FOGSI FOCUS

Prevention of
Pre-Term Labour

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Preface

Preterm Labour is one of the 5 ‘P’ problem of pregnancy. Despite of understanding the problem, the prevalence is static even in developed countries.

The problem of being born to soon is more in babies born before 33 weeks gestation and babies born in developing countries with low resource settings.

This multiauthored FOGSI focus is a comprehensive collection of all aspects of Preterm Labour. The authors have done a great job in rehearsing each topic and compiling relevant information which will be useful to the practising obstetrician.

We hope all FOGSIANS will benefit from this manuscript.

Happy Reading

Jaideep Malhotra, Narendra Malhotra

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1 Epidemiology of preterm labour

Dr. Seema Pandey, MD, FICOG

Out of all the anthropoid species the human neonate is born much more immature, perhaps its nature's mechanism to avoid the large head of the human fetus from becoming impacted in small pelvis of the mother who has adopted to a bipedal gate.

Definition:

as per world health organization (WHO) and federation of international gynecologist and obstetricians (FIGO) Spontaneous preterm labor is "labor resulting in birth before 37 completed weeks (259 days) of gestational age, based on the first day of last menstrual period."

- This definition has no functional basis and must not be confused with prematurity, which is the lack of development of various organ systems (especially lungs leading to respiratory distress syndrome) at the time of birth.
- The concept of completed weeks should not be misunderstood while truncating it to a round of form of weeks. For example a woman with 36 weeks plus 6 days would be considered as 36 completed weeks and not 37. Due to this error up to 10% of preterm babies are mis-classified.
- The main concern and burden comes from those who are born before 33 weeks (90%)

Epidemiology:

- The burden of pre-term labor is much more in developing countries like India.
- There are no accurate recent world wide data regarding the prevalence of preterm labor, but estimate ranges from 5% in developed countries to 25% in third world countries. The prevalence has been static in developed countries for decades and is in the range of 5-10%.
- 28% of total early neonatal deaths (death within 7 days) are due to preterm birth.
- The children who survive, there are major financial burdens due to the morbidity associated with physical and psychological issues.
- Though the incidence of preterm birth is on the rise but events leading to this are not clear and well understood. Etiology is thought to be multifactorial, whether these factors play independently or work in unison is still not clear.

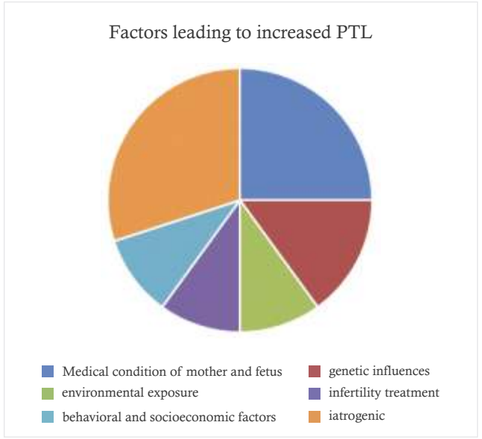

Figure 1- Major categories of Preterm labor

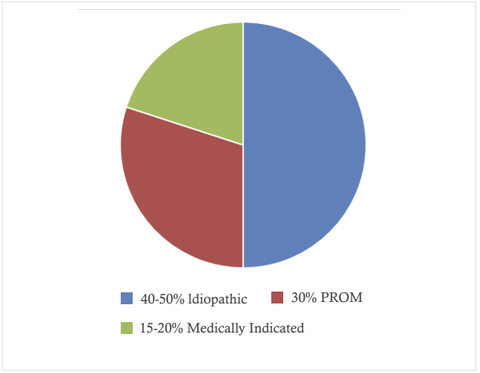

Figure 2- Major causes of PTL

Spontaneous	Iatrogenic
Infection	Hypertension
PROM	Diabetes
Idiopathic contractions	Intra uterine growth retardation (IUGR)
Multiple pregnancies	
Cervical dysfunction	
Antepartum hemorrhage	
Stress	
Malnutrition	

- There are ethnic variations in preterm birth rates and it is higher in black population. This could be associated with an accelerated rate of maturity in black fetus and neonate. Surprisingly the gestation specific mortality rate is lower in these neonates who are born before 38 completed weeks.
- 45-50% preterm deliveries are idiopathic, followed by PROM in 30% and 15-20% are medically indicated planned preterm deliveries,
- Iatrogenic preterm delivery is the main cause in developed countries. These births take place between 28 to 35 weeks mostly due to hypertension and pre-eclampsia.
- The commonest etiological factor worldwide is infection, mainly due to Malaria and HIV.
- Other responsible factors are, multiple pregnancies, intra-uterine growth retardation (IUGR), maternal stress and intense physical labor.
- The main challenge is finding ways to distinguish and quantify very early, early and late pre-term births, which will decide the terms of survival, short and long term morbidity and health resources investments.
- Categorization of pre-term birth (spontaneous vs iatrogenic) is important as this will show the true global trend of PTL and at the same time it will help in making policies and interventions to reduce the risk of preterm labor and deliveries.

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2. P. Steer, faculty of medicine, Imperial college London

2 Causative factors - how much do we know

2.1 Etio-pathogenesis of preterm labor

Dr Asha Reddy

The pathophysiology of preterm birth is multifactorial, very complex and not clearly understood. Several genetic, physiological and environmental factors are associated with preterm birth and contribute to uterine activation, labor and birth. In the recent years increasing assisted reproduction techniques, increasing rates of multiple births and the resultant increasing obstetric intervention have also lead to the increase in preterm labor. Genital infections and inflammation play a significant role in the etiopathogenesis of preterm labor. Uteroplacental ischaemia, endocrine and metabolic disorders are other important causes. Most pathways eventually lead to Fetal inflammatory response (FIRS and the associated morbidity. The diverse etiology of preterm delivery makes its prediction difficult. Understanding the etiopathogenesis and identification of women with risk for preterm delivery is the key for prevention of preterm labor.

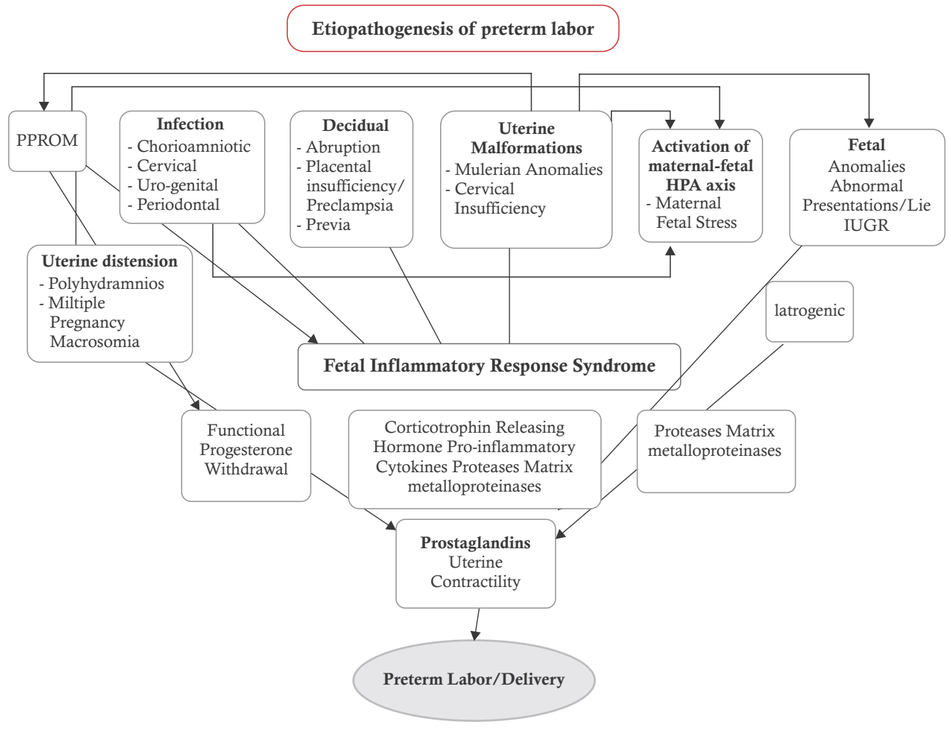
Factors associated with increased risk of Preterm labor /delivery

1) Preterm premature rupture of membranes (PPROM)
2) Previous history of preterm labor/delivery
3) Decidual thrombosis/ hemorrhage (abruption)
4) Maternal smoking during pregnancy,
5) Advanced maternal age,
6) Sub-optimal weight gain during pregnancy,
7) Maternal stress
8) Cervical insufficiency (Idiopathic or Iatrogenictrauma, cervical surgeries/forced dilatation)
9) Mechanical factors such as uterine over distention from multiple gestation or polyhydramnios
10) Uterine distortion (eg, müllerian duct abnormalities, fibroid uterus)
11) Maternal uro-genital infection inflammation/fever (UTI, bacterial vaginosis) systemic infection
12) Intrauterine Infection
13) Hormonal changes (maternal or fetal stress)
14) Uteroplacental insufficiency (hypertension, drug abuse, smoking, alcohol consumption)
15) Fetal-Anomalies, Growth Restriction, Abnormal lie and presentation
16) Environmental
17) Genetic

Etiology and Mechanisms of Preterm Labor

1) Maternal-fetal HPA activation	Stress	Maternal-fetal HPA activation
2) Infection and inflammation	Intrauterine Lower genital tract	Proinflammatory cytokine and prostaglandin cascade
	Systemic	Matrix metalloproteinases
3) Decidual hemorrhage	Thrombophilias, Abruptio placentae	Thrombin
	Autoantibody syndromes	Matrix metalloproteinases
4) Pathologic uterine overdistension	Multifetal gestation	Expression of gap junctions proteins
	Polyhydramnios	Prostaglandins Oxytocin receptors

Causes of preterm labor are multifactorial and vary according to gestational age. Each pathway to preterm labor has its specific initiators. Most of these pathways eventually share uniform effectors of preterm labor. For example, whether it is related to stress or infection, fetal HPA activation plays a role. Similarly, whether they are related to infection, uterine overdistension, or PPROM, MMPs play a role. As a final point, myometrial contractility is initiated by prostaglandins; regardless of the initiating cause.



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2.2 Role of Infection in Preterm Labour

Dr. Arshi Iqbal

Introduction

A strong body of evidence suggests that infection plays a role in the pathogenesis of preterm labour and delivery.

Evidence supporting a role for infection in the onset of labour

- Administration of bacteria or bacterial products to animals results in either abortion or labour.
- Systemic maternal infections such as pyelonephritis, pneumonia, malaria, and typhoid fever are associated with the onset of labour.
- Intrauterine infection is associated with preterm labour and delivery.

Definition of intrauterine infection

The gold standard for the diagnosis of an intrauterine infection is a positive microbiological culture for micro-organisms.Intrauterine infection can be classified according to the location of the micro-organisms into two broad categories: intra-amniotic and extra-amniotic infections. It is possible to obtain biological material for microbiological culture from the amniotic cavity (i.e. fluid) and the chorioamniotic space.[24,25] It is not easy to culture material derived from human decidua. Therefore, in practice, most studies in patients with preterm labour and delivery have focused on microbial invasion of the amniotic cavity (defined as a positive amniotic fluid culture for micro-organisms when the fluid is retrieved by transabdominal amniocentesis).

The amniotic cavity is normally sterile and therefore the isolation of any micro-organism from the amniotic fluid constitutes evidence of microbial invasion. This condition often exists in the absence of clinical signs and symptoms of infection.

Pathways of intrauterine infection

- Micro-organisms may gain access to the amniotic cavity and fetus via any of the following pathways:
- Ascending from the vagina and the cervix
- Haematogenous dissemination through the placenta (transplacental infection)
- Retrograde seeding from the peritoneal cavity through the fallopian tubes
- Accidental introduction at the time of invasive procedures such as amniocentesis, percutaneous

fetal blood sampling, chorionic villous sampling, or shunting.

- Histological chorioamnionitis is more common and severe at the site of membrane rupture than in other locations, such as the placental chorionic plate or umbilical cord
- In virtually all cases of congenital pneumonia (stillbirths or neonatal), inflammation of the chorioamniotic membranes is present
- Bacteria identified in cases of congenital infections are similar to those found in the lower genital tract
- In twin gestations, histological chorioamnionitis is more common in the firstborn twin and has not been demonstrated only in the second twin. As the

membranes of the first twin are generally opposed to the cervix, this is taken as evidence in favour of an ascending infection.

Microbiology of intrauterine infection

Intra-amniotic inflammation is often detected in the absence of infection. This may partly be due to the culturing methods employed in hospital laboratories, which are unable to detect the uncultivated species. two-thirds of the species detected by the culture-independent methods were not isolated by culture. They included both uncultivated and difficult-to-cultivate species, such as *Fusobacterium nucleatum, Leptotrichia (Sneathia) spp., a Bergeyella sp., a Peptostreptococcus sp., Bacteroides spp.,* and a species of the order *Clostridiales* Previously unrecognized, uncultivated, or difficult-to-cultivate species may play a key role in the initiation of PTB.

The most common microbial isolates from the amniotic cavity from women with preterm labour and intact membranes are:

- *Ureaplasma urealyticum,*
- *Fusobacterium species, and*
- *Mycoplasma hominis*
- *Chlamydia trachomatis*

Bactarial Vaginosis:

Although the normal vaginal milieu is characterised by the presence of a large number of bacterial species, under physiologic conditions H_2O_2-producing lactobacilli account for 95% of these and act against the proliferation of other microorganisms by maintaining an acidic vaginal pH. In the normal vaginal ecosystem, the anaerobe to aerobe ratio is normally kept between 2:1 and 5:1. In the presence of BV, the quantity and quality of H_2O_2-producing lactobacilli decrease, the vaginal pH increases, and there is a subsequent shift in the anaerobe to aerobe ratio to between 100:1 and 1000:1. The same bacteria found in the healthy vaginal environment are also found in BV, the difference being not in the quality but in the quantity of the microorganisms present. It is not possible to identify any single species as the cause of BV, although *Gardnerella vaginalis, Prevotella* spp., *Bacteroides* spp., *Mobiluncus* spp. *and Mycoplasma* spp. are the most commonly found in association.

Urinary Tract Infection:

The bacteria causing urinary infection in pregnancy essentially mirror those in nonpregnant patients. Escherichia coli accounts for 80-90% of infections[11] but other Gram-negative bacilli, such as *Proteus mirabilis and Klebsiella pneumoniae*, can be cultured. *Proteus, Klebsiella* and most *Enterobacteriaceaespecies* show urease activity and form urinary calculi, which can act as reservoirs of infection. The coagulase negative cocci, *Staphylococcus saprophyticus*, is the second most frequently cultured uropathogen,[12] while other Gram-positive cocci, such as group B haemolytic streptococci, are less frequently isolated but remain clinically important.[13] Other less common uropathogens include *Staphylococcus aureus* and *Mycobacterium tuberculosis*, which can arise via haematological inoculation rather than ascending infection. Nonbacterial causes include *Chlamydia species* and fungal infections, such as *Candida albicans*.

Group B streptococcal infection:

Vaginal colonisation with group B streptococci is strongly associated with preterm rupture of membranes, labour and delivery and is a proven cause of neonatal sepsis. Evidence relating group B streptococcal bacteriuria with similar consequences is less well established.[14,15] However, treatment for urinary group B streptococcal infection is associated with a significant reduction in preterm, prelabour rupture of membranes and delivery rates.[16] Readers are referred to the Royal College of Obstetricians and Gynaecologists (RCOG) guideline[17] pertaining to prophylaxis of group B streptococcal infection

2.3 Preterm Labor- Anatomical Causes

Dr. Vimee Bindra

- **Pre-term labor has multifactorial etiology, of which the anatomical causes account for 9%.**

- **Cervical Factors: most common anatomical factor**

Cervical length and strength together with the quality of cervical mucus contribute in retaining the pregnancy in the uterus and in preventing the entry of potential pathogens ascending from the vagina.

- Cervical incompetence resulting from

- Short cervix- congenital/developmental (DES exposure)
- Cervical surgery-conisation/ablation/excisional procedure
- Obstetric injuries-difficult instrumental vaginal deliveries, cesarean section after full dilatation.

Pathophysiology: A partially dilated or short cervix, fails in retaining the intrauterine contents - May allow the bacteria to ascend into the lower pole of the uterus, where they act through the toll-like receptors and stimulate the activation of inflammatory cytokines, prostaglandins and incite an inflammatory response.

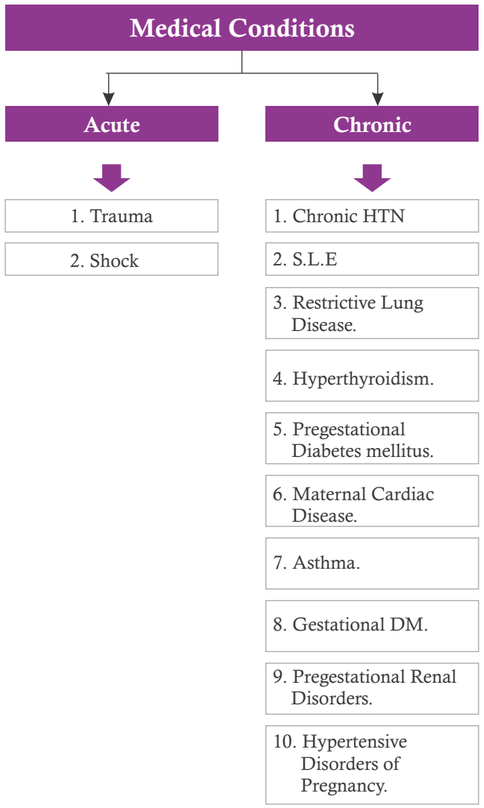
- **Uterine Factors**

- Uterine malformations
- Congenital : Septate uterus Bicornuate, Unicornuate
- Acquired : Intrauterine adhesions
  Fibroids (> 6 cm size, protruding into uterine cavity)

2.4 Medical conditions associated with Pre-Term Birth

Dr. Chaitanya Ganpule

A preterm birth could be spontaneous or indicated means the one that is induced. There are number of maternal medical conditions that are associated with either spontaneous or induced preterm labour.



Majority of these diseases causes placental insufficiency. This limits the delivery of oxygen and nutrients to the baby leading to fetal growth retardation.

In certain maternal conditions like cardiac diseases, the progressive worsening of the condition can mandate "indicated "preterm birth to preserve the well being and health of the mother.

"Underweight" and "Obesity "needs special mention, as these are maternal conditions that can lead to preterm labour.

Low maternal pre-pregnancy weight & Body mass Index have consistently associated with pre term birth. Women with low pregnancy weight & BMI tend to put on less weight during pregnancy as compared to heavier women, On the contrary obesity is associated with less risk of pre term labour

2.5 Twin pregnancies and preterm labour

Dr. Kavitha Gautam

Introduction

Twins contribute 2-4 % of all births. The rate of preterm birth < 37 weeks among twins is approximately 60 % [1].

