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Preterm Labour: Prediction and Prevention

President's Address

Dr. Rishma Dhillon Pai
President FOGSI

I am really happy to see that the new newsletter of ICOG is being released. This issue on 'Preterm Labour' is an excellent update on the new and important aspects of prevention and management of preterm labour.

ICOG the academic wing of FOGSI, under the leadership of Dr. Mala Arora and with the help and support of Dr. S. Shanthakumari and Dr. Sushma Reddy, is working very actively towards promoting all types of academic activities including workshops, articles and net based learning.

I congratulate team ICOG for their interest and efforts towards excellence in the field of education in obstetrics and gynaecology.

Best wishes!

"The beautiful thing about learning is that nobody can take it away from you."

— B.B. King

Chairperson's Address

Dr. Mala Arora
Chairperson ICOG
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Partus Prematorus is delivery prior to 37 weeks of gestation.

Preterm birth is classified as

1. Extreme <28 weeks
2. Very preterm birth 28-31 weeks
3. late preterm birth 32- 37 weeks

Fortunately 85% of preterm births occur between 32 to 37 weeks.

The etiology of preterm birth is varied and may be multifactorial. It is intimately linked to maternal health. Factors that predispose to it are

- Maternal age <18 years or >35 years
- Maternal Nutrition Malnutrition and Obesity
- Maternal addictions Smoking, Alcohol, Cocaine, Marijuana
- Maternal psychological health Stress / Depression / Domestic Violence
- Short interpregnancy interval
- Excessive physical labor Restrict prolonged standing

Empowerment of women especially adolescents, delaying first pregnancy to after teenage, prepregnancy counseling, adequate spacing of pregnancies, providing nutrition counseling during pregnancy and providing post delivery family planning services are some of the social strategies that will go a long way in preventing preterm births.

Judicious use of tocolytics and steroids for fetal lung maturity coupled with in utero transfer to a facility with neonatal intensive care will reduce neonatal mortality and morbidity.

Secretary's Message

Dr. S. Shantha Kumari
Secretary ICOG

Preterm labour remains a clinical enigma for the Obstetricians since the advent of the science. Though extensive study and research has been done in this subject, the exact etiology and physiology eludes us such that there is no single best screening or treatment modality yet identified. Preterm labour can lead to preterm birth which is the most common cause of infant death and is the leading cause of long-term disability in children. Efforts to prevent, detect and manage preterm labour so as to optimise the final perinatal outcome will go a long way in improving the intact survival of babies. This issue of the ICOG newsletter has been planned to revisit the issue to preterm labour and determine the best practices that can be used in managing this persistent clinical challenge in the most reasonable way. The authors have presented the historical and current perspectives of analysis of preterm labour. I am sure that the readers will find this issue very informative and useful in their practice. I wish Dr. Mala Arora, Dr. Monika Gupta and her team all the best!

ICOG Office Bearers – 2017

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To be conscious that you are ignorant of the facts is a great step to knowledge.

- Benjamin Disraeli

From the Editor's Pen

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Greetings to All!

I thank all readers from the ICOG and FOGSI fraternity who have read our previous issues of ICOG campus this year and sent their feedback. Our next step in direction of female healthcare is **'Preterm Labour: Prediction and Prevention'**.

According to a recent Lancet study published in 2012, nearly 24%, or one in four children born prematurely across the globe is from India. Almost 13 % of all children born in India were born too soon, while China ranked second. Being born under 37 weeks, and most importantly under 32 weeks, is the major cause of perinatal morbidity and mortality and accounts for the majority of neonatal deaths.

Increasing the understanding of the pathophysiology of the preterm labor and the strategies to prevent it are essential steps to avoid the consequence of this disease. Recent advances in perinatology and neonatology have increased survival rates, particularly for the extremely preterm baby. This issue of ICOG campus focuses on few important aspects of the physiopathology of the preterm labor i.e. infections and premature rupture of membranes and its diagnosis. This issue also contains a review on newer noninvasive modality of ultrasound to predict fetal lung maturity and an algorithmic approach towards management of preterm labour. Journal scan and brainteasers at the end will stimulate the minds of all the interested readers.

I acknowledge the two guest editors for this issue, Dr. Parul Kotadwala and Dr. Parag Binewale who are senior members of ICOG governing council.

"Success is the sum of small efforts repeated day in and day out"

- Robert Collier

I would like to wish happy reading to all of you.

REVIEW ARTICLE

Intrauterine infection in Preterm labor and Premature rupture of membranes

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INTRODUCTION

The estimated incidence of preterm birth worldwide is 11% with 15 million preterm birth occurring annually[1].[2] Of all preterm births, about 40–45% follow spontaneous preterm labor, 30–35% follow preterm delivery for iatrogenic reasons, and 25–30% follow premature rupture of membranes (PROM).[3] Most preterm PROM occur between 34 and 37 weeks of gestation.[4] Various risk factors have been associated with preterm birth and PROM like previous preterm delivery , low socioeconomic status, maternal age <18 years or >40 years , second-trimester abortions, maternal complications (medical or obstetric), smoking and characteristics of present pregnancy like placental abruption, hydramnios, and multiple pregnancy, stress, infection, and cervical length. The direct association between these factors and preterm birth and PROM is largely unknown however the role of infections in present pregnancy is found to have the most consistent association with preterm labor and PROM (25% of all preterm births).[5]

Understanding etiology of preterm birth and premature PROM (PPROM) and appropriate intervention can decrease the incidence of neonatal and perinatal mortality and also the associated burden of prematurity and early neonatal sepsis in preterm births.

INFECTIONS ASSOCIATED WITH PRETERM LABOR AND PPROM

Both Intrauterine and extrauterine infections are associated with preterm birth. Intrauterine infection is present in around 25–40% of preterm births and PROM. It may exist in amniotic fluid, in the fetal membranes (chorioamnionitis), between maternal and fetal tissues (choriodeciduitis), in the placenta, in the umbilical cord (funisitis), or in the fetus. Majority of women with chorio-amnionitis, as confirmed by histopathological examination or culture, have no symptoms other than preterm labor or preterm PROM.

