore, further research is needed to clarify this association.
08. Antenatal corticosteroids (either B etamethasone or Dexamethasone) and Magnesium sulphate due to their associated reduction in neonatal mortality and morbidity, play a major role in the treatment of preterm labour.

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