Incidence:

Percentage of singletons born less than 37 weeks GA is 11.1 % [2]

Twin born < 37 weeks GA is 61.9 % [2]

Twins < 32 weeks GA 13.3 % [2]

Etiology:

[3-4] Classified into 3 types

- PPROM
- SPM
- Preterm birth due Medical reason

[5] Twin Pregnancies are more liable to

Maternal Hypertension

Fetal Distress

Fetal Growth restriction

TT Syndrome

Discordant

Placental abruption

Maternal obesity BMI > 35 Kg/m2

All above leading to early termination of pregnancy

Incidence of preterm birth is reported higher for IVF/ ICSI pregnancies [6-7]

Mechanisms of Preterm Birth:

[8] The Mechanism for Preterm birth are still unclear

↓

Uterine Over distention

↓

Myometrial contraction

↓

Releases Prostaglandins / up regulates Oxytocin receptors

↓

Induces Labor

Risk is higher in Monochorionic diamniotic twins[9]

Nulliparous women with twin gestation have higher chance of preterm births [10]

Fetal sex appears to be a risk factor for preterm delivery in spontaneously conceived dichorionic twin gestations [11]

Twin pregnancies with one or two male fetuses are at higher risk than females [11]

Prediction of Preterm Birth:

Cervical length measurement using TVS [12]

Timing of cervical length measurement

16 - 24 weeks [13]

13- 34 weeks [14]

20 - 23 measurement followed by 3-5 weeks later at a difference of 25% between each measurement is a good predictor of preterm birth in asymptomatic twins even when cervical length is >25 mm [15]

Funneling:

Cervical funneling seen at midtrimester had a high

sensitivity and specificity for prediction of the preterm birth, which was higher for gestations born <32 weeks than <35 weeks (86% + 54 % specificity 78 % + 82 %) [16]

Funneling seen TVS [16]

Patient is on dorsal lithotomy position with an empty bladder without undue pressure on the cervix [17]

Wait up to 5 min to note any changes; in cervical length and shape [17]

Funneling is defined as dilatation of the internal os >5 mm in width for a period of at least 3 minutes [17]

It differs according to position of patient. Found to be seen more in an upright position[17]

Evaluating the women in the upright position permits earlier detection of funneling [17]

Prevention of preterm birth in Twins:

Cerclage in twins

Is there a Role for Prophylactic Cerclage in Twins?

A prospective study shows an increase in preterm birth in cerclage group when compared to no cerclage group, in <32 weeks [18]

An older meta-analysis reported increase in incidence of preterm birth <35 weeks in twins with a short cervix who underwent cerclage cervix, previous history of preterm birth , in contrast to singletons that had a significant reduction of preterm birth with cerclage[19]

Progesterone

Has a physiological effect on uterine quiescence mediated by a direct effect on intracellular calcium concentration and prostaglandin synthesis [20]

Two large Randomized Controlled study. PREDICT [21] and STOPPIT study[22] showed no reduction of the preterm birth rate with natural vaginal progesterone administration in twin pregnant patients with short cervices [23]

The effect was similar with 17 hydroxy progesterone weekly IM injections [24-25]

A recently published, randomized, controlled study showed that vaginal progesterone and prophylactic cerclage in effective in multiple gestation.

The potential explanation for this is preterm term birth in twins is more often because of uterine distension and contraction than due to cervical problems.

Role of Progesterone in Prevention of Preterm Birth in IVF Pregnancies

A randomized, placebo-controlled study studying the effect of daily 400 mg of vaginal progesterone suppositories for prevention of preterm birth in singleton and twin ICSI pregnancies found a significant reduction in preterm birth rate in the singleton group receiving progesterone where as no difference in given pregnancy group[26]. Thus further strengthening current evidence that progesterone does not prolong twin pregnancies.

Bed Rest

A Cochrane review of randomized trials studying the effect of hospital bed rest in multiple pregnancies found no significant evidence to recommend the same for routine clinical practice [27]

Pessaries

Only one small study reported some positive effect of pesssary insertion in twins preventing preterm birth [28]

Management of Threatened Preterm Birth in Twin Pregnancies

Tocolysis and Treatment of Preterm Birth[29 - 30]

Mechanism of Action of Tocolysis

β **Adrenergic Receptor Agonists**

Ritodrine and Salbutamol (β2 agonists)

Impair intracellular cyclic AMP concentration

Myometrial relaxation

A Cochrane review including 11 randomized, controlled trials, involving 1,332 women reported that these agents were more efficient than placebo for delaying preterm birth for 2 days [30 – 31]

In twins, a Cochrane review shows insufficient evidence to support or refute the use of prophylactic oral betamimetics [32]

Magnesium Sulphate

Decreases calcium intracellular concentration.

Inhibits myometrial contraction.

There is evidence and recommendation to administer magnesium sulphate in expected preterm births, especially

<30 weeks, for neuroprotection and reduction of incidence of cerebral palsy [33]

It is classed as one of the three effective drugs to delay of delivery for > 48 weeks [34]

Its effectiveness was similar in singletons and twins [35]

Prostaglandin-Synthase Inhibitors

Indomethacin, a nonspecific COX inhibitor and Calcium channel blockers, gave the best results to delay delivery for 48 weeks and had the least maternal side effects and reduced reduce respiratory distress syndrome, neonatal mortality.

Indomethacin however, use should be restricted in duration and limited to pregnancies below 32 weeks because of fetal ductus arteriosus closure risk and decreased urine production responsible for oligohydramnios [31, 36 – 38]

Calcium-Channel Blockers

Calcium-channel blockers transfer of calcium ions into myometrium.

Decrease intracellular free calcium concentration and induce.

Myometrial relaxation [36]

Use of calcium channel blockers in acute tocolysis (delay of delivery 48 hours up to 7 days [39] has been proven to be more effective than β adrenergic receptor agonists and with fewer side effects.

However, studies have shown no significant reduction of Perinatal adverse outcome in use of nifedipine as maintenance tocolysis [40]

Nifedipine tocolysis is proven as effective and safe for use in both singleton and twin gestations [41]

In singleton and multiple gestations, the role of tocolysis in the setting of acute preterm labor is to attempt to delay delivery long enough to administer corticosteroids to promote fetal lung maturity [42]

Antibiotics

Incidence of preterm labor due to infection is 20–40 %, especially <30 weeks [43]

In the preterm birth with intact membranes, the antibiotics is not recommended [44], but in case of preterm rupture of the membranes (PROM), antibiotics have shown a significant decrease of preterm delivery and chorioamnionitis [45]

In bacterial vaginosis associated with pregnancy, antibiotics were found to eradicate infection, but they showed no effect on the incidence of preterm delivery [46]

Therapeutic Emergency Cervical Cerclage in Twins

The largest study published so far[47] to check the effectiveness of emergency cerclage on 414 sets of twin gestations and 92 sets of triplet gestations, could not show any significant prolongation of pregnancy duration in the ultrasound indicated cerclage (closed cervical length ≤ 2.5 cm)[48]

In triplets, no benefit from cerclage placement was found even when cervical shortening was documented[49]

Conclusions:

Preterm birth is a major increasing health problem, especially with twins. Although the predictions of pre-term birth become possible with transvaginal ultrasound cervix measurement and fetal Fibronocten measurement, no effective preventive or treatment measure is available for management of pre-term birth in twins.

Reducing the number of twins resulting from ART procedures, such as single embryo transfer and careful monitoring of ovulation induction should help.

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2.6 ART and preterm labour

Dr. Seema Pandey, MD, FICOG

Assisted reproductive technique (IVF, ICSI, egg donation, embryo donation, surrogacy) is a medical procedure where both male and female gametes are handled outside one's body to achieve pregnancy. Since the birth of first IVF baby in 1978 around 5 million babies had been born throughout the world by this procedure. It accounts roughly for 1.5% of total births in America.

ART has been a boon for those childless infertile couples who could not conceive previously. But at the same time one has to pay the cost in terms of various health hazards for the baby like preterm birth, low birth weight, small for gestational age, frequent NICU admissions etc. it's been always a point of debate whether ART itself poses these complications or infertility per say (mainly female factor) is responsible for it.

- Numerous studies have quoted a two-fold rise in spontaneous preterm singleton birth in ART cycles.
- There is no explanation for this association and this effect may fully or partially be confounded with other factors contributing to infertility.
- Looking at a recent meta-analysis done in 2015 on US population, using SMART data (states monitoring assisted reproductive technology), a collaborative project of ART surveillance initiated by center for disease control and prevention (CDC) and Massachusetts, Florida and Michigan public health agencies. It is a population based data set of vital records. The goal of this study was to study the link between increased pre-term birth and ART. Following were the observations of this study-
- 98.8% deliveries were among non- ART users and 1.2% were ART- singleton deliveries.
- The ART-conceived pregnancies were of shorter duration (mean GA 38.3 - 38.7 weeks) than non-ART pregnancies (mean GA 38.8 weeks <.01)
- After adjusting for maternal age, education, race, state and year, it was found that of all four infertility groups female infertility had the highest adjusted odd ratio for preterm birth (aOR 1.60,95% CI, 1.5,1.7).
- The adjusted odd ratios for couples with both female and male infertility and those with male infertility only were 1.49 and 1.24 respectively. Adjusted odd ratio for unexplained infertility was 1.26.
- Among singleton births to primi-paras, those conceived with ART had an increased risk for pre-term birth, even when only the male partner had been diagnosed with infertility. The risk of pre-term birth for ART-conceived infants whose mothers were diagnosed with infertility included the earliest deliveries.
- 38.8% gestations conceived by ART are born preterm
- 36.5% are low birth weight
- 3.8% are small for date
- 37.7% prevalence of twins with IVF
- 33.4% prevalence with ICSI
- Double embryo transfer has higher rates of all these complications as compared to single embryo transfer.

Possible causes leading to preterm birth:

1- ART per se

2- COH and mechanical manipulation

3- Factors responsible for infertility

4- Twin and multifetal gestations

5- Vanishing twin syndrome

6- Transfer of fresh versus frozen embryos

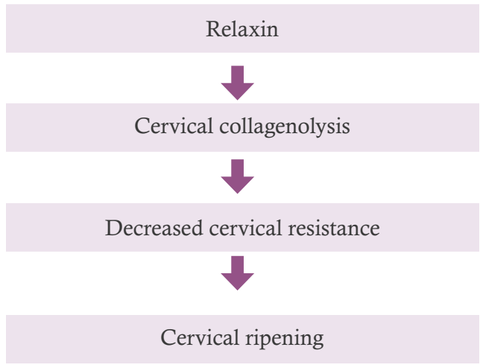
7- Use of donor versus autologous oocytes

8- Iatrogenic (interventions done by treating physician)

Biological explanations-

1. Abnormal rise in Relaxin level throughout the pregnancy conceived by ovulation induction or COH as compared to spontaneous conception. Relaxin is a polypeptide hormone secreted by corpus luteum and decidua.
2. Abnormal placentation

How does Relaxin work



Conclusion:

We can only prevent all these untoward consequences of ART leading to perinatal mortality by-

1 Strict control on indications of ART

2 Promoting SET (Single embryo transfer)

3 Improve the safety of manipulations in the ART process.

4 Strengthen ANC care of ART pregnancies.
There are still a lot of unsolved problems with regard to ART, and we need to do further research on its molecular and cellular level of mechanisms.

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2.7 Iatrogenic Causes and Preterm Labour

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Introduction:

Being born before 37 weeks gestational age or before 259 days, is defined as preterm birth according to the World Health Organization. Preterm birth occurs in 5 to 10% of all pregnancies. About 30% of all preterm births are due to iatrogenic causes (1).

Classification of etiology:

Preterm birth can result from many maternal and fetal causes. Three major clinical subtypes of preterm birth can be identified, namely, iatrogenic (medically indicated) preterm birth, spontaneous preterm birth, and preterm birth following premature rupture of membranes. Recent increases in preterm birth occurred predominantly due to increases in iatrogenic preterm birth at late preterm gestation (34 - 36 weeks) (2). Other factors in the increase in preterm birth have included changes in maternal characteristics (such as increases in older maternal age) and in the frequency of multiple births (3).

Certain other conditions deem a special consideration as iatrogenic causes through modus of various pathophysiology viz - cervical surgery causing cervical incompetence, amniocentesis causing chronic or acute premature preterm rupture of membranes and assisted reproductive techniques causing multiple gestation..

Iatrogenic Pathophysiology of Preterm Labour:

- Pregnancy induced hypertension, eclampsia and its consequences requires early intervention for fetal and maternal health.
- Overt and gestational diabetes, have adverse effect on fetus, in such condition, early delivery is advisable.
- Elderly gravida patients enters pregnancy with co-morbid conditions which can lead to preterm labour.
- Uterine anomalies are one of the factors where interventions and early birthing becomes necessity.

Fetal factors such as intrauterine growth restriction, unstable lie, fetal anomalies can cause early intervention and preterm labour.

- IUGR fetuses require early delivery.
- Fetal anomalies can force obstetrician for early intervention and delivery, to save fetus.

Considering antenatal interventions, such as amniocentesis, cervical cerclage can also lead to preterm labour.

- **Amniocentesis**: As per study done by Medda et al, midtrimester amniocentesis and preterm labour does have as association. Risk of preterm labour increases with midtrimester amniocentesis (4). Third-trimester amniocentesis performed with continuous ultrasound guidance has a high success rate and low risk for complications (5)
- **Cervical Cerclage**: Rescue cerclage has more chances of preterm labour compared to elective cerclage.
- **Cervical Cone Biopsy**: The risk of preterm birth is at most minimally affected by a small excision. Larger excisions, particularly over 15 mm or 2.66 cms are associated with a doubling of the risk of both preterm and very preterm births. The risk does not decrease with increasing time from excision to conception. Close obstetric monitoring is warranted for women who have large excisions of the cervical transformation zone.

There is a view that repeated per vaginal examination during antenatal period to check for short cervix can lead to pre-term birth. The Cochrane data on RDCA does not explain same.

Mode of Delivery in Pre-term Labour:

The optimal mode of delivery for women thought to be in preterm labour is controversial. Claims that planned preterm caesarean delivery reduces the chances of fetal or neonatal death and birth trauma have been met by counter claims that such a policy leads to risk of serious morbidity for both mother and baby.

Mallory 1991 found no evidence that caesarean section can be protective for preterm neonates, especially for very low birth weight infants (less than 1500 g). The same author published further evidence that, for intermediate or late low-risk preterm neonates (32 to 36 weeks), primary caesarean section may in fact increase risk of neonatal mortality and morbidity, such as pulmonary hypoplasia, necrotizing enterocolitis or sepsis (6).

In multifetal gestation mode of delivery depends on presenting part and fetal weight.

How To Prevent Preterm Labour?

Risk assessment in antenatal period.

Physical assessment

The integrity of the cervix and the extent of any prior injury to the cervix may be assessed by speculum and digital examination. The presence of asymptomatic bacteriuria, sexually transmitted disease (STD), and symptomatic BV may be investigated

History

A history of prior preterm deliveries places the patient in the high-risk category. Of the predictors of preterm birth, past obstetric history may be one of the strongest predictors of recurrent preterm birth.

Cervical length

A short cervical length in the early or late second trimester has been associated with a markedly increased risk of preterm labor and delivery. In a study, a cervical length of 25 mm or less at 28 weeks had a 49% sensitivity for prediction of preterm delivery at less than 35 weeks.

Laboratory tests

In patients with a history of midtrimester loss, laboratory tests for risk assessment include the following:

- Rapid plasma reagin test
- Gonorrheal and chlamydial screening
- Vaginal pH/wet smear/whiff test
- Anticardiolipin antibody (eg, anticardiolipin immunoglobulin [Ig] Gand IgM, anti-beta 2 microglobulin)
- Lupus anticoagulant antibody
- Activated partial thromboplastin time
- One-hour glucose challenge test

In addition, one should consider TORCH (toxoplasmosis, other infections, rubella, cytomegalo virus infection, herpes simplex), immunoglobulin G, and immunoglobulin M screening whenever the historical or clinical suspicion is present.

Disturbances in vaginal flora following any procedure can lead to vaginosis or vaginitis.

For procedural, iatrogenic preterm labour prevention, utmost important is asepsis.

DIAGNOSIS:

Contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix at 24-37 weeks' gestation are indicative of active preterm labor.

- **Lab test**: Vaginal Fetal Fibronectin, sample should be collected prior to pelvic examination.

Advntages of Iatrogenic Preterm Labour:

- Increase in medically indicated preterm birth coincided with reductions in stillbirth rates and neonatal mortality rates.
- Infants born following medically indicated preterm birth showed larger reductions in neonatal mortality and serious neonatal morbidity rates when compared with infants born following spontaneous preterm birth.
- Neonatal mortality/serious neonatal morbidity rates among infants born following preterm PROM showed a temporal increase among singletons and no significant change among twins. (7)

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3 How sharp are our diagnostic tools?

3.1 Predicting Preterm Labour

Dr. Raju R. Sahetya M.D.; D.G.O.; D.F.P.; F.C.P.S.; F.I.C.O.G.

Preterm labour and birth are a major cause of perinatal morbidity and mortality. Despite modern advances in obstetric and neonatal management, the rate of preterm birth in the developed world is increasing. The ability to accurately predict when labour will occur remains elusive. This is likely due to the multifactorial aetiology of preterm labour wherein women may display different clinical presentations that lead to preterm birth. The discovery of biomarkers that could reliably identify women who will subsequently deliver preterm may allow for timely medical intervention and targeted therapeutic treatments aimed at improving maternal and fetal outcomes. This short review will highlight recent advances in the field of biomarker discovery and the utility of single and multiple biomarkers for the prediction of preterm birth.

1. Causes of Preterm Birth

Premature birth may be iatrogenic or spontaneous. Iatrogenic premature birth is the result of a medical intervention due to a fetal and/or maternal condition (e.g., fetal growth restriction, preeclampsia) necessitating early delivery. By contrast, spontaneous premature birth often occurs despite best efforts to prolong the pregnancy. It is estimated that up to 80 percent of premature births fall into this category. A prerequisite for the success of this strategy is the reliable prediction/identification of women at risk of preterm birth.

Evidence suggests that spontaneous preterm labour and delivery are a heterogeneous condition with many triggers or precipitating factors including maternal genital tract haemorrhage, cervical dysfunction, idiopathic uterine contractions, infection, malnutrition, multifetal pregnancy, and spontaneous rupture of the fetal membranes.

Four distinct mechanisms for the pathogenesis of preterm labour have been described and include premature activation of the fetal hypothalamic pituitary axis, mechanical stretch, inflammation/matrix remodelling and placental abruption. The temporal convergence of cervical effacement and dilatation, myometrial activation, and the rupture of fetal membranes are common to all spontaneous labour.

2. Current Approaches to the Prediction of Preterm Labour

Current screening tests for the prediction of spontaneous preterm labour can be divided into three general categories: (i) risk factor assessment, (ii) cervical measurement, and (iii) biochemical markers; however, it should be emphasised that significant associations with labour may not necessarily translate into clinical predictive utility.

2.1. Risk Factor Assessment

Clinical risk factors for preterm birth include (i) Low socioeconomic status, poor antenatal care, extremes of maternal age, or malnutrition, (ii) behavioural factors including smoking, illicit drug use, alcohol consumption, or heavy physical work, (iii) obstetric history including familial (genetic) predisposition, uterine malformation, previous preterm labour or preterm PROM, previous cone biopsy or cervical surgery, and (iv) aspects of the current pregnancy such as multifetal gestation, genital tract bleeding and/or infection, fetal malformation, preterm rupture of membranes, shortened cervix, and other pregnancy complications including preeclampsia and gestational diabetes mellitus.

A previous preterm birth before 34 weeks' gestation is amongst the strongest risk factors for subsequent preterm

birth. However, insofar as nulliparous women have no past obstetric history to call upon, any such previous history risk factor - based assessment is inapplicable in their situation.

2.2. Cervical Measurement

In some women, a shortened cervical length can be due to natural biological variation. In other cases early cervical shortening or effacement may be due to haemorrhage or infection leading to inflammation, or due to biophysical effects of uterine over distension (e.g., multifetal gestation) or subclinical contractions. Using transvaginal ultrasound, a cervical length below the 10th centile for gestational age increased by 6- fold the risk of delivery prior to 35 weeks' gestation.