Amongst the various micro-organisms bacteria are considered to be the commonest implicated for intrauterine infection leading to preterm birth or PROM (Table 1). These microbes may reach the amniotic cavity by the following routes (Figure 1)

- Ascent from the vagina (commonest route)
- Hematogenous spread
- Iatrogenic spread during an invasive procedure, such as amniocentesis (AC) or chorion villus sampling
- Retrograde invasion through the fallopian tubes[6]

PATHOGENESIS

The pathogenesis of spontaneous preterm labor and PROM in the setting of subclinical infection is not fully elucidated. There is a growing body of evidence that host mediated response to bacterial products and tissue injury through activation of the macrophage-monocyte system in the presence of bacterial invasion or infection may cause preterm birth and PROM. The mechanism behind infection and preterm labor consists of 3 main components:

Table 1: Infectious agents causing intrauterine infection in Preterm labor and pPROM

Infectious agents	
GENITAL (INTRAUTERINE)	**Bacterial** Bacterial vaginosis, Group B streptococcus, Escherichia coli, Fusobacterium sp., Ureaplasma ureolyticum, Mycoplasmas, Chlamydia, Neisseria, Trichomonas
	Viral Cytomegalovirus, Parvovirus B19, Adenovirus, Enterovirus , Herpes simplex virus ,Epstein-Barr virus, Respiratory syncytial virus
EXTRA- UTERINE	Pyelonephritis ,Typhoid fever , Listeria , Malaria , Pneumonia , Asymptomatic bacteriuria

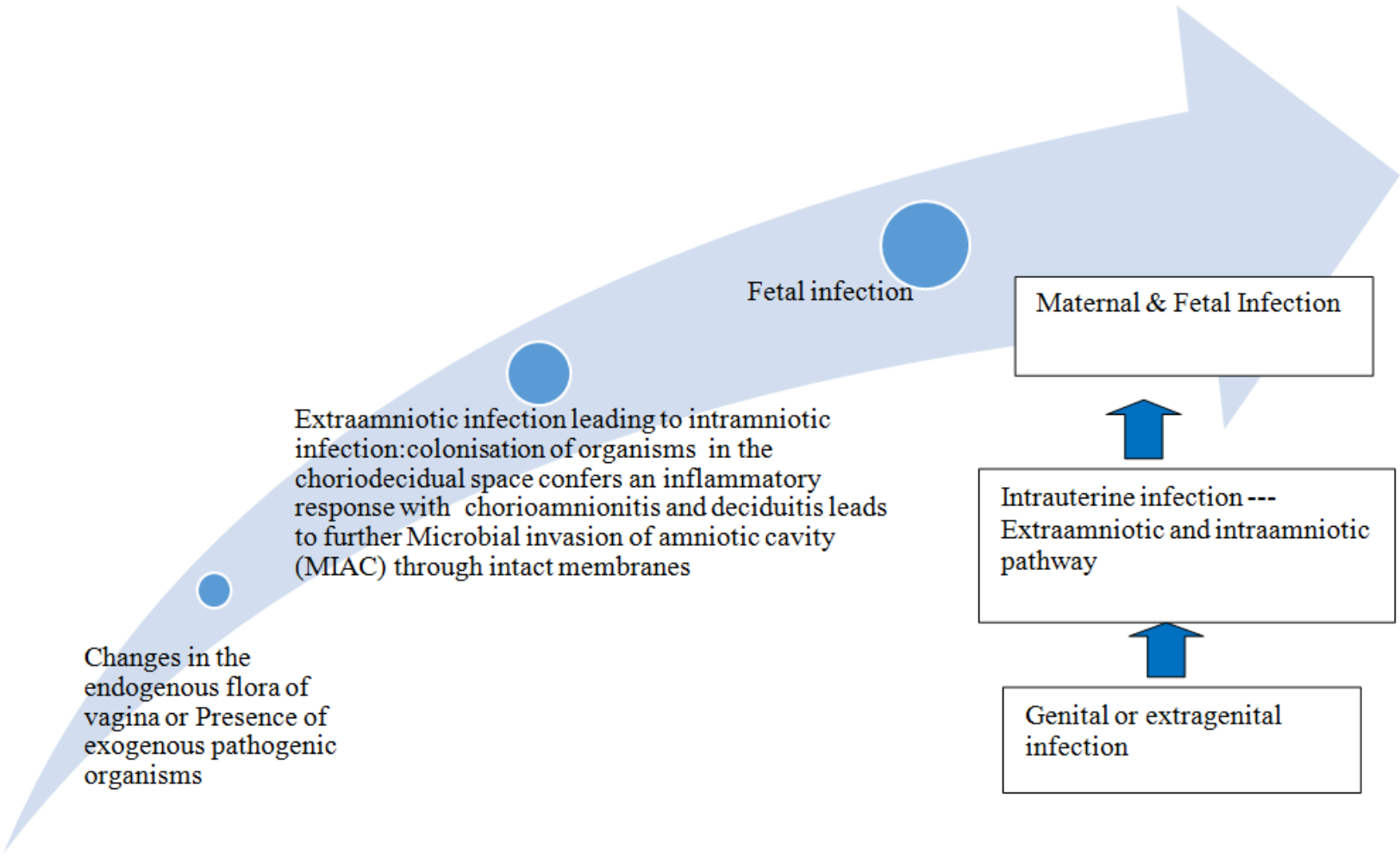

Fig. 1: Cascade of events leading to intrauterine infection and its sequelae

- Maternal inflammatory response
- Fetal infection
- Fetal inflammatory response.

Maternal Inflammatory Response:

- *Activation of macrophage-monocyte system* due to release endotoxins and exotoxins by microbes in choriodecidual space, leads to release of proinflammatory cytokines in both the and fetal membranes. This occurs due to interaction of toxins with Toll like receptors(TLRs) on the surface of leukocytes, epithelial and trophoblast cells.
- *Production of cytokines* like interleukin (IL)-1, tumor necrosis factor (TNF)-a, IL-1b, IL-6, IL-8, an inflammatory cascade, in which prostaglandins are produced, and acute-phase reactants like C-reactive protein (CRP) are released into the circulation, and neutrophils are activated. Neutrophils migrating to the infectious site release proteases such as matrix metallo-proteinases (MMPs-1, 8 ,9) and their regulators, like tissue inhibitors of metalloproteinase -1 (TIMP-1).[7] Prostaglandins (PGs) stimulate uterine contractions, and metallo-proteinases stimulate collagen degradation, leading to cervical softening and preterm labor or rupture of the amniotic membranes.[2]
- *Decreased synthesis of PG dehydrogenase* in fetal membranes due to amnionitis cause resultant decrease in degradation of PGs and thus increased levels of PGs.

Fetal Infection

In many cases, the fetus may be responsible for mounting an inflammatory response to infection by releasing cytokines. Various studies provide strong evidence to suggest that TLRs are expressed from very early in gestational development in developing fetus and their expression is wide- spread in both amniotic fluid-exposed (lung, skin) and internal (brain, spleen, immunocytes) fetal tissues.[8]

In fetuses with infection, there is an increase in both the fetal hypothalamic and placental production of corticotropin releasing hormone (CRH). This results in an increased fetal adrenal production of cortisol, which in turn increases the production of PGs.