2.3. Biochemical Markers

While the direct study of gestational tissues (e.g., vaginal epithelium, cervix, endometrium, myometrium, placenta, choriodecidua, and fetal membranes) may provide more accurate localised information on the state of a pregnancy and impending labour, it is the more easily accessible biological fluids including whole blood/serum/plasma, urine, saliva, amniotic fluid, and cervico vaginal fluid (CVF) that are more likely to be amenable to the creation of a rapid bedside biomarker test for predicting preterm labour or preterm PROM. These body fluids provide rich sources of proteins and metabolites that vary in concentration in response to pregnancy and adverse pregnancy states.

2.3.1. Amniotic Fluid

While the genome and proteome of amniotic fluid have been extensively investigated, particularly in the context of fetal chromosomal abnormality or infection (with or without clinical chorioamnionitis), the sampling of amniotic fluid (amniocentesis) is not likely to become routine practice solely for the purpose of preterm labour prediction. Indeed, the procedure per se can precipitate preterm labour as well as potentially causing fetal trauma and infection.

2.3.2. Saliva

Salivary progesterone has been investigated as a biomarker of preterm birth. A low saliva concentration of progesterone, obtained between 24 and 34 weeks of gestation, has been described in women at risk of early preterm labour (<34 weeks of gestation). This study was conducted on women with a singleton pregnancy with at least one risk factor for preterm birth. Fetal fibronectin (fFN, see below) was also measured at 24 and 27 weeks of gestation in the same cohort of women. However, no observed correlation between fFN and salivary progesterone was demonstrated.

2.3.3. Urine

There is a paucity of data examining chemical biomarkers of preterm birth in urine. With the exception of screening pregnant women for asymptomatic bacteraemia, where antibiotic treatment reduces the risk of infection-mediated preterm birth, little is known of the specific inflammatory mediators that may trigger spontaneous preterm labour.

2.3.4. Blood (Serum or Plasma)

While blood is easily accessible, allowing for rapid sampling that is minimally invasive, its relatively large volume and remote proximity from gestational tissues suggest that chemical biomarkers associated with impending labour may be diluted amongst the thousands of other serum/plasma proteins. The fact that many proteins derived from gestational tissues also reside in the peripheral circulation may further skew any meaningful interpretation of their abundance in relation to labour.

A promising study of plasma urocortin concentration in women with symptoms of threatened preterm labour displayed a sensitivity of 80%, a specificity of 100% with a positive predictive value of 100% for preterm delivery within 7 days of sampling.

2.3.5. Cervicovaginal Fluid

The CVF is a complex mixture of secretions derived from the vagina, endocervix, endometrial decidua, and amniochorion and therefore serves as an important diagnostic site to monitor maternal and fetal health in pregnancy. Unlike the amniotic fluid the CVF is readily accessible and collection is minimally invasive and safe. There are two commonly used clinical biomarker tests for the prediction of preterm labour, namely, fetal fibronectin (fFN) and phosphorylated insulin-like growth factor binding protein-1 (phIGFBP1).

Beyond 16 - 20 weeks' gestation fFN is not detectible in the CVF. If found beyond 20 weeks' gestation, it may suggest a disruption of the choriodecidual interface and has been identified as a predictor of spontaneous preterm labour.

phIGFBP1 is secreted by decidual cells and leaks into cervical secretions when fetal membranes detach from decidua. It has been used to clinically assess cervical maturation. Clinical diagnostic trials indicate that, like fFN, phIGFBP1 is a good negative predictor of preterm birth (92% specificity) but lacks suitable sensitivity and positive predictive value in asymptomatic women. Clearly there is a need for improved biomarker predictive test (s) for preterm labour than currently available tests.

4 .Future Approaches to the Prediction of Preterm labour

Identification of a single biomarker to predict spontaneous preterm labour poses a significant challenge due to the heterogeneity of clinical presentations and of the biochemical mechanisms involved in preterm birth. Presently,none of the common late-pregnancy complications including preterm labour can be predicted with sufficient accuracy (sensitivity and specificity) using a single biochemical marker. For this reason the simultaneous quantification of multiple biomarkers, that may include demographic/risk-factor(s), cervical length and biochemical marker(s), and the development of multivariate classification models represent a promising approach to improving diagnostic efficiency.

5. Conclusion

The ability to accurately predict and therefore prevent preterm labour and birth remains one of the crucial challenges facing modern obstetrics.

Identifying women who are most at risk of preterm birth would allow the tailoring of medical interventions and targeted therapeutic treatments aimed at improving maternal and fetal outcomes.

Current predictive tests display poor positive predictive values and it is likely that no single biomarker will ever achieve the desired predictive efficacy due to the multifaceted aetiology of preterm birth. Therefore multiple biomarker modelling is receiving increased attention.

To this end, the CVF is an ideal biological fluid for the discovery of molecular biomarkers associated with labour due to its proximity to the gestational tissues that undergo change with advancing gestation.

Genomic, proteomic, and metabolomic approaches will ultimately enable the discovery of novel molecular biomarkers involved in the physiology of labour and pathophysiology of preterm birth., but it is becoming increasingly evident that different groups of biomarkers (perhaps comprising risk factors, cervical length, and molecular markers) may be required to distinguish pregnancies experiencing spontaneous preterm labour, spontaneous preterm PROM, and symptomatic (threatened) preterm labour, whether these are in the presence or absence of genital tract infection.

3.2 Biophysical Markers and Ultrasound in Predicting Preterm Labour

Dr. Selvapriya Saravanan

Introduction:

Although preterm birth may occur quiet frequently the severity of infant effects may be less even if a few days are gained in the duration of pregnancy .It would be even great if these complications are anticipated earlier & predicted at the earliest so that the managing team can be alerted well in advance. Here comes the undeniable role of **ultrasound** The identification of risk factors for predicting preterm birth is advantageous because it may provide insights into a better understanding of the mechanisms leading to preterm birth.

Low sensitivity Risk Factors

- Demographic
- Behavioural
- Biological

High sensitivity Risk Factors

- Cervico vaginal fluid
- Amniotic fluid
- Urine
- Saliva
- Serum or plasma (biologic fluid)

Predisposing factors of biophysical markers

- General tract infection
  - Group B streptococci
  - BV
  - Chlamydia
  - Gonorrhea
- Over distended uterine - poly hydramnios, multiple pregnancy
- Uterine Anomalies
  - Unicornuate
  - Bicornuate
  - Septate, arcuate
  - Fibroid
- UTI

Predictors

Clinical	BP	BC
History	Uterine Contraction	Fetal fibroneten
MPG	Bishop score >= 4 cm	IC - 6 & 8
Infection	Cervix length .AFI	TNF - infinite

Role of Cervical Assessment

- Clinical utility of cervical length is limited.
- CL with TVS is the most useful biophysical marker for predicting PTL.
- CL has highest NPV in long cervical lengths.
- But its PPV is very low in short cervical lengths. 55% patients fall inside the non-obvious cervical length range.

Short Cervix

- CL<= 2cm on TVU at 18 - 22 weeks gestation is clinically significant
- Cervical shortening is usually plainless & may be accompanied by a watery vaginal discharge or be a symptomtic.

Cervical insufficiency

Structural weakness of cervix associated with an increase in mid-trimester loss.

Cervical factors scoring

- Cervical length less than 2cms in TVS
- Cervical score less than 1.5 in digital cervical exam.

Cervical score=cervical length cm (-) Cervical dilatation (cm) at the intos

Significance of CL (Limitations & Advantages)

- Best predictive accuracy
- Different population show variation
  - Asymptomatic low risk or high risk women singleton gestations
- Women with twin, triplet pregnancies
  - Symptomatic women with PTL or PProm

Key points

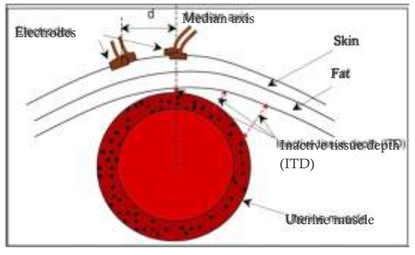
- The finding of a short cervix on routine mid pregnancy USG increases the risk of preterm birth.
- The earlier the short cervix in found the greater the risk of preterm birth
- The risk of preterm birth is further heightened if risk factors are present.
- Women should be able to have an extensive discussion about the risks of preterm birth with a senior obst / neurologist

The uterine electrical activity

The electrical activity of uterine muscle is representative of uterine contractility. Its characterization may be used to detect a potential risk of preterm delivery in women even at an early gestation stage.

The Role of gene-gene

Gene-environmental interaction as well as epigenetics has the potential to further elucidate & improve understanding of the underlying mechanisms or spontaneous preterm birth.



Dark red crown represents the uterine muscle.

The EHG is obtained with surface electrodes placed on the abdomen permitting the recording of the EMG produced by the uterine muscles

Uterine Artery Doppler

Poor predictor of preterm as it has an negligibly low prevalence in preterm.

Consensus from literature

1. Cervical length in the general Obstetrical population is relatively stable over the first 2 trimesters. The natural history of cervical length change may be useful in identifying women to increased risk of spontaneous preterm birth. Because there may be different patterns or a delay in cervical length shortening. Repeat assessment of cervical length may be useful.
2. There is no consensus on the optimal timing or frequency of serial evaluations of cervical length. If repeat measurements are performed ,they should be done at suitable interval to minimize the likelyhood of observation error.
3. Transvaginal sonography can be used to assess the risk of preterm birth in women with a history of spontaneous preterm birth and to differentiate those at higher and lower risk of preterm delivery. The gestational age of a prior preterm birth affects the cervical length in future pregnancy.
4. Cervical length measurements can be used to identify increased risk of preterm birth in asymptomatic women t<24 weeks who have other risk factors for preterm birth (previous excisional treatment for cervical dysplasia, uterine anomaly or prior multiple dilatation and evacuation procedures beyond 13 weeks gestation). However, there is insufficient evidence to recommend specific management strategies, such s cerclage, in these women.
5. No specific randomized trials have evaluated any interventions in asymptomatic women at >24 weeks gestation who are at increased risk of preterm birth (e.g: those who have a history of prior spontaneous preterm birth, previous excisional treatment for cervical dysplasia, uterine anomaly or prior multiple dilatation and evacuation procedures beyond 13 weeks gestation). And who have a short cervical length. This information may help with empiric management of these women, including reduction of activity level, work, or travel, relocation, increased surveillance, and administration of corticosteroids.

6.Transvaginal ultrasound appears to be safe in preterm premature rupture of membranes but its clinical predictive value is uncertain in this context.

7.It is unclear whether ultrasonographic cervical length assessment has significant advantages over clinical examination alone after elective or emergency cervical cerclage placement, although some signs, such funnelling to the stitch are associated with a high risk of preterm premature rupture of membranes . There is no consensus on the frequency or timing of ultrasonographic cervical length assessment post cerclage.

8.It is unclear whether a policy of cervical length surveillance is equivalent to clinicl assessment of the need for elective cerclage in those at risk of preterm delivery.

9.Ultrasonographic cervical length assessment and fetal fibronectin appear to be similar in predictive ability ,and the combination of both in high risk population may be of value. However further research is needed in this area.

Recommendations

1. Transabdominal ultrasonography should not be used for cervical length assessment to predict preterm birth.

2. Transvaginal ultrasonography is the preferred route for cervical assessment to identify women t increased risk of spontaneous preterm birth and may be offered to women at increased risk of preterm birth.

3. Transperineal ultrasonography may be offered to women at increased risk of preterm birth if transvaginal ultrasonography is either unacceptable or unavailable.

4. Because of poor positive predictive values and sensitivities and lack of proven effective interventions, routine transvaginal cervical length assessment is not recommended in women at low risk.

5. In women presenting with suspected preterm labour, transvaginal sonographic assessment of cervical length may be used to help in determining who is at high risk of preterm delivery and may be helpful in preventing unnecessary intervention. It is unclear whether this information results in a reduced risk of preterm birth.

6. In asymptomatic women with a history of spontaneous preterm birth and an ultra-sonographically diagnosed short cervical length (<25 mm) prior to 24 weeks gestation, cervical cerclage should be considered to reduce the risk of preterm birth.

7. In all a symptomatic women who present with membranes at or protruding past the external cervical os, an emergency cerclage should be considered to reduce the risk of preterm delivery.

3.3 Biochemical Markers in Prediction of Preterm Labour

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Preterm birth accounts for about a major proportion of perinatal morbidity and mortality which necessitates the need of early detection of the onset of the preterm labour.

Number of biochemical markers in the body fluids such as in the amniotic fluid, urine, cervical mucus, vaginal secretions, serum or plasma, in saliva has been used in detection of preterm labour.

Extracellular Matrix Degradation Pathway Fetal Fibronectin

It is a glycoprotein secreted by fetal membranes which helps in attachment of chorion to decidua. (1,2)

It is rarely present between 23 to 34 weeks

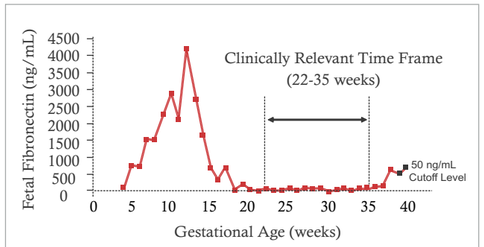
Screening asymptomatic women for the presence of cervical fetal fibronectin at 24 or 26 weeks of gestation had a high sensitivity in predicting more than 60% of preterm birth within the next 4 weeks. (3)

Disruption of the interface results in release of fibronectin.

Levels greater than 50 ng/ml is considered positive

It has negative predictive value of 99% which means that a negative test at 24 weeks is reassuring of not having delivery in 7 days

Fetal Fibronectin vs Gestational Age



Source: Adapted from Garite TJ et al.Contemp Obstet Gynecol. 1996;41:77-93.

Intrauterine Infection

1.**Bacterial vaginosis**- diagnosed by gram stain nugent score or by the amsel criteria. Presence of BV during pregnancy is consistently associated with a twofold increase in risk of spontaneous preterm birth.

Inflammation Pathway Inflammatory-Bacterial invasion of the choriodecidual space activates the production of a number of cytokines and these markers of inflammation (interleukin 1,2,6 and 8,tumor necrosis factors-α, and CRP) have been evaluated as biomarkers in Spontaneous preterm labour

Interleukin 6

- IL 6 secretion increases due to the inflammatory reaction provoked by the bacteria ascending from the vagina reaching to pregnant uterus.
- It initiate the synthesis of prostaglandins (PGs) and matrix metalloproteinases (MMPs) in the deciua,

chorion, amniotic fluid leading to onset of preterm labour.

- Cervical IL-6 concentrations measured at 24 weeks of gestation were elevated in women who delivered at < 32 weeks of gestation.(5)

C-REACTIVE PROTEIN-

- C-reactive protein (CRP) is a maternal systemic inflammatory marker that thus it has been evaluated as an marker of preterm birth
- C-reactive protein (CRP) in early second trimester (14–18 weeks) ranged from 5.6 g/mL to 16.4 g/mL and elevated CRP concentrations in maternal serum shows increased risk of preterm birth.(4). But results from other studies did not corroborated with it.

Fetal Anomalies Pathway

Beta Human Chorionic Gonadotropin

- Elevated levels of-beta human chorionic gonadotropin in cervico vaginal fluid usually in the early second trimester is associated with the increased risk of onset of preterm labour.
- Cervico vaginal beta hCG greater than 77.8 mIU/mL had a sensitivity of 87.5% in detecting women having onset of preterm labour at >34 weeks of gestation.(6)

Alpha Fetoprotein

- Elevated level of alpha fetoproteinat 24 weeks is associated with increased risk of onset of preterm labour. (7)

Estrogen Metabolic Pathway

Estriol

Estriol is the major form of circulating estrogen during pregnancy (8) and measurements of estriol from maternal saliva samples appear to correlate with maternal serum levels. (9,10)

- Early estriol surge or increased level (2.3 ng/ml) may be clinically helpful in identifying women at elevated risk for preterm labor and birth (11,12)

Uses of Multiple Biomarkers

One of three serum biomarkers (S. alkaline phosphatase, maternal serum α-fetoprotein, and granulocyte colony-stimulating factors) had a collective sensitivity of 81% and specificity of 78% for the prediction of spontaneous preterm birth at 32 weeks of gestation and 60% sensitivity and 73% specificity for the prediction of spontaneous preterm at <35 weeks of gestation.

CONCLUSION

Many biomarkers like fetal fibronectin (FFN),α-fetoprotein, C-reactive protein (CRP), multiple members of the interleukin family (interleukin-6,interleukin-8, interleukin-10), matrix metalloproteinases, pregnancy-associated plasma protein A, relaxin, lactate dehydrogenase (LDH), thyroid-stimulating hormone, adrenocorticotrophic hormone, vascular endothelial growth factor (VEGF), ferritin, prolactin, ceruloplasmin, alkaline phosphatase (ALP), glucose, placental protein 13, corticotrophin releasing hormone, tumor necrosis factor-α, tumor necrosis factor-β, estriol and human chorionic gonadotrophin (hCG) have been studied in maternal serum, amniotic fluid, and cervico vaginal fluid (CVF). Not a single biomarker has been evolved till date, which has sensitivity & reliability for the detection of preterm labour. The variability in results across the studies may be due to dissimilarities in study designs, different timings of collection of blood, and different study population.

Key points

- Fibronectin levels in cervico vaginal fluid along with cervical length is a sensitive method of detection of preterm labour.
- Amniotic fluid CRP > 110 ng/ml had a sensitivity and specificity of 80.8% and specificity of 69.5% respectively in prediction of preterm labour at <34 weeks.
- CRP is a nonspecific biomarker as its levels get varied with infection and other pathogenic abnormalities.
- IL-6 in cervico vaginal fluid has the ability to detect onset of prterm labour whereas levels of IL-8 and IL-10 do not correlate with it.
- High serum AFP are strongly associated with preterm birth, pre-eclampsia and placental abnormalities.
- High levels of Beta hCG in cervico vaginal fluid was found in women with preterm labour

Beta hCG test has advantage of low cost and wide availability

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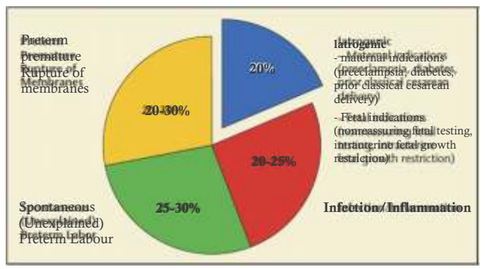
4 Management- where are we today?

4.1 Can we prevent preterm labour

Dr. Anuradha Khar

Preterm birth (PTB) is defined as childbirth occurring at less than 37 completed weeks of gestation [a]. Preterm labour (PTL) is defined as occurrence of regular uterine contractions (4 or more in 20 minutes or 8 or more in 60 minutes) and cervical effacement[3] 1 cm in women with intact fetal membranes and gestational age < 37 weeks [b]. Especially in epidemiological context, the two terms are often used interchangeably.

PTB is an important determinant of neonatal mortality and morbidity. Worldwide the rate of preterm birth is 10-12%,varying widely between developed and underdeveloped countries [c]. In India, incidence of preterm labor is 23.3% and of preterm delivery varies between 10-69% in different settings. In one study, incidence of preterm labor was 22% and that of preterm deliveries 20.9% [d]. The worldwide incidence of PTL is increasing, perhaps due to increasing maternal age, increasing trends of tobacco and alcohol consumption in pregnant women and higher prevalence of maternal medical illnesses such as diabetes and hypertension. Increase in the availability of ART leading to multiple pregnancies, and increased frequency of Caesarean section also due to a changing obstetric practice pattern may also contribute to this increase in PTL [c]



A number of underlying factors are associated with PTL. Intrauterine infections, premature rupture of membranes, and iatrogenic preterm labour in cases where early termination of gestation due to maternal and fetal indications such as preeclampsia and IUGR are important causes. About 30-50% of all PTL maybe spontaneous or unexplained [e]. (Fig 1). Many risk factors for PTL have been identified. (**Table 1**)

Table 1. Risk factors for Preterm labour

Prior Preterm labour	Smoking
Age < 18 and > 40 years	Anemia
Nutritional factors	UTI
Poor socioeconomic status	Physical stress
Cervical factors	Genital infections
Uterine anomalies	Twins, polyhydramnios etc

Some Antenatal factors are known to increase the chances of preterm labour. Three factors have been specifically identified in a Cochrane review by Piso et al to increase PTL. Treatment of asymptomatic trichomonas infection in pregnancy with metronidazole leads to an increased risk of PTL. [g]. Vitamin C supplementation has been associated with higher chances of PTL.[h] And lastly Estrogen supplementation especially diethylstilbestrol during pregnancy for various indications is known to increase PTL risk[i]. Estrogen supplementation has been abandoned in recent obstetric practice.

Interventions to prevent Preterm labour:

Cervical cerclage: Transvaginal ultrasonography of the uterine cervix identifies women at risk of preterm labour. Both cervical length measurement and funneling, alone or in combination, have been shown to be useful in predicting spontaneous preterm birth in asymptomatic women in an analysis of 46 trials [j]. There may be some benefit of cervical cerclage in pregnant women with short cervix. In a meta analysis of five trials Vincenzo et al found that In women with previous spontaneous preterm birth, singleton gestation, and cervical length less than 25 mm, cerclage significantly prevents preterm birth and composite perinatal mortality and morbidity.[k]. In a large study, Owen et al showed that in women with a prior spontaneous preterm birth less than 34 weeks & cervical length less than 25 mm, cerclage reduced preterm birth and perinatal mortality. In pregnancies between 34 & 35 weeks, the same study showed beneficial effect of cervical cerclage when the cervical length was less than 15 mm (l). There is however no evidence to support cerclage in women with prior preterm labour without ultrasound evidence of short cervix as well as emergency cerclage procedures

Progesterone supplementation: Recent data suggest that progesterone is crucial for maintaining uterine quiescence in the latter weeks of pregnancy. Functional withdrawal of Progesterone activity at the uterine level is seen at the onset of labour, both at term and preterm [m]. This observation is the basis of progesterone supplementation in prevention of preterm labour. A number of recommendations have been made for oral, injectable and vaginal progesterone supplementation for this purpose. (**Table 2**)

In women with preterm premature rupture of membranes, there seems to be no evidence to support the role of injectable progesterone supplementation [n, o], despite the common practice of oral progesterone in these patients. In multiple pregnancies, especially in twins and triplets there is clear evidence that progesterone supplementation has no effect in preventing preterm labour [p].

Aspirin: Low dose aspirin, cyclooxygenase inhibitors and other anti-platelet agents are considered as a strategy to improve outcomes in high risk pregnancies. Specifically, pre-eclampsia is associated with deficient intravascular production of prostacyclin, a vasodilator, and excessive production of thromboxane, a vasoconstrictor and stimulant of platelet aggregation. However, among all of the agents tried, only low dose aspirin has been shown to reduce preterm labour, that too only in women at high risk for preeclampsia. In an analysis of 29 trials that studies 31,151 women at high risk for pre-eclampsia it was shown that there was an 8% relative risk reduction of preterm labour [q]

Smoking cessation: Shah and Bracken, in an analysis of 20 studies showed that there was a dose-dependent association between maternal smoking and preterm labour [r].

The other important interventions that are shown to be beneficial are:

a. Fetal fibronectin testing
b. Bed rest for hypertension during pregnancy
c. Dietary magnesium supplementation in hypertension in pregnancy
d. Treatment of clinical hypothyroidism with levothyroxine
e. Calcium supplementation In patients with high risk of developing pre-eclampsia

Table 2. **Recommendations for Progesterone Supplementation to Prevent Preterm Birth**

Indication	Progesterone Indicated?	Dose and Route of administration
Prior spontaneous preterm birth	Yes	17_-hydroxyprogesterone caproate 250 mg intramuscularly weekly. Start 16-20 weeks till 36 weeks
Cervical shortening <24 weeks	Yes	Progesterone suppository 100-200 mg vaginally each night from time of diagnosis till 36 weeks of gestation
Multiple pregnancy	No	
Preterm PROM	No	

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4.2 Tocolytics- Evidence Based Update

Dr. Neema Acharya

Tocolysis word is derived from Greek word tokos, childbirth, and lytic, capable of dissolving. Tocolytics are pharmacological agents were first recognised for their ability to suppress uterine contractions in 1959, when Hall et al observed the tocolytic effects of magnesium sulphate (Hall et al, 1959). Following this in 1961, the beta-agonist isoxuprine was described as a first-line tocolytic (Bishop and Woutersz, 1961).

The fact that there are many tocolytic agents available for clinical use there is no single effective or perfect tocolytic without side-effects.

Five classes of tocolytic agents have been described:

1. Betamimetics
2. Calcium Channel Blockers
3. Oxytocin Receptor Antagonists
4. Nonsteroidal Anti-Inflammatory Drugs (Nsaids)
5. Magnesium Sulphate
6. Nitric Oxide Donors
7. Progesterone

(Ethanol, Potassium channel openers are also known as tocolytic agents but in practice are rarely used.)

Rationale of tocolysis -Various meta analysis and research reviews prove tocolytic agents are effective for up to 48 hours and may prolong pregnancy for up to 7 days, but this has not been equated to a significant reduction in perinatal morbidity or mortality. Therefore it is considered clinically reasonable both to use or not to use tocolytics, depending on the clinical scenario. It is the administration of steroids which improves preterm neonatal outcome and tocolytics give time for its action by prolonging the pregnancy. Hence it is reasonable to administer tocolytics to optimize time in-utero, so as to allow for the administration of corticosteroids and to facilitate transfer of the patient to a tertiary referral centre. There is no reliable national or international data on current use of each particular tocolytic class; however it is likely that oxytocin receptor antagonists (Atosiban) specifically developed for use as a tocolytic, and calcium channel blockers (Nifedipine) are the most widely used in clinical practice. ACOG in its practice guidelines has warned against the use of beta mimetics as tocolytics due to associated complications like pulmonary edema, cardiac failure. Recent Cochrane review concluded that though use of a progestational agent may reduce the frequency of uterine contractions, prolong pregnancy and attenuate the shortening of cervical length there is insufficient evidence to advocate progestational agents as a tocolytic for women presenting with preterm labour.

Indications for Tocolytic Therapy-Regular uterine contractions of at least 30 seconds duration at a rate of 4 per 30 minutes

- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of 50%
- a gestational age from 24 until 33 completed weeks
- a normal foetal heart rate

Fig 1 Site of action of tocolytic agents at cellular level

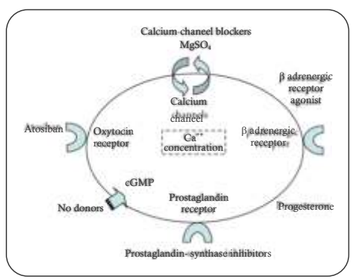

Table 1 showing details of administration of tocolytics

SR NO	TOCOLYTIC AGENT	DOSE/ROUTE PF ADMINISTRATION	BEFORE STARTING WATCH FOR /RULE OUT	SIDE EFFECTS
1	**NEFIDIPINE**	20 mg orally, followed by 20 mg orally after 30 minutes 20 mg orally every 3-8 hours for 48-72 hours with a maximum dose of 160 mg/d.	–	Hypotension tachycardia headache
2	**MAGNESIUM SULPHATE**	The initial recommended loading dose is 4-6 g IV over 20 minutes, followed by a maintenance dose of 1-4 g/h	Urine output Kidney function	Cardiac aarhythmia hypocalemia
3	**INDOMETHACIN**	100 mg PR followed by 50 mg PO every 6 hours for 8 doses.	Kidney function Amniotic fluid	Premature Ductus closure
4	**NITRIC OXIDE DONORS**	Inj ntg 50 to 100 mcgm/ml Nitroderm patch 10 mg	–	Headache. Hypotension
5	**BETAMIMETICS**	–	Cardiac / thyroid disease Severe anaemia	Tachycardia Tremors hypotension
6	**OXYTOCIN RECEPTOR**	Please refer to chapter on this topic	–	–
7	**PROGESTERONE**	**Dydrgestrone-10 mg bd orally daily Micronized progesterone 200 mcg twice a daily Vaginal progesterone 100mcg daily**	–	Drowsiness malaise

Practice guidelines summary for

- No particular tocolytic agent has been proven optimal for PTL. Tocolytic agents have not been proven to reduce perinatal or neonatal mortality; therefore it is also reasonable not to use tocolytics in the setting of PTL. They just help to prolong pregnancy to few hour or days and time needed for steroids to act is achieved.
- Both calcium channel blockers (Nifedipine) and Atosiban have similar efficacy in delaying pregnancy for up to 7 days but nifedipine may be more likely to delay delivery for 48 hours.
- Use of Progesterone for tocolysis has not been found to be effective and needs more research.
- Evidence supports not using them as mainatainance or repeat therapy as both do not appear to improve perinatal outcome and therefore is not recommended. Particular caution should be exercised if tocolytics are considered in multiple gestations due to the increased risk of adverse effects.
- All tocolytics have potential side effects and more so observed when used for PTL in multiple pregnancy.
- Use of multiple tocolytic agents should be avoided due to the risk of increasing adverse effects. Particular caution should also be exercised if nifedipine is used in combination with magnesium sulphate, either in the setting of tocolysis, or if magnesium is being used for neuroprotection.

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Evidence based tocolytic therapy

Meta analysis of tocolytic therapy showed following results of the 3263 titles initially identified, 95 randomized controlled trials of tocolytic therapy were reviewed. Compared with placebo, the probability of delivery being delayed by 48 hours was highest with prostaglandin inhibitors (odds ratio 5.39, 95% credible interval 2.14 to 12.34) followed by magnesium sulfate (2.76, 1.58 to 4.94), calcium channel blockers (2.71, 1.17 to 5.91), beta mimetics (2.41, 1.27 to 4.55), and the oxytocin receptor blocker atosiban (2.02, 1.10 to 3.80). No class of tocolytic was significantly superior to placebo in reducing neonatal respiratory distress syndrome. Compared with placebo, side effects requiring a change of medication were significantly higher for beta mimetics (22.68, 7.51 to 73.67), magnesium sulfate (8.15, 2.47 to 27.70), and calcium channel blockers (3.80, 1.02 to 16.92). Prostaglandin inhibitors and calcium channel blockers were the tocolytics with the best probability of being ranked in the top three medication classes for the outcomes of 48 hour delay in delivery, respiratory distress syndrome, neonatal mortality, and maternal side effects (all cause). The evidence says Prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes.

4.3 Atosiban in obstetrics

Dr. Neharika Malhotra, Bora, **Dr. Amreen Singh,** Rainbow IVF, AGRA

Introduction

Prematurity remains the leading cause of neonatal morbidity and mortality. Preterm babies are prone to serious illness or death during the neonatal period. Tocolysis aims not only to inhibit uterine contractions but also to allow a safe transfer of the pregnant patient to a tertiary care centre. It gives the opportunity to administrate corticosteroids for preventing neonatal risks associated with prematurity[1] There are many tocolytic drugs, atosiban is recently introduced drug in India. In India atosiban was approved in Oct 2014

Inhibition of uterine contractions with atosiban was first demonstrated in nonpregnant women. The first published reports of oxytocin antagonists for tocolysis came from Scandinavian studies at the end of the 1980s.

Atosiban is a oxytocin antagonist, that have the nonapeptide structure of oxytocin. In addition to oxytocin antagonist, atosiban is also an antagonist of vassopres in receptor[2] Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days. Atosiban is gaining popularity as it utero specific and can be safely used in expanded blood volume, Anemia, Where use of other tocolytics predispose to pulmonary edema.

Atosiban crosses the placenta in an average fetal versus maternal ratio of 0.124. Drug concentrations in the fetal circulation do not increase with longer infusion rates, suggesting that the drug does not accumulate in the fetus.

Mechanism of action

Atosiban inhibits the oxytocin-mediated release of inositol trisphosphate from the myometrial cell membrane. As a result, there is reduced release of intracellular, stored calcium from the sarcoplasmic reticulum of myometrial cells, and reduced influx of Ca^{2+} from the extracellular space through voltage gated channels. In addition, atosiban suppresses oxytocin-mediated release of PGE and PGF from the decidua.[3]

Pharmacokinetics

Steady state plasma levels are reached within an hour of starting the infusion. Atosiban clearance, volume of distribution and half life are independent of the dose. Once the infusion is stopped, plasma concentrations decline rapidly with an initial and terminal half life of 0.21 ± 0.01 and 1.7 ± 0.3 hours respectively.

Indication

Atosiban is indicated to delay imminent pre-term birth in pregnant adult women with:

- regular uterine contractions of at least 30seconds duration at a rate of ≥ 4 per 30 minutes
- a cervical dilation of 1 to 3 cm (0-3 for nulliparas) and effacement of ≥ 50%
- a gestational age from 24 until 33 completed weeks
- a normal fetal heart rate

Dose and Administration

Regime recommended by RCOG is a three-step procedure: an initial bolus dose of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours, then 6mg/hour for

up to 45 hours to a maximum of 330 mg .

In case a re-treatment with atosiban is needed, it should also commence with a bolus injection of atosiban 7.5 mg/ml, solution for injection followed by infusion with atosiban 7.5 mg/ml, concentrate for solution for infusion.

Atosiban should be stored at 2 - 8 0c. Monitoring of uterine contractions and fetal heart rate during administration of atosiban and in case of persistent uterine contractions should be done. The onset of uterus relaxation following atosiban is rapid, uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence (4 contractions/hour) for 12 hours.[4] Atosiban have effectiveness in delaying birth for up to seven days.[5]

Side effects

Gastrointestinal (>10%), Nausea (14%) Cardiovascular: Hot flush, hypotension, tachycardia Central nervous system: Dizziness, headache, Endocrine & metabolic: Hyperglycemia, Gastrointestinal: Vomiting, Local: Injection site reaction

Contraindications

Atosiban must not be used in the following conditions:

- Gestational age below 24 or over 33 completed weeks
- Premature rupture of the membranes > 30 weeks of gestation
- Suspected intrauterine infection
- Antepartum uterine haemorrhage requiring immediate delivery
- Intrauterine foetal death
- Eclampsia and severe pre-eclampsia requiring delivery
- Fetal distress
- Placenta praevia
- Abruptio placenta
- Any other conditions of the mother or fetus, in which continuation of pregnancy is hazardous
- Hypersensitivity to the active substance

Atosiban and other tocolytics

Apart from the atosiban, none of the tocolytics are uterospecific. Atosiban have superior efficacy without the conventional cardiovascular side effects compared to β-agonist. Beta agonists have less efficacy and higher rate of maternal adverse drug reaction such as tachycardia (frequent), pulmonary oedema, myocardial ischemia (rare) or metabolic changes. Other non-utero-specific agents as magnesium sulphate, calcium channel blockers and non-steroidal anti-inflammatory drugs have been used for tocolysis.

Nifedipine is also not uterospecific and have multiorgan side effects. Nifedipine has no licence or approval for use in pregnancy or spontaneous preterm labour. Reported adverse effects for nifedipine, the most widely used calcium antagonist, include flushing, palpitations, nausea and vomiting and hypotension. Nifedipine is contraindicated if the woman has cardiac disease and should be used with caution if she has diabetes or multiple pregnancy, owing to the risk of pulmonary oedema.[6]

Magnesium sulphate has minimal side effects but its effectiveness is questionable .

Atosiban in PPROM

Little evidence exists for the use of atosiban in cases of preterm prelabour rupture of membranes (PPROM). Studies have looked at the use of other tocolytics in PPROM and found no benefit in prolongation of pregnancy[7]

Atosiban in Multiple Pregnancy

There is only limited clinical experience in the use of atosiban in multiple pregnancies or the gestational age group between 24 and 27 weeks, because of the small number of patients treated. The benefit of atosiban in these subgroups is therefore uncertain

Future trends

Newer generation of oxytocin receptor antagonists such as barusiban, could be more efficient and have less affinity for the vasopressin receptors. It is a selective OT antagonist and has higher potency and prolonged duration of action than atosiban.

Other newer generation is retosiban, it has been shown to be an effective tocolytic. By intravenous and oral administration it produces a dose-dependent decrease in oxytocin-induced uterine contractions in non-pregnant female rats. These both drugs are under medical trial.[8]

Conclusion

Atosiban appear to have comparable effectiveness in delaying delivery, with fewer maternal adverse effects and less risk of rare serious adverse events than alternatives. It

appears to be the preferred tocolytic for use in view of its improved tolerability and equal efficacy to the alternative agents. Cost is one of the limiting factor for use of the drug in India. Still the discussion continues however, as to the overall use of tocolysis in cases of threatened preterm labour in developing countries like India .

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4.4 Management of Preterm Labour: Role of Antibiotics

Dr Paresh R Solanki, MD, Harnish Hospital, Deesa

- Maternal infections outside of the uterus are a relatively frequent cause of preterm labour. Approximately 5% to 10% of patients in preterm labour have an infection outside of the uterus, most commonly in the urinary tract.
- Evidence suggest that chorioamnionitis is the cause of 20% to 30% of all cases of preterm labour

Infection outside uterus		Infection inside
Systemic	**Local**	**chorioamnionitis**
Urinary tract infection most common- 5-10 %	Bacterial vaginosis, mixed vaginal infection, fungal infection	Ureaplasma urealyticum, Gardnerella vaginalis, Group B streptococcus, E coli, Bacteroids sp, Mycoplasma hominis, Fusobacterium sp, Listeria monocytogenes, Lactobacillus sp, Peptostreptococcus sp, Chlamydia trachomatis
Asymptomatic bacteriuria	Gardnerella vaginalis	
Respiratory tract infection	Chlamydia infection	
Other systemic infection	Group B streptococcus	
	Vaginal trichomoniasis	
	Culture may help in identifying type of infection as well sensitivity to drug	20-30 % of all preterm labour are caused by chorioamnionitis

Antibiotics for prevention of preterm labour:

Treating infections may be the most important preventive measure in patients at risk for preterm labor. Do per speculum examination and treat bacterial vaginosis or chronic cervicitis

Gardnerella vaginalis	First choice: Metronidazole 500 mg twice daily For 7 days 2nd choice : Ampicillin 500 mg 4 times daily for For 7 days For penicillin sensitive patients : Erythromycin, 250 mg 4 times daily For 7 days
Chlamydia	Amoxicillin (500 mg) or Erythromycin (250 to 500 mg) 4 times daily for 7 days
Group B streptococcus	Penicillin or Trimethoprim (160 mg)/ sulfamethoxazole (800 mg) twice daily for 10 days
Resistant cases	1. Treat husband / use of condom / abstinence 2. Take culture from vagina and treat accordingly
No visible infection on P/S examination	For at risk patients, do culture examination and treat infection, if any (group b streptococcus may not be indentified clinically)

Treatment of systemic infection:

Urinary tract infection (UTI)	Cefodoxime or cefelosporin group medicine or depending on sensitivity, and safe in pregnancy antibiotics can be used
Asymptomatic bacteriuria	Nitrofurantoin, 200 mg per day for 10 days to treat infection and then 100 mg daily can be given till term safely to prevent recurrence of infection At risk to preterm delivery, must under go urine examination, microbiology, and if bacteriuria is present, need to treated with appropriate antibiotics
Respiratory tract infection	Azythromycin 500 mg twice daily for 3 to 5 days or amoxicillin 500 mg 3 to 4 times daily for 5 days
Other infection	Need to be treated accordingly

Treatment of chorioamnionitis :

Once chorioamninitis evident clinically or by lab investigation or in established pre term labour.