Fetal Inflammatory Response

Fetal inflammatory response syndrome (FIRS) is a subclinical condition described in fetuses of women presenting with preterm labor and PROM and is defined as elevated fetal plasma IL-6 levels (more than 11 pg/ml) which is a major mediator of host response and is an independent risk factor for developing severe neonatal morbidity. Fetal plasma IL-6 levels have also been shown to be significantly associated with inflammatory lesions in the chorioamnion, leading to the conclusion that funisitis and chorioamnionitis are histological markers of FIRS. Even though FIRS is possible in the absence of intraamniotic infection, the strongest fetal inflammatory response is associated with a culturable amniotic infection. Thus, it is important to take into account the magnitude of amniotic-fluid inflammation when predicting pregnancy outcomes.[9] Fetuses have shown to induce the immune response via the secretion of pro-inflammatory cytokines to signal the onset of labor and exit a hostile intrauterine environment for survival. Hence, among women with PROM, FIRS is also associated with the impending onset of preterm labor. While, mechanism behind sterile inflammation is, instead, considered to involve stimuli leading to release of endogenous molecules, called alarmins, which evoke a host response through Toll-like receptors (TLRs), leading to an inflammatory process and causing sterile chorioamnionitis.[4]

DIAGNOSIS OF INTRA AMNIOTIC INFECTION

Clinical chorioamnionitis: Clinical chorioamnionitis has been defined by Gibbs criteria as maternal fever ≥ 38 ºC with at least one or two of the following criteria:[10]

- Uterine tenderness,
- maternal tachycardia
- fetal tachycardia,
- foul-smelling or infectious discharge from the uterine cervix, or
- total maternal white blood cell (WBC) count > 20 x 109/L[11]

Intrauterine infection is often chronic and usually asymptomatic. In these scenario, Amniotic fluid, cervical and/or vaginal secretions, maternal serum, cord blood, histopathological examination and culture of choriodecidual membrane, cord stump, placenta can be used for diagnosing intra amniotic infection. Of all these, the best-studied source is amniotic fluid.

Amniotic Fluid:

- Gram-staining,
- Glucose levels
- Culture sensitivity (can detect both aerobic and anaerobic bacteria but a negative culture cannot definitively exclude the presence of intra-amniotic infection.)
- Elevated concentration of inflammatory markers, such as IL-6,and matrix metalloproteinase -8 (MMP-8)
- Polymerase chain reaction (PCR):- in women with negative cultures, the presence of microbial footprints can be detected by PCR.

Importantly, microbial colonization in amniotic fluid, per se, is not considered consistent with infection, an inflammatory component is necessary[12]

Cervical/Vaginal Secretions

- These can be subjected to wet smear examination, Gram-staining, and culture sensitivity for the diagnosis of BV, trichomoniasis, and gonorrhea.
- Fetal fibronectin is a protein of the placental membranes and can be measured in cervical/ vaginal secretions. It is the best predictor of spontaneous preterm delivery and is strongly associated with subsequent chorioamnionitis and neonatal sepsis.[13]
- High cervical concentration of ferritin also predicts subsequent spontaneous preterm delivery
- IL-6 and IL-8 in cervical fluid samples have also shown an association with intra-amniotic infection /inflammation and histological chorioamniotis.[14]

Ultrasonography

- Short cervix correlates with several markers of infection and chorioamnionitis in preterm birth and PROM.
- Ultrasound approaches to predict fetal systemic inflammatory response are also being increasingly recognized. For example, possible changes in the fetal spleen can be evaluated in response to chorioamnionitis as well as small size of the fetal thymus has been linked to intra uterine infection, chorioamnionitis and funisitis.[15]

Maternal Serum Markers

- Serum C-reactive protein
- Ferritin concentration: - levels doubling within a week shows progressive intrauterine infection.
- Serum IL-6 levels are found to be increased in pregnancies complicated with intra- amniotic inflammation.[16]

Cord blood sample

- Complete blood count especially, differential count,
- C-reactive proteins,
- Pro-inflammatory cytokines like IL-6, IL-8.

Placenta, fetal membranes, and cord stump should be subjected to histopathological examination and culture sensitivity.

ROLE OF ANTIBIOTICS IN PRETERM LABOR AND PPROM

Inconsistent and poor results have been documented in various trials using different antibiotics to prevent preterm births. A Cochrane review of trials on the use of prophylactic antibiotics for inhibiting preterm labor with intact membranes, observed no definite benefit on neonatal outcomes. On the contrary, increased neonatal mortality was observed in those who received antibiotics.[17]In pregnancies with intact membranes and the threat of preterm labor, antibiotic prophylaxis is not recommended in the absence of signs and symptoms of chorioamnionitis because of its possible further harm to the neonate.[18]Similarly, American College of Obstetricians and Gynecologists (ACOG) also opines that administration of antibiotics solely for the prolongation of pregnancy in women with preterm birth and intact membranes is not justified.[19] Meanwhile, development of clinical chorioamnionitis is the major risk factor associated with expectant management of pPROM and antibiotic prophylaxis has shown to reduce the incidence.

In a systematic Cochrane review, prophylactic antibiotics had no effect on the rates of respiratory distress syndrome(RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), or perinatal death. Prophylactic antibiotics were, however, associated with prolongation of pregnancy after PPROM, reduced numbers with neonatal infection, reduced need for surfactant, and reduced consumption of oxygen.[20] Thus, there is a potential for prophylactic antibiotics in women with pPROM [21]

Also, recent antenatal screening programmes for detecting aysmptommatic lower genital tract infections in pregnant women for prevention of preterm birth were found to be cumbersome as well as ineffective. Hence, more randomized controlled trials (RCTs) are needed, especially from the developing countries to support these programs.[22] Screening for bacterial vaginosis is not indicated in women at low risk for preterm labor and the current evidence is insufficient to assess the balance between the benefits and harms of routine screening of women at high-risk of preterm birth.[23]

CONCLUSION

- Infection is the only pathologic process which has a firm causal relationship with preterm birth and PROM.
- A number of organisms such as bacteria, viruses etc. have been implicated as a cause of intrauterine infection, bacteria being the commonest
- The intrauterine infection is mostly asymptomatic and subclinical as the causative organisms are usually of low virulence. The earlier the gestation at which preterm birth or PROM occurs, the higher is the incidence of subclinical infection.
- The maternal as well as fetal inflammatory response to microbial invasion have been implicated in the pathogenesis of preterm birth and PROM.
- Diagnosis of intrauterine infection is a major challenge due to the absence of any definite clinical signs and symptoms.
- The diagnosis can be made by detecting the presence of markers of infection and/or inflammation in the amniotic fluid, cervical and/or vaginal secretions, maternal serum as well as histopathological examination and culture of choriodecidual membrane.
- There is no role of either routine screening of pregnant women for the organisms associated with preterm labor or administering prophylactic antibiotics for prevention of preterm birth.
- However, antibiotics should be prescribed

to women with PROM to prolong the latency or duration of pregnancy to improve neonatal outcomes.

More RCTs are needed, especially from the developing countries to evaluate the role of screening pregnant women for infections and the role of antibiotics in prevention of preterm births and PROM.

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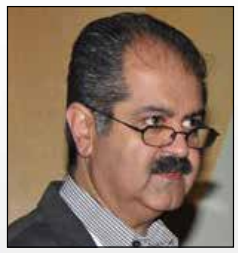
To raise new questions, new possibilities, to regard old problems from a new angle requires creative imagination and marks real advance in science.

- Albert Einstein

Ultrasound Evaluation of Fetal Lung Maturity: An update



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INTRODUCTION

In developed countries, and particularly in the United States of America and many institutions in the UK, the premise that is followed is that in patients with poor dating and with indications for late preterm or early-term delivery, amniocentesis for fetal lung maturity may be of benefit in determining the timing of delivery. Testing for fetal lung maturity is performed before semi-elective but medically indicated births < 39 weeks when this information impacts the balance between maternal-fetal risks of continuing the pregnancy versus the fetal risks of prematurity. In most clinical settings, the test is omitted because either delaying delivery, because of lung immaturity, would place the mother or fetus at significant risk, or because the fetus would benefit from delaying delivery, even if lung maturity is documented, and delaying delivery does not place the mother at significant risk.

The lungs are the last of the fetal organ systems to mature, both functionally and structurally. Because the immature pulmonary system may not oxygenate the neonate adequately, preterm birth can lead to significant neonatal morbidity or mortality. Fetal lung maturity is sometimes assessed before iatrogenic preterm delivery and can be a factor in determining the timing of delivery in these cases.

Thus, prenatal diagnosis of fetal lung maturity is essential to avoid an untoward outcome for the fetus or the mother, or both. Specifically, it helps in managing the remaining weeks of the pregnancy, determining the outcome of the pregnancy, planning for possible complications during birth, planning for problems that may occur in the newborn infant, deciding whether to continue the pregnancy, and finding conditions that may affect future pregnancies.

RCOG guidelines currently suggest that clinicians should offer a single course of antenatal corticosteroids to women between 24+0 and 34+6 weeks of gestation who are at risk of preterm birth. Unfortunately, the assessment of risk of prematurity is not always straightforward and the question that also needs to be addressed is what about those fetuses that do not deliver within the next one week or in the following weeks?

A single dose of corticosteroid given to pregnant women expected to give birth preterm within 1 week significantly reduces mortality, respiratory distress syndrome, and intraventricular hemorrhage in their preterm newborns. Repeat steroids increase rates of neonatal and maternal infection, may result in fetal, neonatal and maternal adrenal suppression, decreased fetal and neonatal somatic and brain growth, increased incidence of necrotising enterocolitis and retarded neuronal myelination and increased perinatal mortality. The administration of repeat doses, therefore, needs to be addressed with respect. Additionally, information on fetal lung maturity may be helpful in estimating the level of newborn care that will be required.

EVALUATION OF FETAL LUNG MATURITY

Several attempts to assess fetal lung maturity (FLM) in a non-invasive way have been made since 1999 but have failed the test of time[1,2,3].

Ultrasonography is a non-invasive procedure that is harmless to both the fetus and the mother. It can be used to determine fetal size, gestational age and the condition of placenta. Ultrasound cannot measure any of the biochemical parameters of fetal lung maturity, nor can it provide direct histologic information about fetal lung development. However, it is reasonable to assume that both morphological and biochemical changes alter the diffuse scattering and other propagation properties of fetal lung. This may change the textural appearance of sonogram.

Recent research, approaching the problem through computerized textural analysis of ultrasound images is a validated development.[4] Specifically, texture analysis approaches are computerized methods that can analyze medical images and identify subtle changes in the aspect, or texture, that are invisible to the human eye. These textural patterns can then be used to train algorithms to predict clinical information. Recent studies have demonstrated that texture analysis of fetal lung ultrasound images is able to identify patterns of features that correlate strongly with gestational age, or with the results of FLM tests on amniotic fluid.

An image of the fetal lung is obtained by routine ultrasound in the following way:

- Acquisition frequency must range within 2 and 6 MHz
- Harmonics must be activated during acquisition
- Pre-sets for cardiac applications are to be used
- Axial section at 4-chamber view level
- Fetal spine must appear in the horizontal axis (3h or 9h)
- Fetal thorax must take up the complete ultrasound image. Avoid the use of zoom in order to achieve thorax occupation across the whole screen (use depth)

The image obtained is then uploaded on the dedicated internet site as a Dicom and the near lung is outlined (Figure 1). The image is then sent for analysis. Within minutes the results of the analysis are available for use. The results report the percentage of risk of lung prematurity in the background of usual fetal lung maturity at the given gestational

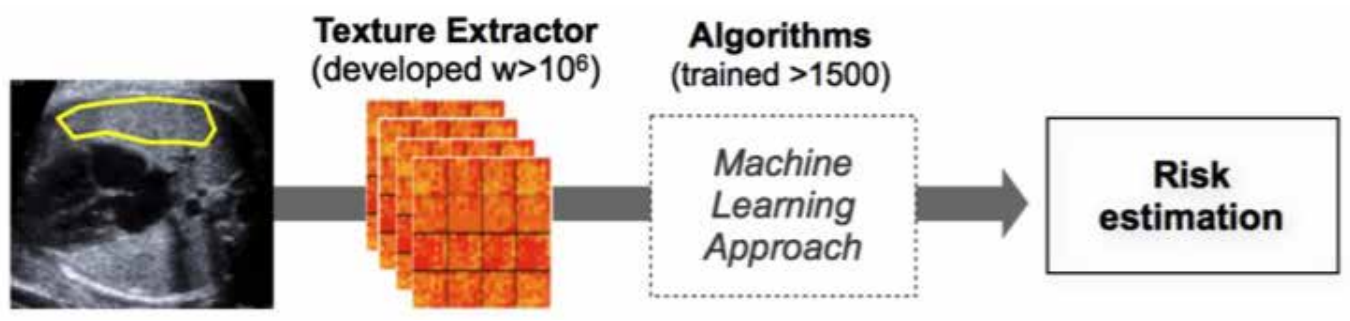

Figure 1: Four chamber view of the heart is the correct plane of section for this evaluation. This is uploaded into the software and sent for analysis. Analysis involves a technology based extraction and an algorithm which has a machine learning approach. This is then translated into the report of risk estimation.