Antibiotics has no Role in Prevention or Prolonging Delivery.

But antibiotics must be started to arrest further progress of infection, to new born and mother.

Iv antibiotics (all three)

1. Ampicillin/sulbactum, 3gm IV every 8 hourly or amoxicillin/clavulinic acid, 625 IV 8 to 12 hourly or Cefoparazone/sulbactum 2gm IV 8 to 12 hourly.
2. Metronidazole 500 mg IV 8 hourly.
3. Gentamycin 80 mg or Amikamycin 500 mg IV 12 hourly has to be given no need to continue tocolysis with clinically established chorioamnionitis, and require faster delivery.

Prevention of infection :

1. Education of patient for local hygiene
2. Better nutritional status
3. Coital abstinence or use of condom
4. Avoid frequent pelvic examination, better to do per speculum examination to check for any infection

Conclusion:

Infection whether systemic or local infection can cause preterm labour, chorioamnionits is well established infection in uterus will lead to delivery.

Need to prevent infection, and if there is local or systemic infection, need to be treated to prevent preterm labour.

Once preterm labour is established, antibiotics has no role in preventing labour, but definitely needed to arrest infection process.

There are other causes of preterm labour (Like placental insufficiency uterine anomaly, short cervix, twins, polyhramnious), need to evaluate case properly, and in such cases antibiotics has no role.

The use of probiotics (live organisms species) has been shown to be effective in treating Bacterial Vaginosis (BV), but evidence that probiotics treatment reduces the risk of preterm birth is lacking.

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4.5 Role of Progesterone in Preterm labour

Dr. Seema Pandey

- Progesterone derives its name from 'progestational steroid hormone' due to its primary function of preparing and maintaining the uterus for conception.
- The history of using progesterone as a therapeutic agent in preterm labour and threatened abortions dates back to 1960s. recent trials and studies have re-ignited this interest once again.
- Progesterone is a naturally occurring steroid hormone produced by gonads, adrenals, nervous system and placenta during pregnancy. It is a derivative of cholesterol.
- The natural progesterone is chemically identical to the progesterone secreted by ovaries, and it is synthesized from Mexican Yam or Soybean extracts or animal sources.
- Micronization decreases its particle size, increases its surface area and thus improves the absorption. This also results in exponential rise in bio availability but decreased metabolic and vascular side effects.[1]

How does progesterone work:

- Progesterone is a vital hormone in carrying pregnancy till term.
- Contrary to the popular belief, progesterone's key action appears to be on the cervix and thus it has a significant role in preventing pre-term labour than treating it. That's why progesterone is also known as 'gate keeper of pregnancy'.[2]

Progesteron
suppression of

↓

Calcium calmodulin-myosin light chain kinase system
Reduced calcium flux

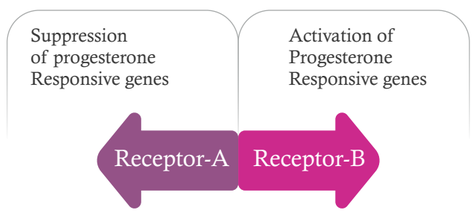
↓

Uterine quiescence (altering the resting potential of smooth muscles)

Another noted action of progesterone is its Anti-inflammatory action and if we believe the literature, through this pathway progesterone controls preterm labour.

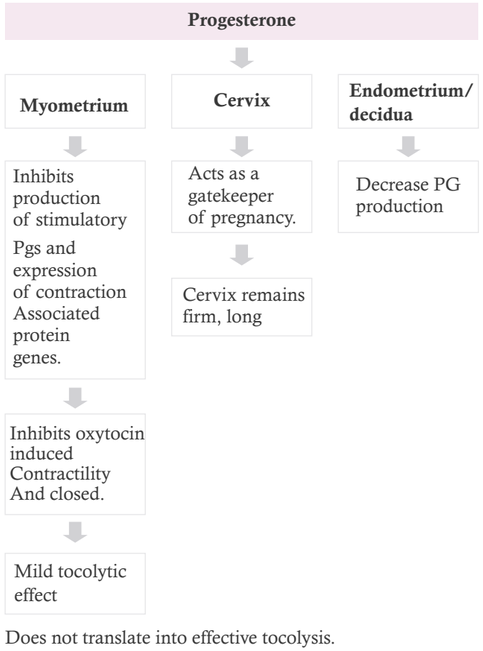
Molecular level action of progesterone:

- As per the recent concepts, especially in human beings, there is a decrease local responsiveness of progesterone also known as 'functional withdrawal' which leads to ultimate cervical ripening.
- Progesterone basically works through two of its receptors, PR-A and PR-B by effecting the gene transcription.[2,3]



The ratio of PR-A/PR-B determines progesterone action Due to decreased PR Co-activators, there is impaired progesterone-PR action which leads to reduced expression of Progesterone genes

Mediators of PR expression: prostaglandins, cytokines and/or estrogen.[4,5,6]



Does not translate into effective tocolysis.

Exogenous progesterone supplementation may effectively restore the same above actions, but not all, of its action to maintain uterine quiescence. This explains why sPTB is preventable in some but not the all women.[6]

Pharmacokinetics by route of administration:

- The peak blood concentration is better achieved by parental (intra muscular) route but its availability in many countries is an issue.
- For 100 mg vaginal progesterone pessary the peak blood concentration is achieved 3-8 hours after application due to avoidance of first pass hepatic metabolism.
- This route further adds its advantage by increasing the absorption rate in multiples and at the same time it bypasses the first pass hepatic metabolism, resulting in sustained plasma concentration and high bioavailability especially in locally in the target organ uterus. This has been termed as the "first uterine pass effect".
- 96-99% of progesterone in blood is bound to protein mainly albumin.[1,6]

Safety and tolerability:

- Parental administration usually results in undesired side effects like alteration in lipid profile, glucose metabolism, a hypercoagulable state, vasomotility, edema.
- CNS side effects like, sedation, fatigue, dizziness and dysphoria. GI side effects like, abdominal cramps, backache, nausea and constipation. Reproductive side effects like, vaginal bleeding and breast tenderness.

All these systemic side effects are almost eliminated if vaginal micronized form is used.

- Side effects with vaginal route: discharge, pruritus, drowsiness, nausea and feeling of coolness in vagina.
- Vaginal gel is better than suppositories as it has superior acceptability and tolerability. Side effects are, vaginal buildup, cloudy discharge, vaginal irritation (2-4%).

Progesterone is supposed to be safe for mother and fetus and till date no reported teratogenicity or serious maternal side effects. PREDICT trial done by Rode and Colleagues, they found no difference in neurodevelopmental milestone between progesterone and placebo groups.

What does evidence say:

Cochrane review - Latest meta-analysis done in 2014, included 8 randomized trials, involving 563 women, used data from 7 studies from a total of 538 women with threatened or established PTL with intact membranes contributed data for this recent updated review. They divided the effects of progesterone in following-

Primary outcome measures

Very preterm birth<34 weeks
Decreased
Birth weight <2500 grams
Decreased

Secondary outcome measures

Respiratory distress syndrome
Neonatal ICU Admissions
Need for mechanical ventilation
Intra-ventricular hemorrhage
Necrotizing enterocolitis
Oxygen requirement on D7 & D8

Limited evidence suggests that the use of progesterone, as a co-treatment, may reduce the preterm deliveries at less than 37 weeks and also of infants born less than 2500 grams but there was no beneficial effect noted on

secondary outcome measures so we need more randomized studies to advocate 'progestational agents' as a lone tocolytic agent for women having preterm labour.[9]

Other reviews and meta-analysis:

1 Dodd and colleagues 2008:

a For women with a past history of spontaneous PTB, progesterone was associated with a reduction of birth rate before 34 weeks but there was no significant difference in perinatal deaths.

b There was a significant reduction in the risk of infant birth weight below 2500 grams but no difference in secondary outcomes.

c No difference was noted in perinatal death among those women who had short cervical length on USG and were given progesterone to prolong the gestation but a significant reduction in birth before 34 weeks.

d Uncertain effect on women with multiple gestations.

e Progesterone decreased the need of antenatal tocolysis in other groups as well.

f For women with 'other risk factors' progesterone was not associated with a significant difference in perinatal outcome.[1]

2 Meis and Paul in 2005:

a There is no known teratogenic side effect of 17 hydroxy progesterone, if given weekly in women with past history of PTB.

b If started early in second trimester and continued weekly until 36 weeks, for women with previous history of PTB, the delivery is prolonged till its use.

c Like other studies, no effect on multifetal gestation, short cervix and other factors leading to preterm labour.[8]

3 SMFM clinical guidelines:

a In singleton pregnancies, no prior PTB, and short cervix < 20mm, at <24 weeks gestation, vaginal progesterone either 90 mg gel or 200 mg suppository, is associated with decrease in preterm birth and perinatal morbidity and mortality, and progesterone can be offered,

b Cervical length screening without a past history of preterm birth can not be made mandatory and it's an individual choice.

c In singleton pregnancies with prior sPTB, 17-hydroxy progesterone depot 250 mg weekly, started around 16-20 weeks and to be continued till 36 weeks, is recommended. Cervical cerclage can also be offered if the cervical length is <25 mm at <24 weeks.

4. **The use of vaginal progesterone suppository after successful parental tocolysis was associated with longer latency preceding delivery but failed to reduce the incidence of re-admission for PTL.**[10]

Conclusion:

Looking at the multifaceted etiology of preterm labour and huge financial burden involved in tackling perinatal morbidity, due to a preterm birth we can coclude that using progesterone as a co-treatment to prevent preterm labour specially in women with a definitive history of sPTB in past and those with accidental short cervical length on routine screen would be a safer bet as its cheap, easily available and doesn't pose any serious threat to either mother or the fetus. At the same time a blanket approach or taking Progesterone as a panacea cannot be recommended and we need to find other more effective medications to improve the perinatal outcome which is our primary aim in prolonging a labour. Further randomized trials are needed to advocate its use in other indications like multiple birth or 'other causes' of preterm birth.

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4.6 Role of steroids in preterm labour

Dr. Apoorva Pallam

Prematurity continues to be the most important cause of neonatal morbidity and mortality, with more-severe outcomes with lower gestational age at birth. Antenatal corticosteroid administration for anticipated preterm labour is the most efficient therapy available for improving neonatal outcome.

This chapter aims to summarize the available literature in using steroids.

Preterm (24 weeks -34 weeks 6 days)

All women with anticipated preterm labour should receive a single course of antenatal steroids when the delivery is projected in the next 7 days.

A meta-analysis that included 21 controlled and randomized studies (n= 4,269 newborns) revealed a significant reduction in the incidences of respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, and neonatal death, without increased incidences of maternal and neonatal infections when a single course of antenatal steroids were used. (1)

Early Preterm (<24 weeks):

The decision of administering antenatal steroids to women before 24 weeks should be taken by a senior gynaecologist after discussing with family. There have been encouraging evidence supporting the use in previability period.

Neonatal Research Network observational cohort revealed a reduction in death and neuro-developmental impairment at 18–22 months for infants who had been exposed to antenatal corticosteroids and born at 23 0/7 weeks through 23 6/7 weeks of gestation (83.4% versus 90.5%), 24 0/7 weeks through 24 6/7 weeks of gestation (68.4% versus 80.3%), and 25 0/7 weeks through 25 6/7 weeks of gestation (52.7% versus 67.9%). At 22 0/7 weeks through 22 6/7 weeks of gestation, no significant difference in these outcomes was noted (90.2% versus 93.1%) (2)

Late Preterm (>34 weeks 6 days)

A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. Late preterm administration of antenatal corticosteroids is not indicated in women diagnosed with clinical chorioamnionitis (intrauterine infection). It is noteworthy that tocolysis should not be used in an attempt to delay delivery in order to administer antenatal corticosteroids in the late preterm period .

Steroid Course:

2 doses of 12 mg Betamethasone intramuscularly 24 hours apart.

Or

4 doses of 6 mg of Dexamethasone intramuscularly 12 hours apart each.

Repeat Courses:

In view of the deleterious long term neurological side effects, it is NOT recommended to give repeated doses of corticosteroids.

In addition to not having neonatal benefit, administration of multiple courses of corticosteroids to foetuses brings about impairment of growth with reductions in head circumference, weight, and stature at birth in the short term when compared with the use of a single course. In the long-term impairment of cerebral myelination and other neurological anomalies, alterations of pulmonary tissue

growth,and developmental disorders of the hypothalamicpituitary-adrenal axis have already been observed in animal studies. (3)

Single Rescue Repeat Dose:

Some authors have recommended to administer a second course of corticosteroid when premature delivery is imminent (< 34 weeks) and more than 2 weeks had passed after the initial cycle.

Timing:

Steroids should be administered only if the delivery is anticipated within the next 7 days. Efficacy of steroids is at its maximum potential when the delivery occurs 24 hours after the last dose and within 7 days.

Type of Corticosteroid:

Betamethasone and dexamethasone are equally effective in promoting the acceleration of lung maturation. However, in most studies, the use of betamethasone is preferred because long-term follow-up data of fetuses exposed to dexamethasone are still limited.

The recommended regimen (two 12 mg doses separated by 24 h) was established to mimic the natural secretion of steroid hormones in preterm infants, which allows for 75% saturation of steroid receptors in foetal tissues. The 24-h dosage (two 12 mg doses separated by 12 hours) interval was selected based on the fact that prior to the second dose, the cord blood levels of betamethasone decrease to those observed in untreated children. The administration of a total dose of 24 mg is most likely the utmost important factor for maximal neonatal benefits, but a lower single steroid dose may be useful to reduce maternal side effects, including those in patients with overt diabetes

Indian Scenario:

Dexamethasone: It is listed in the WHO essential medicines list, is inexpensive and widely available in facilities for multiple indications.

Betamethasone: In India, the salt Betamethasone acetate + phosphate, which requires only two doses at 12 hourly interval, is not available. The available salt in India is Betamethasone phosphate which is short acting and requires more frequent administration as compared to the former. Hence, the dosage schedule of Betamethasone phosphate is similar to that of the Dexamethasone and has no added advantage over Dexamethasone. Further, Betamethasone is more costly and less stable than Dexamethasone at high temperatures.However, in individual cases where Inj. Dexamethasone is not available the service provider may use Inj. Betamethasone phosphate to give the advantage of corticosteroids to the newborn.

Route of Administration:

Corticisteriods are effective only when given by parenteral route. Oral administration is not recommended. Although there have been some trails supporting the direct administration of corticosteroids to the intrauterine fetus under ultrasound guidance, further randomized controlled trials are required focusing on the benefits and harms of transplacental versus direct fetal corticosteroid treatment before making it a routine recommendation.(4)

Special Cases:

A single course of corticosteroids can be safely given in all cases of gestational diabetes, overt diabetes, PPROM, PROM, multifetal gestation.

Fetal Side Effects:

A single course of corticosteroid administration is not associated with an increased risk short term (neonatal sepsis, hypoglycaemia) or long term (nuerological impairment) side effects.

Maternal Side Effects:

Pregnant women receiving steroids might show a steep variation in the blood sugar levels after administration. Hence close blood sugar monitoring is advised specially in diabetic mothers. PPROM and PROM mothers without overt chorioamnionitis donot exhibit increased chances of sepsis after single course of steroid administration.

Parameter	ACOG Committee Opinion 2016	New Zealand & Australian Clinical Practice Guidelines 2015 (5)	Ministry of Health & Family Welfare Government of India. (operational guidelines for ANM) 2014	RCOG Green top guidelines 2010	Cochrane Reviews
Early Preterm (<24 Weeks)	May be beneficial. Administration of steroids depends on family's decision regarding resuscitation.	NA	NA	Decision should be made at a senior level taking all clinical aspects into consideration	NA
23 0/7 – 23 6/7 weeks of gestation	Considered for women who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number	Maybe administrated after careful consideration of benefit and risks with parental consultation	NA	Should be considered for women who are at risk of preterm birth.	NA
24 0/7 weeks and 33 6/7 weeks	A single course of corticosteroids is recommended	Use a single course of antenatal corticosteroids	Single course of injection of Dexamethasone to be administered to women with preterm labour (between 24 and 34 weeks of gestation)	Clinicians should offer a single course of antenatal corticosteroids.	Definite fetal benefit of offering antenatal steroids with no additional side effects to the mother.
34 0/7 weeks and 36 6/7 weeks	A single course of betamethasone is recommended for pregnant women who have not received a previous course of antenatal corticosteroids.	No benefit	No recommendation	Antenatal corticosteroids should be given to all women for whom an elective caesarean section is planned prior to 38+6 weeks of gestation.	Prophylactic betamethasone appeared to significantly decrease the risk of admission to the neonatal intensive care unit for respiratory Morbidity. However, no statistically significant reduction was found in the incidence of neonatal respiratory distress syndrome, transient tachypnoea of the newborn, need for mechanical ventilation & length of stay in neonatal intensive care unit (6)

PPROM	Current data suggest that antenatal corticosteroids are not associated with increased risks of maternal or neonatal infection regardless of gestational age. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation		Recommended
Multiple Gestation With Preterm Labour	one course of antenatal corticosteroids should be administered to all patients who are between 24 0/7 weeks and 33 6/7 weeks of gestation and at risk of delivery within 7 days, irrespective of fetal number	Use a single course of antenatal corticosteroids for women with a multiple pregnancy at risk of preterm birth. Do not use steroids prophylacticall y in multiple gestation	Clinicians should continue to offer a single course of antenatal corticosteroid treatment to women with multiple pregnancy at risk of imminent iatrogenic or spontaneous preterm delivery between 24+0 and 34+6 weeks of gestation.
OPTIMAL TIME	The optimal time to administer antenatal corticosteroids is when preterm birth is planned or expected within the next 48 hours.	Antenatal Corticosteroid therapy has maximal effect if the fetus is delivered 24 hours after the last dose and up to 7 days thereafter. Partial effect is evident within a few hours before birth and is worth it. Thus, even if the delivery occurs in the course of treatment regimen, there are clinically important benefits	Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids. 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

REPEAT COURSES	A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously	Use repeat antenatal corticosteroids in women at risk of early preterm, (< 32 W 6D) birth following a single course of antenatal corticosteroids.	Repeated courses/more frequent doses are not useful. Multiple courses in fact could have harmful neuro-developmental effects in the baby	Weekly repeat courses of antenatal corticosteroids reduce the occurrence and severity of neonatal respiratory disease, but the short-term benefits are associated with a reduction in weight and head circumference. Weekly repeat courses are not recommended.	The short-term benefits for babies of less respiratory distress and fewer serious health problems in the first few weeks after birth support the use of repeat dose (s) of prenatal corticosteroids for women still at risk of preterm birth seven days or more after an initial course. associated with a small reduction in size at birth. no significant harm or benefit in early childhood, although no benefit.(7)
DOSE OF REPEAT COURSE		A single repeat dose of 12 mg betamethasone. Use up to a maximum of three single repeat doses. A single repeat course of 24 mg betamethasone in divided doses completed within 24 hours. No need of further doses.		A rescue course of two doses of 12 mg betamethasone or four doses of 6 mg dexamethasone should only be considered with caution in those pregnancies where the first course was given at less than 26+0 weeks of gestation and another obstetric indication arises later in pregnancy	
RESCUE COURSE	Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario			A single rescue course may be considered with caution in pregnancies where the initial course was given at less than 26+0 weeks of gestation. Senior opinion should be sought if a rescue course is to be considered.	