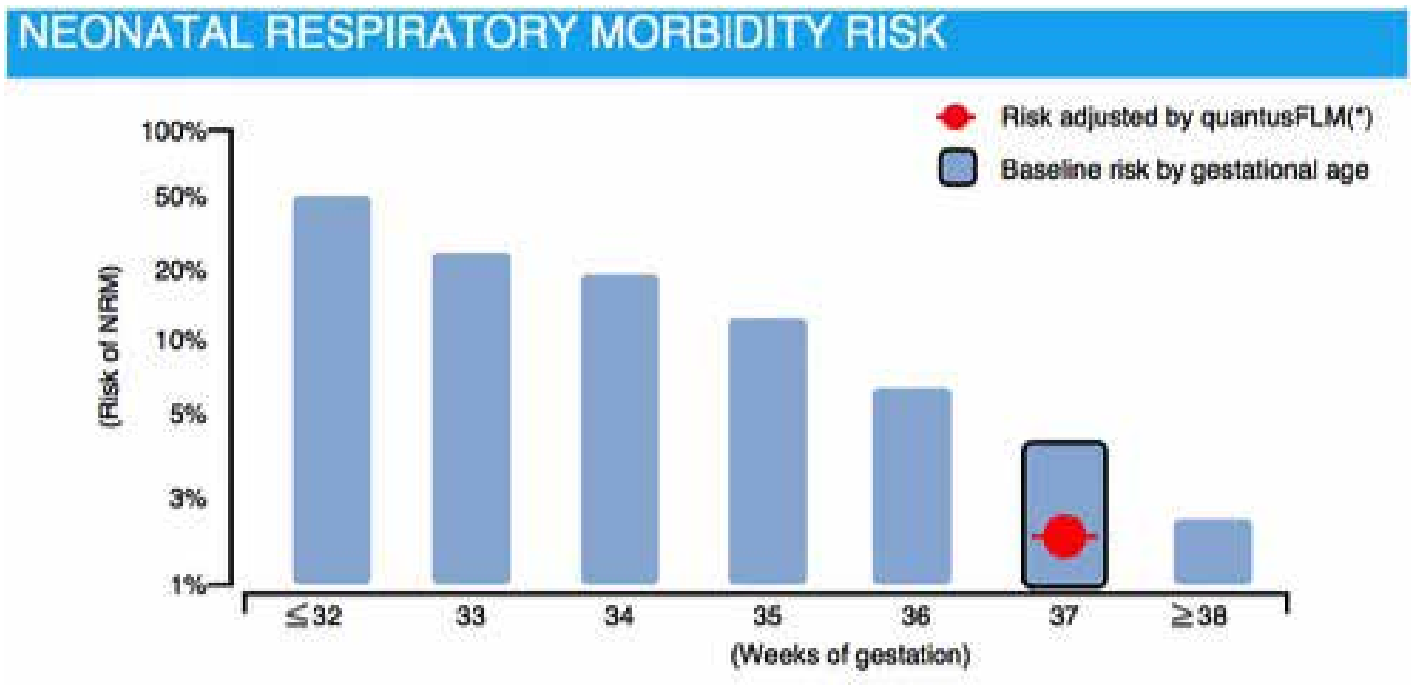

Figure 2: Standard report indicating mature lung at 37 weeks of gestation.

age. Results are comparable to those of evaluation of Lecithin-Sphingomyelin ratio and Lamellar Body evaluation in an amniotic fluid sample for sensitivity, specificity and negative predictive value. The results have a far superior positive predictive value. The test is now widely available in India.

In a recent study conducted by Beck et al correlation between the ultrasound lung maturity [gray-scale histogram (GSH) technique] and the incidence of neonatal respiratory distress in females with singleton pregnancies in two groups 28 to 35+6 weeks and those with >36 weeks gestation was done.[5] They concluded that the evaluation of fetal lung maturity through GSH was more effective than the subjective method in predicting respiratory distress among newborns.

CONCLUSION

Despite improvements in clinical practices of obstetrics and neonatology such as administration of prenatal corticoids and postnatal surfactant, respiratory morbidity remains a leading cause of neonatal morbidity and mortality in those delivered late preterm (34+0 to 36+6 weeks' gestation) and even in early term (37+0 to 38+6 weeks) gestations[6]. It is clear that, for some indications, delivery should occur regardless of FLM results. However, there is an open debate about the value of FLM testing in the decision-making process for relative indications or borderline clinical situations in which late-preterm or early-term delivery may seem a reasonable option but delivery could be postponed if fetal lung immaturity was assessed.

Determining FLM without the need for an invasive technique might have a tremendous impact on the clinical management of such cases. Aside from economic implications, avoiding the need for amniocentesis would be associated with less discomfort and fewer related complications for the patient, and controversies about indications for FLM assessment could be approached from a different perspective.

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Our greatest weakness lies in giving up. The most certain way to succeed is always to try just one more time.

- Thomas A. Edison

Managing Preterm Labour: What does Evidence say?

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INTRODUCTION

Preterm labour refers to the onset of regular uterine contractions between 20 to 37 completed weeks of gestation resulting in changes in the cervix. In 1976 the WHO and the FIGO first promoted the definition that preterm infants were those who were delivered before 37 completed weeks, that is, ≤ $36^{6/7}$ weeks.[1] In India 2010-data suggest that out of 27 million babies born every year, 3.5 million are premature (12.96%)[2]. Preterm birth complications are the leading cause of under 5 childhood mortality, responsible for nearly 1 million deaths in 2015.[3] Preterm birth is responsible for around 70% of neonatal mortality, 36% of infant mortality & 25-50% of long-term neurologic impairment.[4] Three-fourth of them could be saved with current, cost-effective interventions.[3]

Several methods have been developed to predict the onset of preterm labour such as home uterine activity monitoring (HUAM), measuring of fetal fibronectin (FFN) levels, bacterial vaginosis (BV) screening, salivary estriol, assessment of cervical length. ACOG does not recommend any of these tests as screening strategies for asymptomatic, at risk women as they are neither useful nor cost effective.[4]

PREVENTION OF PRETERM BIRTHS

Till date, none of the methods give promising results in prevention of preterm labour in general population. But measures have been developed to prevent recurrence in next pregnancy. These measures include vaginal progesterone and cervical cerclage.

Vaginal progesterone

A multi-centre, randomized controlled trial on vaginal progesterone gel for asymptomatic women with a singleton pregnancy and a sonographic short cervix (10–20 mm) at 19 + 0 to 23 + 6 weeks of gestation was associated with a remarkable reduction in the rate of preterm delivery (< 33 weeks), substantial decrease in rate of RDS. The treatment-related adverse events in patients allocated to progesterone or placebo gel were similar.[5]

Cervical cerclage

Several randomized controlled trials found a significant reduction in preterm labour in high risk women with the use of cervical cerclage[6]. Whereas other studies say that cervical cerclage does neither decrease the preterm labour risk nor found useful in low risk pregnancy[7] and twin gestation[8].

Role of cervical pessary

A cervical pessary is a silicone transvaginal device which supports the cervix and directs it towards the sacrum thereby reducing direct pressure from the uterus on the cervical canal.

Randomised controlled trials failed to show any reduction in the chances of preterm labour before 34 weeks in singleton[9] and twin gestation[10] using pessaries. Further studies are required to make a recommendation regarding pessary use.

ACOG (2012) RECOMMENDATIONS

- Progesterone supplementation or cervical cerclage from 16-24 weeks of gestation in a woman with a singleton gestation with prior preterm singleton birth regardless of cervical length.
- Vaginal progesterone in asymptomatic woman with singleton gestation without prior preterm birth with an incidentally identified very short cervix (≤ 20mm) before or at 24 weeks of gestation.
- Adding alternative form of progesterone is not recommended in a woman already receiving preventive progesterone therapy identified with a short cervix.
- Switching of progesterone from its one form to another is not recommended.
- Progesterone supplementation is not recommended to reduce the incidence of preterm birth in women with multiple gestation.
- Cervical cerclage increases the risk of preterm labour in women with multiple gestation, thus is not recommended.
- Progesterone and cerclage together in reducing risk of preterm labour, is not recommended.

NICE GUIDELINES (2015) RECOMMNENDATIONS[11]

- Prophylactic vaginal progesterone or cervical cerclage in women with a history of spontaneous preterm birth or mid-trimester loss between 16+0 and 34+0 weeks of gestation and a cervical length of <25 mm between 16+0 and 24+0 weeks of pregnancy.
- Prophylactic vaginal progesterone to women with no history of spontaneous preterm birth or mid-trimester loss but a cervical length of < 25 mm between 16+0 and 24+0 weeks of gestation.
- Prophylactic cervical cerclage for women with cervical length of < 25 mm between 16+0 and 24+0 weeks of gestation and with either of the two conditions:
  - Preterm prelabour rupture of membranes (P-PROM) in previous pregnancy
  - History of cervical trauma.

TREATMENT OF PRETERM LABOUR

Because of poor predictive methods of preterm labour, its incidence has changed only a little in this era of modern obstetrics but salvage of preterm neonates have become much better using drugs and modern equipment. There are some measures adopted that may either halt preterm labour or improve survival of the preterm neonate. These are tocolytics, corticosteroids, antibiotics and magnesium

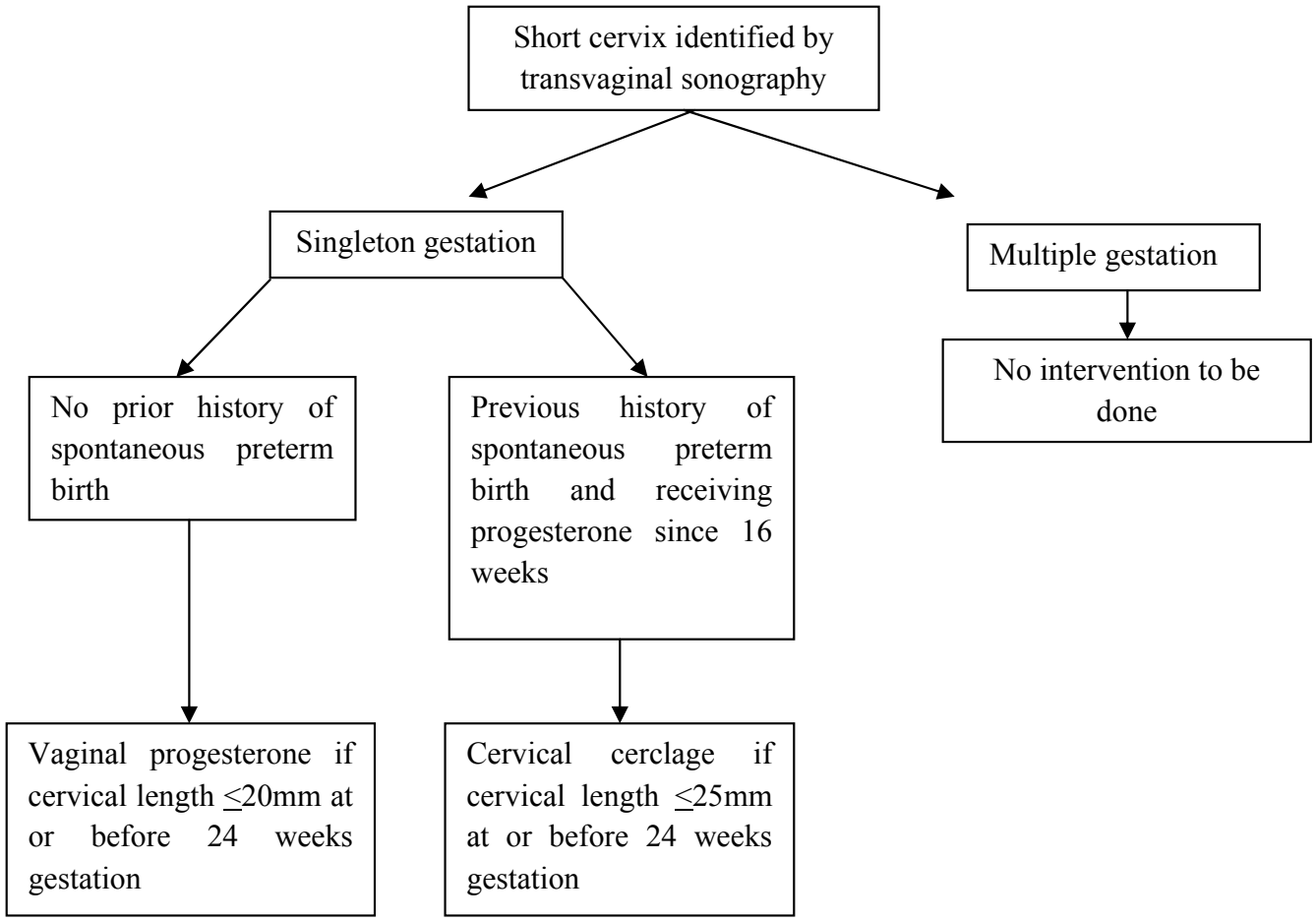

Figure 1: Management algorithm of a woman with short cervix in second trimester[12]

Table 1 : Profile of various tocolytics used in Preterm Labour

Tocolytic Agent	Dosage	Contraindications	Maternal Side Effects	Foetal or neonatal Side Effects
Terbutaline	0.25 mg subcutaneously every 20 min, to a maximum of 2 doses (pulse should be<120/ min)	Tachycardia Hypersensitivity Cardiac disease Uncontrolled diabetes mellitus	Tachycardia, hypotension, tremors, palpitations, chest discomfort, shortness of breath, pulmonary edema, hypokalemia, hyperglycemia	Foetal tachycardia
Magnesium Sulfate	4-6 gram bolus over 20 min then 2 gm/hr iv infusion	Myasthenia gravis Avoid concomitant use with Nifedipine	Flushing, lethargy, headache, diplopia, muscle weakness, dry mouth, pulmonary edema, cardiac arrest	Lethargy, hypotonia, respiratory depression, bone demineralization with prolonged use
Nifedipine	30 mg loading dose, then 10-20 mg every 4-6 hrs for 24-48 hrs	Cardiac disease, Renal disease, hypotension (<90/50)	Dizziness, flushing, hypotension, elevation of hepatic transaminases	Not known
Indomethacin	loading dose 50-100 mg orally or 50 mg rectally then 25-50 mg orally every 6 hr for 48 hr	Platelet dysfunction Hepatic dysfunction, Gastrointestinal ulcer, renal dysfunction, Coagulopathies Asthma (in women who are hypersensitive to aspirin)	Nausea, gastritis	Premature closure of ductus arteriosus, oligohydramnios, necrotising enterocolitis in preterm newborns

sulfate.