DRUG, DOSE & TIMING	two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone administered intramuscularly every 12 hours	Betamethasone 24 mg in divided doses, completed between 12 and 36 hours. Dexamethasone 24 mg in divided doses completed between 24 and 40 hours	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 maturation.	It remains unclear whether one corticosteroid (or one particular regimen) has advantages over another. Dexamethasone may have some benefits compared with betamethasone such as less IVH, and a shorter length of stay in the NICU
“accelerated dosing,	No additional benefit has been demonstrated for courses of antenatal corticosteroids with dosage intervals shorter than those outlined previously, often referred to as “accelerated dosing,” even when delivery appears imminent	Giving 2 doses of betamethasone 12 hours apart increased the number of patients completing the course.		
SIDE EFFECTS			Women may be advised that the use of a single course of antenatal corticosteroids does not appear to be associated with any significant short-term maternal or fetal adverse effects. Evidence on the longer-term benefits and risks of a single course of antenatal corticosteroids shows no clear difference in adverse neurological or cognitive effects.	

CAUTION	Gestational Diabetes Mellitus	Maternal diabetes, pre-eclampsia and hypertension are NOT contraindications for using injection corticosteroid in pregnant women.	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
CONTRA INDICA-TIONS	Gestational Diabetes Mellitus	Frank chorioamnionitis is an absolute contraindication for using antenatal corticosteroids.	Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis or s epsis.

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4.7 Surgical Management of Preterm Labour

Dr. Vimee Bindra, Dr Shaik Meera Esha

Prediction of Preterm Labour - women with suspected cervical insufficiency may be managed with elective cervical cerclage or by serial ultrasound to measure the cervical length and if needed to insert the cerclage.

- TVS measurement of cervical length can be used to predict the risk of preterm labor in both low risk and high risk pregnancies and also in women who are symptomatic.
  - Either serial measurement of cervical length throughout the second trimester and early third trimester or
  - Single measurement of cervical length between 18-22 weeks.
  - At any given gestational age, there is a direct relationship between cervical length and the risk of preterm delivery, and the risk is higher in multiple pregnancies (Honest et al. 2002)
- It is the absolute cervical length, rather than the funnelling of the cervix, which is principal predictor of preterm labour.

Prevention of Preterm Labour -

- At present there is no prophylactic therapy, which is demonstrated to be beneficial in prevention of preterm labour.
- Commonly used therapies include Cervical Cerclage, Progesterone, NSAIDs.

Surgical Mangement of Preterm Labour During Pregnancy

With the susupected cervical insufficiency cervical cerclage is the best modality for preventing preterm labour. Principal behind cerclage is to provide physical support for a structurally weak cervix and it may also help in retaining the mucous plug and in turn improving the immunological barrier.

When to Insert Cervical Cerclage ?

- First is history of preterm birth or classically painless mid-trimester miscarriages
- Second is ultrasound evidence of shortening of cervix
- Third is physical examination reveals short or dilated cervix.

Indications of Cerclage

History-indicated cerclage

- Insertion of a cerclage as a result of factors in a woman's obstetric or gynaecological history which increase the risk of spontaneous second-trimester loss or preterm delivery.
- A history-indicated suture is performed as a prophylactic measure in asymptomatic women and normally inserted electively at 12–14 weeks of gestation.

Ultrasound-indicated cerclage

- Insertion of a cerclage as a therapeutic measure in cases of cervical length shortening seen on trans vaginal ultrasound.
- Ultrasound-indicated cerclage is performed on asymptomatic women who do not have exposed fetal

membranes in the vagina.

- Sonographic assessment of the cervix is usually performed between 14 and 24 weeks of gestation.
- The insertion of an ultrasound-indicated cerclage is not recommended in women without a history of spontaneous preterm delivery or second-trimester loss who have an incidentally identified short cervix of 25 mm or less.

Rescue cerclage

- Insertion of cerclage as a salvage measure in the case of premature cervical dilatation with exposed fetal membranes in the vagina.
- This may be discovered by ultrasound examination of the cervix or as a result of a speculum/physical examination performed for symptoms such as vaginal discharge, bleeding or 'sensation of pressure'.
- Insertion of a rescue cerclage may delay delivery by a further 5 weeks on average compared with expectant management/bed rest alone. It may also be associated with a two-fold reduction in the chance of delivery before 34 weeks of gestation.
- Advanced dilatation of the cervix (more than 4 cm) or membrane prolapse beyond the external os appears to be associated with a high chance of cerclage failure. (5,6)

Types of Cerclage

Transvaginal cerclage (Mcdonald)

A transvaginal purse-string suture placed at the cervico-vaginal junction, without bladder mobilisation.

High Transvaginal cerclage (Shirodkar)

A transvaginal purse-string suture placed following bladder mobilisation, to allow insertion above the level of the cardinal ligaments.

Transabdominal cerclage

- A suture performed via a laparotomy or laparoscopy, placing the suture at the cervico-isthmic junction.
- A transabdominal cerclage is usually inserted following a failed vaginal cerclage or extensive cervical surgery or having a very low volume cervix.
- Once in place requires a hysterotomy or caesarean for delivery.
- It is associated with increased maternal morbidity.

Occlusion cerclage

Occlusion of the external os by placement of continuous non-absorbable suture. The theory behind the potential benefit of occlusion cerclage is retention of the mucus plug.

Pre-requisites For Cerclage

- Ultrasound fetal assessment for viability
- Ultrasound assessment for fetal abnormalities
- Pre-operative genital tract screening in women with prior pregnancy loss or preterm delivery due to chorioamnionitis, with a history of bacterial vaginosis or other pathogens in genital tract.
- Contraindications should be excluded

Contraindications for Cervical Cerclage

- Active preterm labour
- Clinical evidence of chorioamnionitis
- Continuing vaginal bleeding
- PPROM
- Evidence of fetal compromise
- Lethal fetal defect
- Fetal death

Complications of Cerclage

- Rupture of membranes
- Suture displacement
- Chorioamninitis

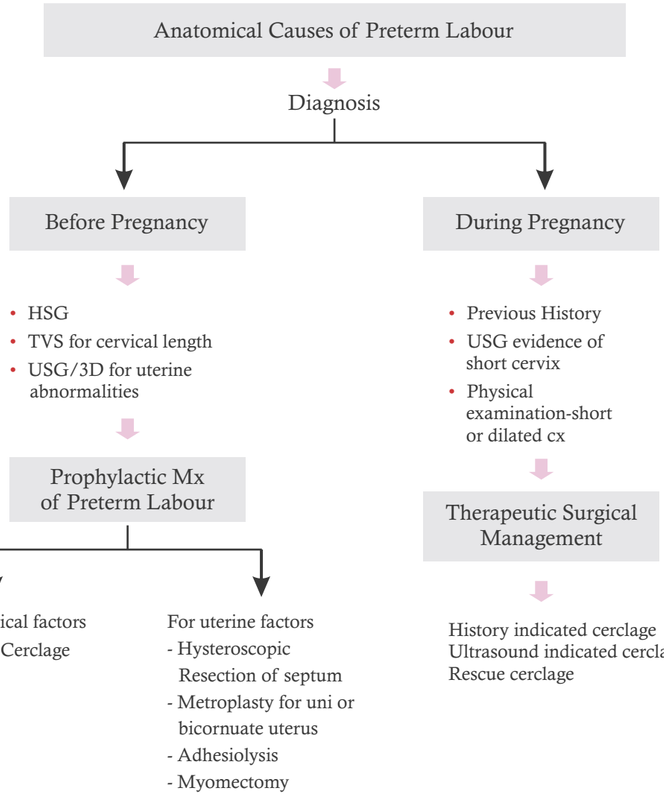
Surgical Management of Uterine Abnormalities for Predicted Preterm Labour

Uterine Abnormalities

- Hysteroscopic resection of septum
- Metroplasty for bicornuate or unicornuate uterus
- Adhesiolysis
- Myomectomy

Cervical Factors

- Interval Cerclage



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4.8 Techniques of caesarean section in preterm births

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Introduction

Preterm is defined as babies born alive before 37 weeks of pregnancy are completed. There are sub-categories of preterm birth, based on gestational age:

- extremely preterm (<28 weeks)
- very preterm (28 to <32 weeks)
- moderate to late preterm (32 to <37 weeks).

Induction or caesarean birth should not be planned before 39 completed weeks unless medically indicated.

Preterm births can occur due to following reasons

1. Spontaneous preterm birth spontaneous onset of labor or following pre labor premature rupture of membranes)
2. Iatrogenic preterm birth (defined as induction of labor or elective caesarean birth before 37 completed weeks of gestation for both maternal (high risk pregnancies) and fetal indications.

Caesarean section has been postulated to have a theoretical advantage over vaginal delivery in premature infants. This benefit may be the result of the avoidance of prolonged labour, allowing a less traumatic birth . On the other hand, preterm Caesarean section can be technically difficult and may require performing a classical Caesarean section with adverse risks like scar dehiscence in future pregnancy. It also has other maternal risks associated with Caesarean section. Hence, vaginal birth is the preferred mode in the absence of other obstetric indications due to reduced maternal complications. However, it involves the risk of hypoxia and future neurodisability to the baby. Balancing the fetal versus maternal risks and safety continues to pose challenges.

Technique for caesarean section in preterm births

Skin incision: (image1)

1.Pfannensteil Incision:

It is curved skin incision, two fingers above the symphysis pubis. It is associated with less postoperative pain, has cosmetic appeal, low wound dehiscence and less chances of herniation.

2.Transverse (Joel Cohen's Incision) :

Joel Cohen incision is a straight skin incision 3 cm above the pubic symphysis. Here subsequent tissue layers are opened bluntly (scissors used for extension), has shorter operating time and reduced postoperative febrile morbidity

Uterine incision (image 2)

It is an important surgical step and should be planned preoperatively. Type of incision must be mentioned in case notes and all other records.

1. Lower segment Transverse (Kerr) incision: It is most commonly used, 1-2 cm cut, extended transversely with scissors / digitally when lower segment is well formed, blunt rather than sharp extension of the incision should be used as it reduces blood loss intra-operative haemorrhage and need for blood transfusion.

2 T-shaped incisions: If required J-shaped or U-shaped incisions are preferred to T incision. These incisions may be required in case of difficult delivery. It is associated with poor healing and increased postoperative morbidity thus should be reserved in special situations only.

Delivery of baby

Everyone is familiar with the technique of baby delivery in a cephalic presentation. Maintaining the flexion of the fetal head during delivery reduces the diameter and eases the delivery. This also reduces undue extensions of the uterine incision and excessive hemorrhage and time required for the CS. One must avoid hasty baby delivery. Also the person doing should be well versed with different maneuvers for baby delivery during a CS and ask for prior assistance.

Difficult baby deliveries:

a. High floating head: Rupture of membranes followed by suctioning of liquor, allow vertex to descend to incision site, then flexion and delivery. Use of vacuum or short forceps is also possible.

b. Deeply engaged head: Disimpaction with vectis or manually, abdomino-vaginal method or Patwardhan's maneuver as appropriate.

c. Breech: should be delivered with same care as in vaginal breech delivery. Head is delivered by either Burn's Marshall technique or Mauriceau Smellie Veit method or using forceps

Preterm Cesarean Delivery En Caul (image 3)

We made a pfannestiel or vertical skin incision and opened the abdominal wall, layer by layer, to expose the uterus. A transverse lower segment uterine incision was made without incising the membranes. It is very important to make the uterine incision large enough to allow delivery of the whole sac without tearing into the uterine arteries and veins. The operator's fingers pass between the membranes and uterine wall to separate the placenta gently. An assistant helps by pulling the angle of the uterine incision wound, the rectus abdominis muscle and skin wound, to make the opening as large as possible. With fundal pressure the whole sac including the placenta is delivered intact (Figure). The sac delivers in transverse position, and ruptured artificially after delivery. Then the baby is delivered.

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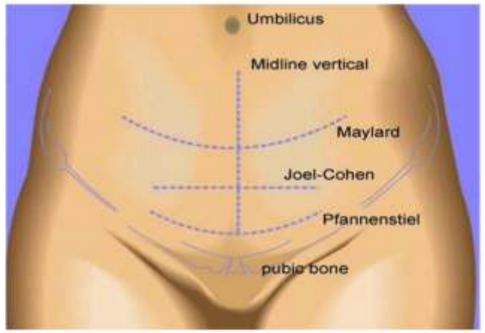

Image 1: Skin Incisions (Source Google images)

A: J-shaped incision B : T-shaped incision

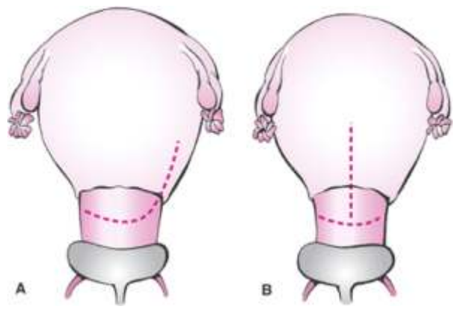

Image 2: Types of Uterine Incisions (Source Google images)

Image 3: En caul baby birth (Source Google images)

4.9 Intranatal Management of Preterm Labour

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Introduction

Preterm labor refers to the onset of uterine contractions of sufficient strength and frequency to effect progressive dilatation and effacement of cervix between 24 and 37 weeks of gestation.

According to NICE guidelines 2015 PTL can be categorized as:

Suspected preterm labour: A woman is in suspected preterm labour if she has reported symptoms of preterm labour and has had a clinical assessment (including a speculum or digital vaginal examination) that confirms the possibility of preterm labour but rules out established labour.

Diagnosed preterm labour: A woman is in diagnosed preterm labour if she is in suspected preterm labour and has had a positive diagnostic test for preterm labour.

Established preterm labour: A woman is in established preterm labour if she has progressive cervical dilatation from 4 cm with regular contractions.

Intranatal Management of Preterm Labour

Intranatal management of pre-term labour depends upon the above mentioned category to which PTL belongs, gestational age of mother and facilities of neonatal care available.

On the basis of gestational age pre term gestation is divided into:

Extremely pre term (<28 weeks)

Very pre term (28 to 32 weeks)

Moderate pre term (32 to 34 weeks)

Late pre term (34 to 36 + 6)

Modalities of management: To prevent progression into active labour :

(A) Tocolysis: Short term tocolysis for 48 hours is indicated in women with gestational age of 24+0 to 33+6 weeks of gestation when the woman is in suspected or diagnosed preterm labour and there is no contraindication to prolongation of pregnancy. Indications for short term tocolysis are -

- To complete a course of corticosteroids
- In utero transfer to centre with neonatal care facilities.
- Effect of short term tocolysis:-
  1) May Prolong pregnancy for up to 7 days
  2) No significant effect on preterm birth
  3) No clear effect on perinatal or neonatal morbidity.
- According to RCOG Greentop Guidelines-2011 "**Maintenance tocolysis is not recommended**"
- If the decision is made to use a tocolytic drug, nifedipine and atosiban appear to have comparable effectiveness in delaying delivery, with fewer maternal adverse effects and less risk of rare serious adverse events as compared to ritodrine or in domethacin hence nifedipine and atosiban should be preferred.
- Dose of Nifedipine: An initial oral dose of 20mg followed by 10-20 mg three to four times daily, adjusted according to uterine activity for up to 48 hours.
- Dose of Atosiban: Initial bolus dose of 6.75 mg over 1minute, followed by an infusion of 18 mg/h for 3h, then 6 mg/h for up to 45 hr. (to a maximum of 330 mg).

(B) To improve fetal lung maturity: Maternal corticosteroids

Maternal corticosteroids should be offered to women between 24+0 and 33+6 weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have P-PROM. (ACOG 2016)

- **Dose of corticosteroid:**
- Betamethasone: 12 mg given IM in two doses 24 hours apart or
- Dexamethasone: 6 mg given IM in four doses 12 hours apart.
- A single course - at risk of preterm delivery within 7 days.
- Single repeat course (2 doses)-in women whose prior course was at least 7 days previously and who remain at risk of preterm delivery before 34 weeks. (**Rescue dose**).

C) For Neuroprotection: Magnesium sulfate

Magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks.

- **Inclusion criteria:**

Gestational age 24 to 31+6 weeks

In established preterm labour or having a planned preterm birth within 24 hours.

- **Exclusion criteria:**

Active labour at greater than 8 cm dilatation.

Major fetal anomalies

Maternal contraindications to MgSO4 (pulmonary hypertension, myasthenia gravis, class II-IV cardiac disease, severe acute pulmonary disease and pulmonary insufficiency)

Discontinue any tocolysis if MgSO4 is being used.

- **Dose:** 4g intravenous bolus of magnesium sulfate over 15 minutes, followed by an intravenous infusion of 1g per hour until the birth or for 24 hours (whichever is sooner).
- **Monitoring of MgSO4:**

Clinical signs of magnesium toxicity should be monitored at least every 4 hours by recording pulse, blood pressure, respiratory rate and deep tendon reflexes.

(D) Transfer to appropriate facility level:

Neonatal outcomes of infants requiring NICU management are better for those transferred in-utero than those transferred as neonates, especially for pre term infants born at less than 30 weeks of gestation.

ACOG 2016 recommends "NO" use of antibiotics for prolongation of pregnancy in cases of PTL with intact membrane as there are no evidence of benefit.

(E) Fetal monitoring:

During first stage of labour :

- The preterm fetus should be monitored closely for signs of hypoxia during labour, preferably by continuous electronic fetal monitoring. A normal cardiotocography trace is reassuring and indicates that the baby is coping well with labour, but an abnormal trace does not necessarily indicate that fetal hypoxia or acidosis is present. Fetal scalp electrode and fetal blood sampling should be avoided.
- Antibiotic prophylaxis should be given in countries with high incidence of group B streptococcal infection.

During second stage of labour:

Mode of delivery: When assessing the evidence from the literature for the optimum mode of delivery in prematurity in terms of neonatal mortality and severe morbidity, several variables need to be taken into account, such as fetal presentation, indication for pre term birth (eg, PTL, severe IUGR, pre-eclempsia), the initially intended route of delivery and the fetal status on admission.

PTL with IUGR: Cesarean section should be preferred. Vaginal delivery can be considered when woman is in labour. Induction of labour can be considered with continuous electronic fetal heart monitoring in favorable obstetric situations and in absence of severe fetal hemodynamic disturbance.

PTL with breech: Cesarean section should be preferred as it reduces neonatal mortality and morbidity as compared to vaginal delivery.