Tocolytics

A tocolytic drug relaxes the uterine musculature by inhibiting uterine contraction leading to abolition of preterm labour. The ACOG has mentioned that tocolytic agents do not prolong gestation markedly but may delay delivery for up to 48 hours, thus helping

transport of the patient to a tertiary care and buy time for corticosteroid therapy to act. It also concludes that maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcome and thus, not recommended. Women with preterm contractions without cervical change (threatened preterm labour), generally should not be treated with tocolytics. Beta-adrenergic agonists, calcium-channel blockers, indomethacin, magnesium sulphate are the commonly tocolytic agents for such short-term use (up to 48 hours).[13,14,15] Atosiban can be used for maintenance. Tocolysis is not recommended beyond 34 weeks of gestation. NICE guidelines recommend only Nifedipine or Atosiban for tocolysis from 24+0 to 33+6 weeks with intact membranes.[11]

According to Cochrane analysis, β2-agonist drugs (Ritodrine and Terbutaline) can delay delivery by 48 hours, but because of their greater side-effect profile than other agents they should not be used,[16] and magnesium sulphate is ineffective.[17] The FDA, on 30th May, 2013, issued a safety announcement against using magnesium sulphate injection for more than 5-7 days to abort preterm labour because of risk of hypocalcemia and bone problems in the developing foetus, including osteopenia and fractures.

In 2011, US FDA warned regarding the use of terbutaline to treat PTL because of maternal side effects.[18] ACOG recommends that terbutaline should not be used as a tocolytic agent other than as an intermittent acute therapy for preterm contractions without labour (e.g. 1-2 subcutaneous doses for preterm contractions) or in the setting of uterine tachysystole.[4] Although Indomethacin, the cyclo-oxygenase inhibitor, reduced the occurrence of preterm birth compared to placebo and other agents in some trials, the Cochrane analysts did not found firm evidence regarding it's efficacy.[19]

Corticosteroids

Randomised controlled trials and meta-analyses confirm that corticosteroids reduce chances of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, patent ductus arteriosus, bronchopulmonary dysplasia and overall neonatal death.[20]

RCOG[22], ACOG, NICE[11] and WHO[23] recommends that antenatal corticosteroids should be administered from 24 to 34 weeks of gestation but ACOG[4] had extended its recommendation of betamethasone use

Table 2: Corticosteroids used in lung maturity in PTL[21]

Agent	Dose	Route	Total dose
Betamethasone	12 mg, 24 hours apart	Intramuscular	2
Dexamethasone	6 mg, 12 hours apart	Intramuscular	4

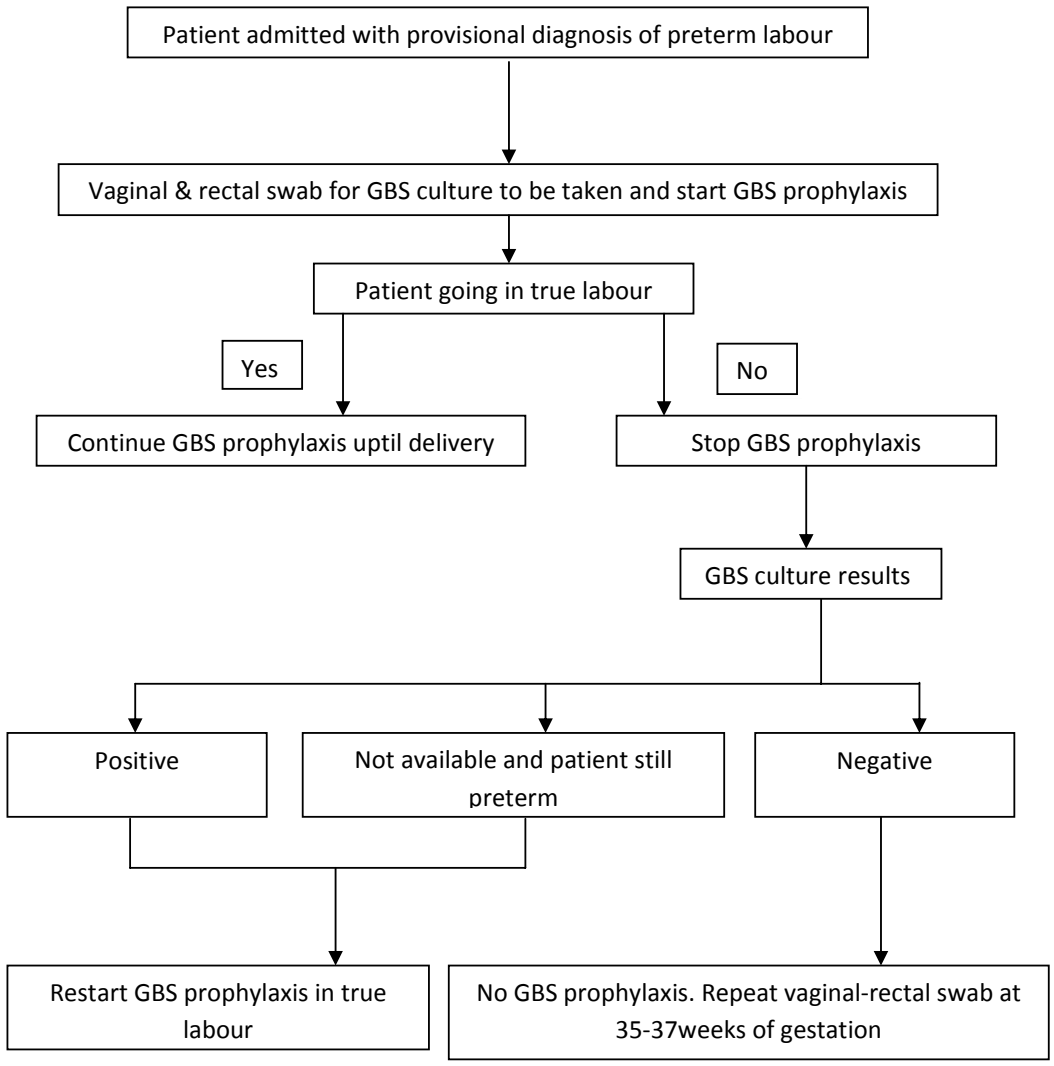

Figure 2: Algorithm regarding use of antibiotics in preterm labour.