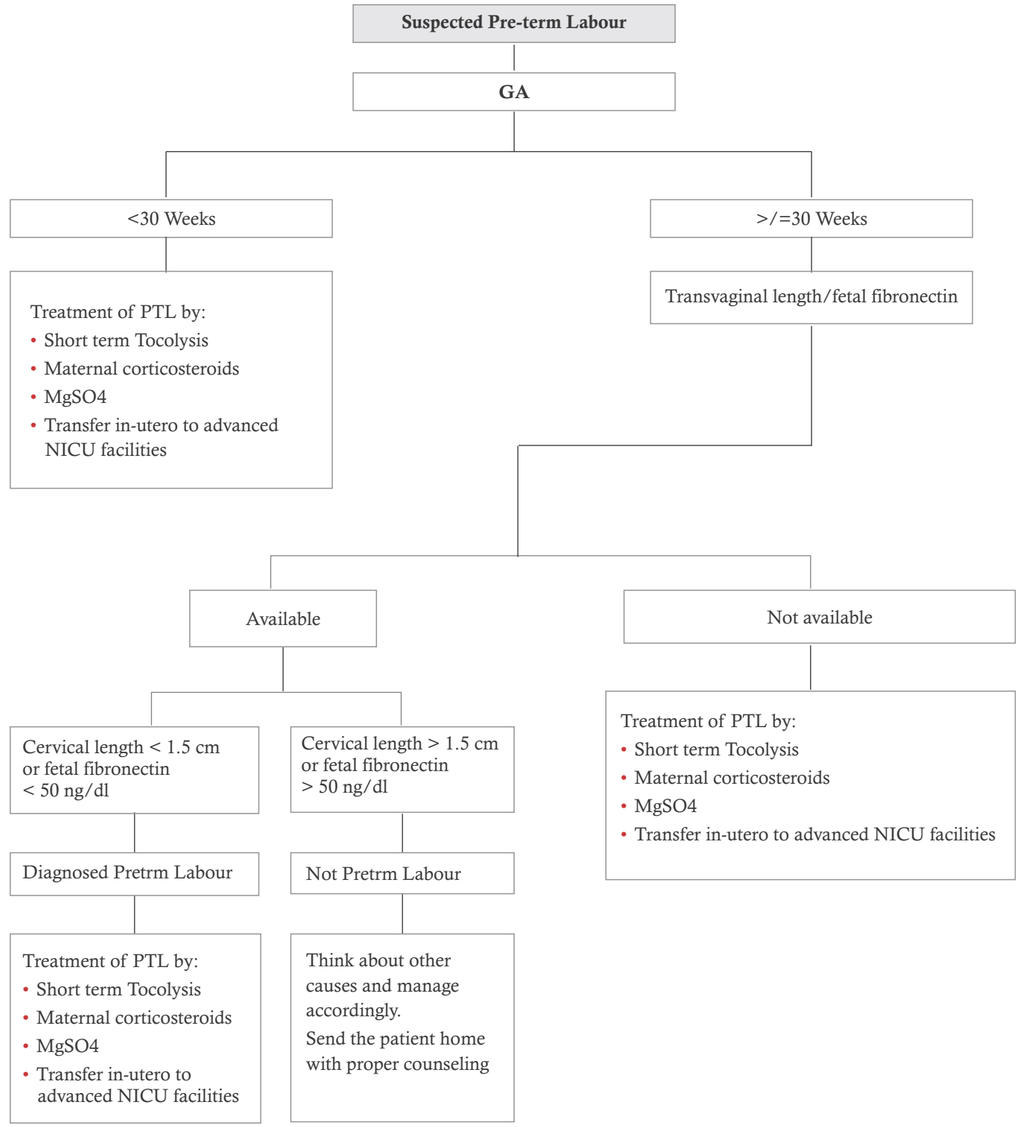
PTL with cephalic presentation: Vaginal delivery should be preferred. Caesarian section should be done only for obstetric indications. "There are no known benefits or harms for the baby from caesarean section, but the evidence is very limited" – NICE 2015.

Special care during delivery -

1) Gentle and slow delivery should be done.
2) Liberal Episiotomy - to avoid compression of fetal head
3) Presence of expert neonatologist capable of dealing with complications of prematurity.
4) Ventouse is contraindicated in preterm deliveries & forceps should be avoided routinely
5) **Cord clamping :** If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding cord should be clamped as soon as possible after milking the cord and if the

mother and baby are stable cord should be clamped after at least 30 seconds, but no longer than 3 minutes

6) Baby should be positioned at or below the level of the placenta before clamping the cord. – NICE 2015
7) Cord should be kept long as exchange transfusion may be needed



4.10 Twin Gestation & Pre-Term Birth

Introduction:

Twins contribute 2-4 % of all births. The rate of preterm birth < 37 weeks among twins is approximately 60 % [1].

Incidence:

Percentage of singletons born less than 37 weeks GA is 11.1 % [2]

Twin born < 37 weeks GA is 61.9 % [2]

Twins < 32 weeks GA 13.3 % [2]

Etiology:

[3-4] Classified into 3 types

- PPROM
- SPM
- Preterm birth due Medical reason

[5] Twin Pregnancies are more liable to

Maternal Hypertension

Fetal Distress

Fetal Growth restriction

TT Syndrome

Discordant

Placental abruption

Maternal obesity BMI > 35 Kg/m2

All above leading to early termination of pregnancy

Incidence of preterm birth is reported higher for IVF/ ICSI pregnancies [6-7]

Mechanisms of Preterm Birth:

[8] The Mechanism for Preterm birth are still unclear

↓

Uterine Over distention

↓

Myometrial contraction

↓

Releases Prostaglandins / up regulates Oxytocin receptors

↓

Induces Labor

Risk is higher in Monochorionic diamniotic twins [9]

Nulliparous women with twin gestation have higher chance of preterm births [10]

Fetal sex appears to be a risk factor for preterm delivery in spontaneously conceived dichorionic twin gestations [11]

Twin pregnancies with one or two male fetuses are at higher risk than females [11].

Prediction of Preterm Birth:

Cervical length measurement using TVS [12]

Timing of cervical length measurement

16 - 24 weeks [13]

13 - 34 weeks [14]

20 - 23 measurement followed by 3 - 5 weeks later at a difference of 25% between each measurement is a good predictor of preterm birth in asymptomatic twins even when cervical length is >25 mm [15].

Funneling:

Cervical funneling seen at midtrimester had a high sensitivity and specificity for prediction of the preterm

birth, which was higher for gestations born <32 weeks than <35 weeks (86% + 54 % specificity 78 % + 82 %) [16]

Funneling seen TVS [16]

Patient is on dorsal lithotomy position with an empty bladder without undue pressure on the cervix [17].

Wait up to 5 min to note any changes; in cervical length and shape [17].

Funneling is defined as dilatation of the internal os >5 mm in width for a period of at least 3 minutes [17]

It differs according to position of patient. Found to be seen more in an upright position [17].

Evaluating the women in the upright position permits earlier detection of funneling [17].

Prevention of preterm birth in Twins:

Cerclage in twins

Is there a Role for Prophylactic Cerclage in Twins?

A prospective study shows an increase in preterm birth in cerclage group when compared to no cerclage group, in <32 weeks [18]

An older meta-analysis reported increase in incidence of preterm birth <35 weeks in twins with a short cervix who underwent cerclage cervix, previous history of preterm birth, in contrast to singletons that had a significant reduction of preterm birth with cerclage [19].

Progesterone

Has a physiological effect on uterine quiescence mediated by a direct effect on intracellular calcium concentration and prostaglandin synthesis [20].

Two large Randomized Controlled study. PREDICT 21 and STOPPIT study 22 showed no reduction of the preterm birth rate with natural vaginal progesterone administration in twin pregnant patients with short cervices [23].

The effect was similar with 17 hydroxy progesterone weekly IM injections [24-25]

A recently published, randomized, controlled study showed that vaginal progesterone and prophylactic cerclage in effective in multiple gestation.

The potential explanation for this is preterm term birth in twins is more often because of uterine distension and contraction than due to cervical problems.

Role of Progesterone in Prevention of Preterm Birth in IVF Pregnancies

A randomized, placebo-controlled study studying the effect of daily 400 mg of vaginal progesterone suppositories for prevention of preterm birth in singleton and twin ICSI pregnancies found a significant reduction in preterm birth rate in the singleton group receiving proge sterone where as no difference in given pregnancy group[26]. Thus further strengthening current evidence that progesterone does not prolong twin pregnancies.

Bed Rest

A Cochrane review of randomized trials studying the effect of hospital bed rest in multiple pregnancies found no significant evidence to recommend the same for routine clinical practice [27].

Pessaries

Only one small study reported some positive effect of pesssary insertion in twins preventing preterm birth [28]

Management of Threatened Preterm Birth in Twin Pregnancies

Tocolysis and Treatment of Preterm Birth [29 - 30]

Mechanism of Action of Tocolysis

β Adrenergic Receptor Agonists

Ritodrine and Salbutamol (β2 agonists)

Impair intracellular cyclic AMP concentration

Myometrial relaxation

A Cochrane review including 11 randomized, controlled trials, involving 1,332 women reported that these agents were more efficient than placebo for delaying preterm birth for 2 days [30 – 31]

In twins, a Cochrane review shows insufficient evidence to support or refute the use of prophylactic oral betamimetics [32]

Magnesium Sulphate

Decreases calcium intracellular concentration

↓

Inhibits myometrial contraction

There is evidence and recommendation to administer magnesium sulphate in expected preterm births, especially <30 weeks, for neuroprotection and reduction of incidence of cerebral palsy [33].

It is classed as one of the three effective drugs to delay of delivery for > 48 weeks [34].

Its effectiveness was similar in singletons and twins [35].

Prostaglandin-Synthase Inhibitors

Indomethacin, a nonspecific COX inhibitor and Calcium channel blockers, gave the best results to delay delivery for 48 weeks and had the least maternal side effects and

reduced reduce respiratory distress syndrome, neonatal mortality.

Indomethacin however, use should be restricted in duration and limited to pregnancies below 32 weeks because of fetal ductus arteriosus closure risk and decreased urine production responsible for oligohydramnios [31, 36 – 38]

Calcium - Channel Blockers

Calcium channel blockers transfer of calcium ions into myometrium.

Decrease intracellular free calcium concentration and induce.

Myometrial relaxation [36].

Use of calcium channel blockers in acute tocolysis (delay of delivery 48 hours up to 7 days 39 has been proven to be more effective than β adrenergic receptor agonists and with fewer side effects.

However, studies have shown no significant reduction of Perinatal adverse outcome in use of nifedipine as maintenance tocolysis [40].

Nifedipine tocolysis is proven as effective and safe for use in both singleton and twin gestations [41].

In singleton and multiple gestations, the role of tocolysis in the setting of acute preterm labor is to attempt to delay delivery long enough to administer corticosteroids to promote fetal lung maturity [42].

Antibiotics

Incidence of preterm labor due to infection is 20–40 %, especially <30 weeks [43].

In the preterm birth with intact membranes, the antibiotics is not recommended [44], but in case of preterm rupture of the membranes (PROM), antibiotics have shown a significant decrease of preterm delivery and chorioamnionitis [45].

In bacterial vaginosis associated with pregnancy, antibiotics were found to eradicate infection, but they showed no effect on the incidence of preterm delivery [46].

Therapeutic Emergency Cervical Cerclage in Twins

The largest study published so far 47 to check the effectiveness of emergency cerclage on 414 sets of twin gestations and 92 sets of triplet gestations, could not show any significant prolongation of pregnancy duration in the ultrasound indicated cerclage (closed cervical length 2.5 cm) [48].

In triplets, no benefit from cerclage placement was found even when cervical shortening was documented [49].

Conclusions:

Preterm birth is a major increasing health problem, especially with twins. Although the predictions of preterm birth become possible with transvaginal ultrasound cervix measurement and fetal Fibronocten measurement, no effective preventive or treatment measure is available for management of preterm birth in twins.

Reducing the number of twins resulting from ART procedures, such as single embryo transfer and careful monitoring of ovulation induction should help.

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5 Miscellanious

5.1 PROM and Preterm Labour

Dr. Rakhi Singh, DGO,FICOG, FIAOG, DRM.

Incidence:

- The incidence of PROM in all pregnancies is 10% and PPROM is 3%.
- The incidence of PROM in Preterm labour is 30% and PPROM is 10%.

Mechanisim of PROM.

- The weakness of the chorioamniotic membrane occurs by either mechanical causes, infections or inflammatory process.
- This causes the degradation or reduction in the collagen content of the chorioamniotic membrane there by reducing the elasticity and the strength of the membrane making it suseptable to rupture easily.

Risk factors for PROM

A. Preconceptional causes:

The detailed history should be taken in the pre conceptional counselling and the adequate corrective measures to be taken before and during the expected pregnancy.

- Previous history of PROM in the previous pregnancy
- Repeated genitourinary infections
- Cervical incompetence
- Chronic cervicites / cervical erosion
- Cervical incompetence
- Repeated second trimester abortions
- Obesity-BMI to be calculated using the prepregnant weight.
- Bad oral hygiene

B. Social factors for PROM:

These cause high incidence of PROM

- Low socioeconomic status
- Anaemia and poor nutrition
- Smoking
- Irregular antenatal checkups
- Increased coital frequency in the third trimester

C. Pregnancy related causes of PROM:

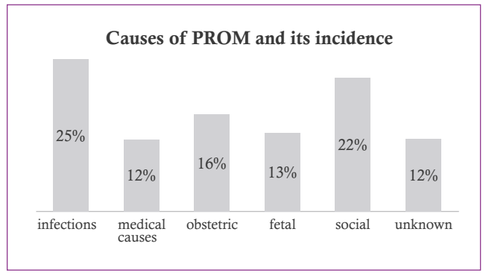
- Malpresentation of fetus
- Polyhydramnios
- Fetal abnormalities
- Bleeding in the second or third trimester
- Cervical encirclage

D. Genital tract infections:

- Fungal infections-candida
- Chalamidia tracomatis
- Tricomonas vaginalis
- MYcoplasma
- Bacterial vaginosis
- Staphylococcus
- Entrococcus
- Lactobacillus
- E.coli
- Gardenella
- Mixed infection

E. Iatrogenic and others causes:

- History of fall / trauma
- Amniocentesis
- Fetal fibrinonectin
- Fetal blood sampling



At risk patients for PROM and PTL:

- Correction of the nutritional status and anaemia of the patient.
- Antibiotic coverage to be given for the genital infections and corrected in the pre conception phase and also during pregnancy to avoid PROM and PTL.
- Resistance to the penicilline group of antibiotics is seen in Indians, mostly antibiotics used are Ampicilline, Amoxicilline, Cefotaxime, Gentamycine.
- Patient should be made aware the importance of regular ANC.
- HVS to be taken during pregnancy when the patient complains of amniotic fluid leaking and treated with broad spectrum prophylactic antibiotics.
- Corticosteroid administration should be done to enhance lung maturity in suspected cases and also PROM cases.

Examination and confirmation of diagnosis:

- Patient gives history of excessive watery vaginal discharge wetness or just a trickle leaking.
- Vitals of the patient along with the fetal position and fetal heart monitoring to be done.
- A sterile per speculum examination shows clear amniotic fluid coming out of cervix or on the cough reflex.
- High vaginal swab to be taken along with the urine culture.
- Amniotic fluid is alkaline and the vaginal PH is acidic in nature a simple pH paper test can tell, but false positive can occur in the presence of blood.
- Digital examination of the cervix to be avoided and done to the minimum to avoid infections.
- Ultrasound needs to be done in the preterm prom patients to see for the confirmation of the gestational age, fetal weight, fetal presentation, and the amount of the amniotic fluid index, the internal os with cervical length.
- It is required to have a confirmed the diagnosis of PROM in PTL as it involves hospitalization and preterm delivery having high risk for neonatal morbidity.
- If the expectant management is planed and genitor urinary or chorioamnionitis is suspected then amniocenticis to be done and send culture.

Councelling and discussion:

- Once the diagnosis is made discussion with the patient and the family members need to be done.
- In preterm PPROM discussion to be done with the neonatologist regarding the fetal outcome and the need of NICU and the foetal infection.
- Take a written informed consent and discuss regarding the prognosis in the expectant management and about fetal and the maternal complications and the risk factors like chorioamnionitis, endometritis, PPH, retained placenta and the need of curettage.

Role of corticosteroid treatment:

- Corticosteroids should be given to the preterm fetus to accelerate the lung maturity and decrease the neonatal morbidity.
- Steroids can cause increase in the incidence of infection and is the area of conflict but the risks should be outweighed in regard to the benefits.
- In high risk patients where we are suspecting PROM and PTL corticosteroids can be given to enhance lung maturity.

Expectant management monitoring of the fetus:

- It's given if the fetus is less than 34 weeks, and no proven ascending infection and the leaking has stopped.
- Corticosteroids are to be given.
- Put the patient on the antibiotic coverage preferably on erythromycin 250 mg four times a day for 10 days or till the expected delivery. Aamoxiclav on long term use can lead to neonatal necrotising entrocolitis as reported.
- Monitor the patient for temperature, pulse every 4hrly and check for total leucocytes count and the CRP.
- Tocolytics to be started.
- Fetal heart monitoring to be done and also the USG monitoring for the amount of liquor and growth of the fetus.

When to end Expectant management and deliver the fetus:

- Deliver the fetus when maternal and fetal complications start setting in due to PROM and PTL.
- Risk of Chorioamnionitis is 10% if the fetus is delivered within 24 hrs of PROM and it increases to 40% if delivered after 24 hrs without antibiotic coverage.
- Maternal amniotic fluid infection can lead to endometritis, PPH, retained placenta.
- Fetal distress.
- Fetal maturity is attained .
- Skeletal and joint deformaties due to oligohydramnios.

Fate of PROM and mode of delivery:

- Broad spectrum antibiotics to be started to reduce the incidence of chorioamnionitis and continuation of pregnancy till the viability or lung maturity of the fetus.
- 60% of the patients go into spontaneous labour and deliver by 24 hrs of PROM.
- Infection is one of the serious complication of PROM for mother and the fetus.
- Vaginal delivery mostly occurs in patients after the maturity.

Conclusion:

To identify the cause in the pre-conceptional or during pregnancy and timely management will lead to the decrease in the maternal and fetal morbidity.

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5.2 Precipitous Labour Synonym: Express Dilivery

Dr. Shalini Chauhan

It is a hypertonic dysjunction of uterus
Defined as labor duration < 3hrs (hughes 1972).

Due to

(A) Abnormally strong uterine & abdominal contractions.

(B) Abnormally low resistance of soft parts of birth canal.

C) Or rarely from absence of painful sensation

Short labor: when rate of cervical dilatation
>= 5am/hr in primiparous
>= 10 cm/hr in multiparous

Incidence of express delivery - 2.26% (cdc)
- 2% (martin and co-worker 2009).

Causes

Possible Gentic & Physical Basis

- An above average pelvic outlet
- A well aligned pelvis, pubic bone & birth canal
- An unusually small baby
- A baby positioned extremlly well to come out
- Familial
- Other: premature labor, induction of labour & previous similar history

Diagnosis

- Usually retrospective->because patient seen in 2nd/3rd stage of labour.
- If seen during 1st stage–partogram will show very rapid progress.
- If seen after delivery – examination of mother & infants should be clone.

Complications

Maternal

- Laceration of cervix, vagina & perineum, at times uterine rupture
- Amniotic fluid embolism.
- Atonic PPH, retained placenta & inversion of uterus.

Fetal

- Intracranial haemorrhage & other fetal injuries
- Avulsion of cord.
- Neonatal sepsis.
- Erb's & duchenne brachial palsy. (acker & colleagues 1998).

Management

- A patient with part history: admit at the first perception of pains.
- If seen during delivery: GA (inhalational anesthesia by nitrous oxide & o2) may be given .
- If seen after delivery - exploration of birth canal for any injury & manage accordingly.
- Prophylactic antibiotics if delivery occured in unsuitable conditions.
- Proper examination of fetus.

5.3 Guidelines in Preterm Labour: A literature review

Dr. Parul Mittal, Dr. Neha Agarwal

Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix between fetal viability and 37 weeks.

- Most important single determinant of adverse infant outcome in terms of both survival and quality of life.
- Globally, every year, about 15 million babies are born preterm and >1 million deaths are directly attributable to preterm birth.
- A spontaneous preterm birth before 34 weeks is the best predictor for its recurrence.
- Short cervix (cervical length 20mm in women with no prior preterm delivery and < 25mm in women with a prior preterm delivery between 16-28 weeks on TVS) is associated with an increased risk of spontaneous preterm birth.

Prevention of Preterm Labour

Diagnosis and treatment of asymptomatic bacteriuria
Progesterone therapy in asymptomatic women with previous preterm birth or a short cervix
Cervical Cerclage

Diagnosis

- Clinical - regular uterine contractions with cervical changes, vaginal bleeding, leaking. Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days.
- Positive fetal fibronectin, short cervix, Insulin-like growth factor-binding protein-1 may be used however they should not be used exclusively to direct management in the setting of acute symptoms.

Management

Approximately 30% of preterm labor spontaneously resolves and 50% of patients hospitalized for preterm labor actually give birth at term.

Bed rest and hydration have not been shown to be effective and are not routinely recommended.

Antenatal Corticosteroids

- A single rescue course of corticosteroids is recommended for pregnant women between 24 weeks and 34 weeks of gestation who are at risk of delivery within 7 days (ACOG, WHO)
- Reduces the risk of respiratory distress syndrome, intra-ventricular haemorrhage, necrotising enterocolitis and neonatal mortality.
- Betamethasone 12 mg i.m 24 hours apart, 2doses or Dexamethasone 6 mg i.m 12 hours apart, 4 doses. No additional benefit has been demonstrated with dosage intervals shorter than these.
- A single repeat course of corticosteroids can be considered in women whose prior course of steroids was given >14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. (ACOG)

Tocolysis

Recommended to delay delivery to

- Facilitate in utero transfer to tertiary centre
- Give time for corticosteroids and magnesium sulfate to act

Drug	Dose	Comments	Maternal side effects	Fetal side effects
Nifedipine (CCB)	Nifedipine (CCB)	First line treatment in most centers.	Dizziness, flushing and hypotension	No known adverse effects
Atosiban (Oxytocin receptor antagonist)	IV bolus 6.75 mg Then 300 µg/min infusion for 3 hrs Then 100 µg/min for up to 45 hrs (max. 330 mg)	Recommended by RCOG, not approved by FDA.	Hypersensitivity, injection site reactions	Minimal
b-agonists (Ritodrine)	IV infusion 0.05-0.1 mg/min Increased at 15 min intervals to 0.35 mg/min	Not recommended by RCOG due to maternal side effects	Tachycardia, hypotension, tremors, palpitations, pulmonary edema, hypokalemia, hyperglycemia	Fetal tachycardia
Indomethacin	50-100 mg loading dose (oral or per rectal) Followed by 25 mg orally every 4-6 hrs	Should not be given >48 hrs due to fetal side effects	Nausea, esophageal reflux, gastritis, emesis, platelet dysfunction	In utero constriction of ductus arteriosus, renal dysfunction, oligohydramnios, necrotizing enterocolitis in preterm newborns and PDA in neonates

In 2011, the FDA issued a warning regarding the use of terbutaline because of reports of serious maternal side effects.

Not enough evidence to continue tocolytics after 48 hrs.

Maintenance therapy is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended.

Contraindications to tocolysis:

Intra-uterine fetal demise, lethal fetal anomaly, nonreassuring fetal status, severe pre-eclampsia or eclampsia, chorioamnionitis, APH, maternal contraindications to tocolytics.

Magnesium sulfate for fetal neuroprotection

- Maternal administration of magnesium sulfate in women expected to have preterm delivery within 24 hrs has consistently demonstrated a decreased risk of cerebral palsy and severe motor dysfunction in offspring, especially between 24 and 32 weeks' gestation.
- Dosage - 4g i/v loading dose over 15 min. followed by 1g/hr infusion until birth / 24 hrs, whichever is sooner.
- None of the trials demonstrated significant pregnancy prolongation when it was given for neuroprotection.
- Because of potential serious maternal complications, beta-adrenergic receptor agonists and calcium-channel blockers should be used with caution in combination with magnesium sulfate. Before 32 weeks of gestation, indomethacin is a potential option for use in conjunction with magnesium sulfate.

Antibiotics

Routine antibiotic administration is not recommended for women in preterm labour with intact amniotic membranes and no clinical signs of infection.

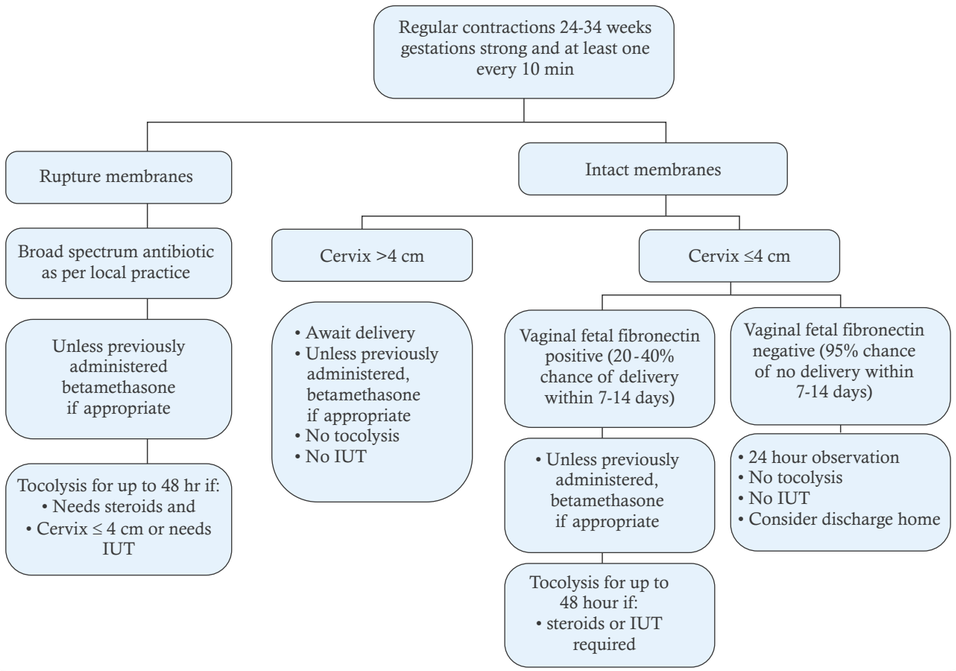
Erythromycin is recommended in cases of pPROM for antibiotic prophylaxis.

Routine delivery by caesarean section for the purpose of improving preterm newborn outcomes is not recommended, regardless of cephalic or breech presentation.

Preterm labour Management

- 34 weeks - Proceed to delivery (usually by induction), GBS Prophylaxis
- < 24 weeks-Patient counselling, Expectant management/ induction of labour, Corticosteroids not recommended
- 24-34 weeks - fig.1

Fig. 1: Flowchart for management of preterm labour < 34 weeks gestation



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5.4 Preterm Neonate: Management

Dr Swati Upadhyay

- The last decade has witnessed some major changes in care of preterm babies. The chances of survival of tiniest babies have increased drastically over several years.
- Care of preterm neonate is multidimensional; the goal being not only survival, but intact survival free of neurodevelopment impairment,bronchopulmonary dysplasia and extra-uterine growth retardation.
- With prematurity being one of the leading causes of neonatal mortality and morbidity in our country, it is the need of the hour to lay down and follow practices which help in improving survival without disability in these babies.[1]
- The neonatal outcomes can be improved through interventions provided to the mother before birth, or to the preterm infant after birth.
- The key areas involved in preterm birth care, aimed at obtaining optimal outcome, are as follows:

A. Antenatal Care

1. Early identification of at risk patients and **in-utero transfer** to a **specialized centre** having facilities and expertise for management of preterm babies (**Strong recommendation**, low quality evidence).[2]
2. **Antenatal counselling** and preparing the family for expected outcome, long hospital stay and expected cost of treatment.
3. **Antenatal interventions (recommended by WHO)** to improve preterm birth outcomes:[1]

Recommendation	Neonatal Outcomes	Strength of recommendation and quality of evidence
1. Antenatal corticosteroids for women at risk of preterm birth from 24 weeks to 34 weeks of gestation	**Reduction in:** • *neonatal deaths* • rate of respiratory distress syndrome (RDS) • occurrence of *cerebroventricular haemorrhage* • infant *systemic infection in the first 48 hours* of life and • *necrotizing enterocolitis*	**Strong recommendation** moderate-quality evidence
2. ***Antibiotics*** for women with preterm prelabour rupture of membranes	**Reduced risk of :** • *infection, including pneumonia* • having *positive blood culture* • *major cerebral abnormality*	**Strong recommendation** moderate-quality evidence
3. Antenatal ***Magnesium sulphate*** for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy in the infant and child.	**Reduced risk of:** • *substantial gross motor dysfunction* compared to controls and • *cerebral palsy*	**Strong recommendation** moderate-quality evidence

4. Role of tocolytics: Short-term use of tocolytic drugs should be considered in very preterm pregnancies only to allow completion of a course of prenatal corticosteroids and/or in utero transfer to a perinatal centre (Strong recommendation, moderate quality evidence).[1]

B. Care During Delivery and Immediate Post Natal Period:

1. Optimal mode of delivery:

Routine delivery by caesarean section for improving preterm newborn outcomes is not recommended, regardless of cephalic or breech presentation. (Conditional recommendation based on very low-quality evidence).[1]

2. Delayed cord clamping:[3]

For preterm babies not requiring immediate resuscitation, delaying cord clamping by at least 30-60 seconds is associated with

- Reduced need for blood transfusions
- Better circulatory stability
- Less IVH (all grades)
- Lower risk of NEC.

3. Need for resuscitation:

- Preterm babies are more likely to need resuscitation at birth.
- Additional equipments like T-piece resuscitator, Oxygen blender and plastic wrap are necessary.
- Prior preparation of both equipment and trained personnel is critical.

4. Respiratory stabilisation of babies with Respiratory Distress Syndrome (RDS):

- Delivery room CPAP (Continuous Positive Airway Pressure) is recommended for babies with RDS not requiring intubation (*Strong recommendation, moderate quality evidence*).[1,2]
- Surfactant administration in labour room to be considered for babies requiring intubation (*Strong recommendation, moderate quality evidence*.[2]
- Oxygen for resuscitation should be controlled using blender-resuscitation to be initiated at 21-30% Fio2. Further titration should be done to maintain spO2 between 91-95%.[1,2]

5. Thermal stabilisation:

- Plastic bags or occlusive wrapping under radiant warmers should be used during stabilization in the delivery room for babies < 28 weeks gestation to avoid hypothermia.[2]

C. Care in NICU:

1. Routine **care which involves care of eyes, skin, cord and administration of Vitamin K.**
2. **Vitals monitoring** as per hospital protocol, preferably using Multipara monitors.
3. **Respiratory Stabilisation/ Management of babies with RDS:**
   - Non invasive ventilation: ***CPAP*** should be used as primary mode of respiratory support in preterm babies with RDS not requiring intubation.[2]
   - ***Surfactant therapy*** is recommended for intubated & ventilated newborns with RDS.[1,2]
   - ***Early rescue surfactant*** is strongly recommended as and when indicated.[1,2]
   - Mechanical Ventilation strategies: Among various invasive modes of ventilation, ***Volume Targeted Ventilation*** has been shown to result in a ***reduction*** in the combined outcome of death or bronchopulmonary dysplasia, reductions in pneumothorax, days of ventilation, hypocarbia and the combined outcome of periventricular leukomalacia or grade 3-4 intraventricular haemorrhage.[2,4]
   - ***Caffeine therapy*** should be used routinely in babies < 1250 gm to minimize the need for ventilation and reduce the risk of BPD.[2]
   - ***Non - invasive respiratory support*** should be preferred over invasive ventilation as far as possible.[2]
   - Beyond 1–2 weeks, ***steroids*** should be considered **to *facilitate extubation*** if the baby remains ventilated; but this remains ***controversial***.[2]
   - ***Oxygen should be used judiciously***.
   - ***Oxygen saturation target*** 91-95%.[5]

4. Temperature Control:

- Normal body temperature to be maintained at all times (36.5 - 37.5 degrees Celsius) as even a 1 degree drop in body temperature is associated with increased mortality and morbidity
- All unstable preterm babies less than or equal to 2000 gms should be cared for in a **thermoneutral environment**
- Use of **radiant warmers or incubators** is strongly recommended.[1]

- **Kangaroo mother care** is strongly recommended for the routine care of newborns weighing 2000 g or less at birth, and should be initiated in hospitals as soon as the newborns are clinically stable.[1]

5. Nutritional Management:

- It is advisable to have a unit based feeding policy based on gestation and weight criteria---***Standard Feeding Regimen***
- ***Enteral feeding*** should be initiated as early as clinically appropriate, preferably within 24 hours.[6]
- ***Trophic feeds*** should be provided, if volumes cannot be increased.[6]
- ***Expressed Breast milk*** is the milk of choice, followed by ***donor breast milk*** and ***preterm formula milk***, in that order.[7]
- ***Early parenteral nutrition*** should be initiated in ELBW and VLBW babies along with trophic feeds.[8]
- Multicomponent fortification of the breast milk reserved for preterms infants < 32 weeks and < 1500 gms who fail to gain weight despite adequate breast milk feeding.[6,7]
- All VLBW babies should receive ***Vit D, Calcium, Phosphorus and Iron supplementation*** as per the existing guidelines.[6,7]

6. Infection control policies

- ***Hand washing*** and use of ***alcohol based hand rub*** is recommended.
- Early introduction of ***breast milk*** lessens the risk of infections.
- ***Bundle care*** approach should be followed to minimize handling and infections
- Protocols should be in place for ***Central line care***, for prevention of Central line Associated blood stream infections (CLABSI)
- ***VAP care bundles*** should be religiously followed to prevent Ventilator associated pneumonia.
- ***Skin injuries*** should be minimized and taken care of.
- ***Antibiotic stewardship*: *Antibiotics*** should be ***stopped*** as soon as infection is ruled out.

7. Prompt recognition and early management of

- ***Hypoglycaemia***
- ***Shock***
- ***Jaundice***
- ***Sepsis***
- Ventilator Associated Pneumonia
- Mechanical complications related to Ventilation
- Feed intolerance/ NEC

8. **Fluid and electrolytes** management based on weight, electrolytes, urine output, perfusion status and sugars values.

9. Management of

- Apnea of prematurity
- PDA
  - Remains controversial
  - Treatment options in **symptomatic babies with hemodynamically significant PDA** include Indomethacin, Ibuprofen and surgical ligation in face of failed medical management.[9]
- Anemia
- BPD
  - No proven therapy for treatment of established BPD so far.
  - Proven strategies for prevention of BPD include
- Early CPAP.
- Caffeine therapy for babies less than 1250 gm.[10]
- Volume targeted ventilation.[4]
- IM Vitamin A in ELBW babies, but this remains controversial.[11]
- Intraventricular haemorrhage
  - Head circumference monitoring should be done twice weekly
  - More frequent Neurosonogram may be done for early identification of post hemorrhagic hydrocephalus
  - Medical or surgical intervention as and when clinically indicated

10. Screening for

- **Preterm Brain Injury:**[6]
  - All preterm babies ***<32 weeks and <1500 grams*** birth weight must undergo screening neurosonograms at ***1-2 weeks and 36-40 weeks corrected age***.
  - Ultrasound may be performed more often if baby has symptoms like seizures, apnea or hemodynamic instability
- **ROP:**[6]
  - Screening for ROP should be performed in all preterm neonates who are born ***<34 weeks gestation and/or < 1750 grams birth weight*;** as well as in babies 34-36 6/7 weeks gestation or 1750-2000 grams birth weight if they have risk factors for ROP.
  - The ***first retinal examination*** should be performed not later than 4 weeks of age or 30 days of life in infants born ≥ 28 weeks of gestational age
  - Infants born <28 weeks or <1200 grams birth weight

should be screened early, by 2-3 weeks of age, to enable early identification of AP-ROP.

- ***Laser photocoagulation*** delivered by the indirect ophthalmoscope is the mainstay of ROP treatment.

- Metabolic bone disease (MBD): 12
- Screening for metabolic bone disease should be done in all preterm babies
  - less than 28 weeks of gestation
  - birth weight < 1500 g
  - who have received TPN > 4 weeks
  - On bone active medications like methylxanthines, steroids and diuretics
  - Who are unable to reach full fortified feeds
- ALP, Serum Phosphorus, Calcium and TRP (Tubular reabsorption of phosphate) are used for screening MBD.
- Screening should begin at 4-6 weeks of post natal age, and thereafter every 1-2 weeks.
- Treatment includes Phosphorus and Calcium supplementation in recommended doses.
- **Hypothyroidism**
  - Thyroid function tests should be done at 72 hours of life followed by repeat testing in second week of life. (American Academy of Paediatrics)
- **Anaemia and hyponatremia**

11.Weekly monitoring of Growth parameters --- ***weight, length and OFC*** on growth charts

12.Pain and sedation protocols:[2]

- Protocols should be in place for monitoring pain and discomfort.
- Nonpharmacological methods of minimizing procedural pain should be used as and when required
- Opiates should be reserved for more invasive procedures

13.Developmentally supportive Care:

- Includes nesting, noise reduction in NICU, light cycling, non nutritive sucking, KMC, systemic tactile stimulation like oil massage
- May have some benefit in improving outcomes, however, the evidence in favour of these interventions is limited and conflicting in multiple studies.[13]

14.Early intervention

- Early stimulation programs to be started as and when indicated.[6]

15.Evaluation of Growing preterm babies for

- Heart disease
- Hemangioma
- Hernia
- Hepatosplenomegaly
- Rash

} Management to be optimized as per the existing guidelines

D. Care of late Preterm Babies[14]

1. Late preterm babies ***(34-0/7 to 36-6/7 weeks' gestational age)*** constitute major chunk of preterm babies.
2. Many of them may not have immediate serious morbidities like smaller babies born earlier, and therefore, morbidities in these babies are ***often underestimated***.

3. Care of these babies include:

- ***Respiratory*** stabilisation in those with RDS
- ***Thermal*** stabilisation
- ***Feeding*** management
- Monitoring for ***hypoglycaemia, jaundice and infections.***
- Long term follow up, as these babies are also known to have long term morbidities like ***learning disabilities, behavioural problems, reactive airway disease and cardiovascular problems.***
- These infants should have closer follow-up during infancy and early childhood with focus on ***neurodevelopmental and respiratory long-term morbidity***

E. Discharge and Follow Up:[6]

1. Before discharge, a detailed medical and neurological assessment, neurosonogram, ROP screen and hearing screen should be initiated and readiness of the family should be assessed.
2. Follow up services require establishment of ***multidisciplinary team.***
3. Should include ***Ophthalmologist, Audiologist and Speech therapist, Physiotherapist, Child psychologist***
4. The follow up protocol should include assessment ***of growth, nutrition, development, vision, hearing and neurological status.***
5. Formal developmental assessment must be performed at 4, 8 and 12 months of age corrected for gestation, and repeated yearly thereafter till 6 years of age, preferably upto adolescence.

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