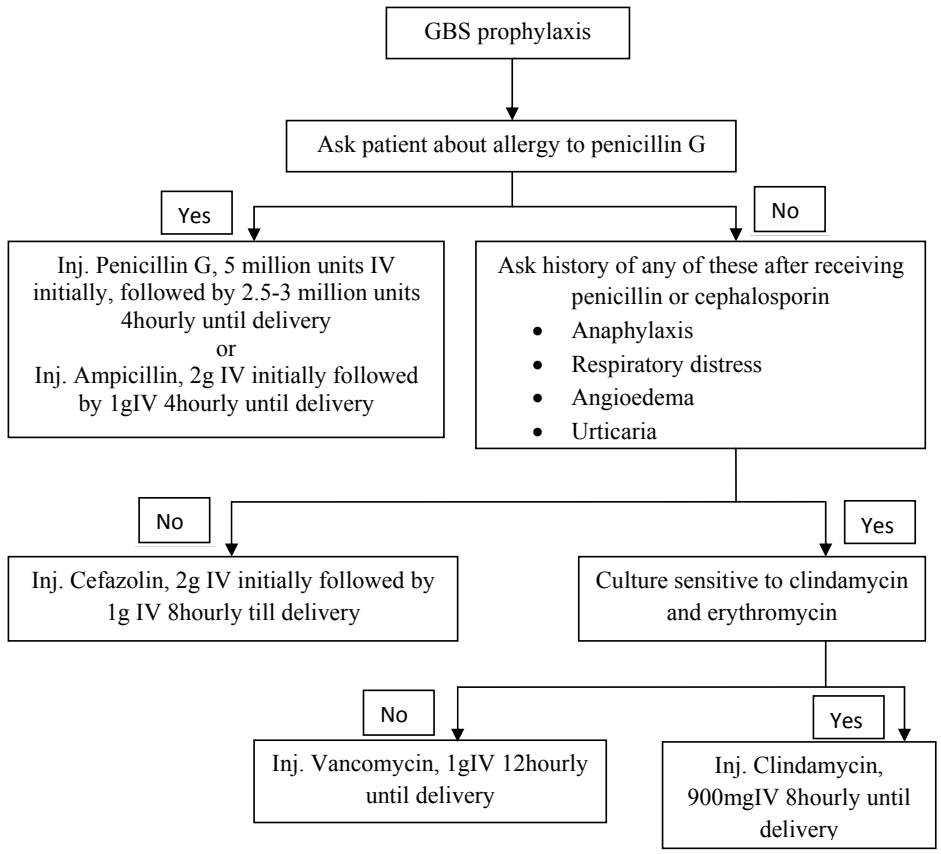

Figure 3: Antibiotic regimen for intrapartum GBS prophylaxis ACOG

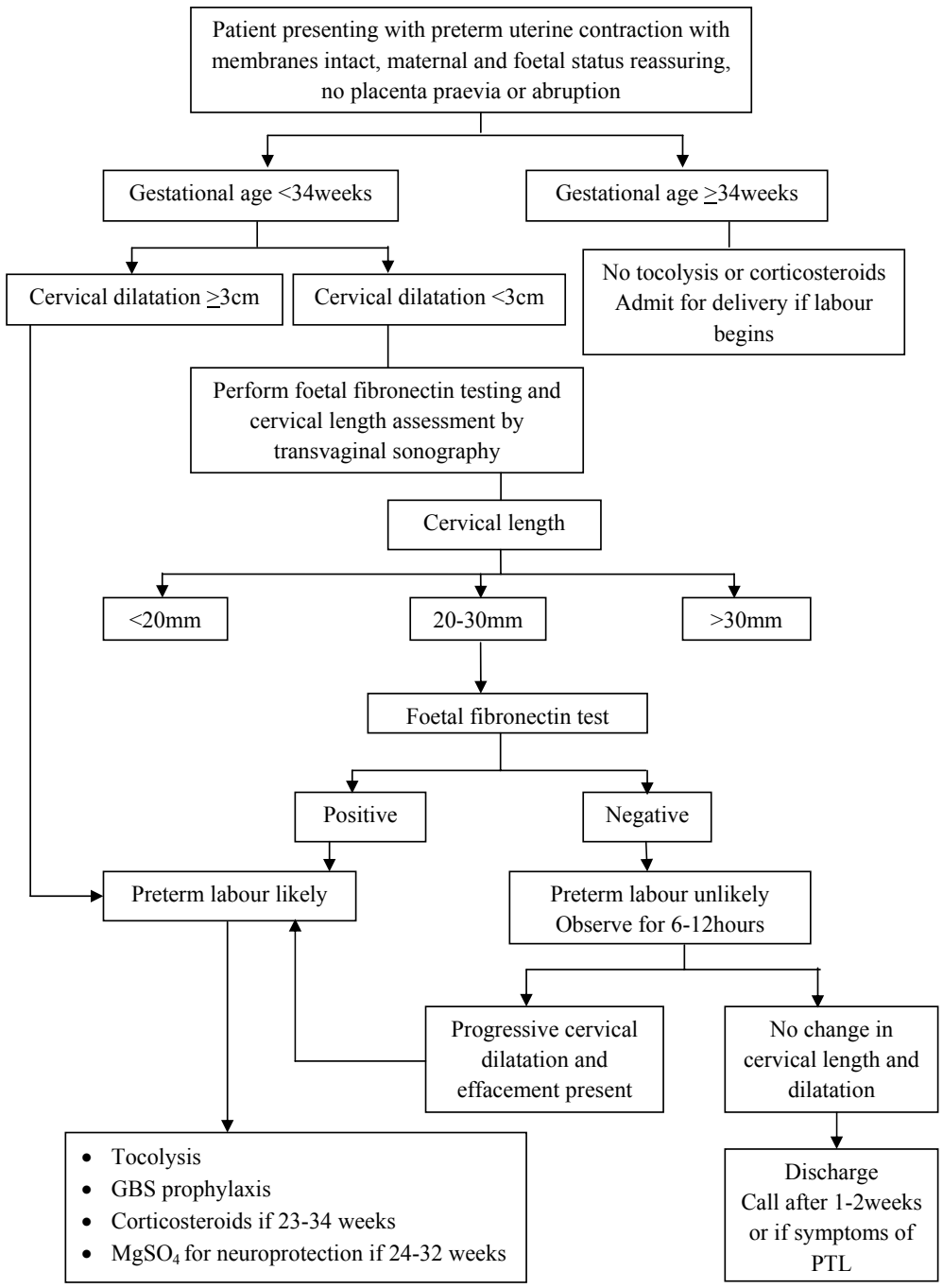

Figure 4: Management algorithm for woman coming with preterm labour[27]

for women with a singleton pregnancy at $34^{0/7ths}$ to $36^{6/7ths}$ weeks of gestation at high risk of preterm birth within 7 days. NICE has also considered corticosteroid use till 35^{+6} weeks.[11]

RCOG does not routinely recommend corticosteroid use beyond 34 weeks but allows for women who must undergo scheduled caesarean delivery before $39^{/07th}$ weeks of gestation.[22] WHO had not extended its recommendations regarding this.[23]

ACOG also considers corticosteroid course at $23^{0/7}$ weeks of gestation who are at risk of preterm delivery within 7 days, irrespective of membrane rupture status and foetal number, if family consents regarding resuscitation.[4] It allows a single repeat course of corticosteroids before $34^{0/7}$ weeks of gestation who are at risk of preterm delivery within next 7 days, and first course was administered 14 days prior. WHO also recommends single repeat course of corticosteroid if delivery does not occur within 7 days of initial dose, and if there is likelihood of preterm birth in coming 7 days.[23] NICE does not recommend repeat course routinely. ACOG and WHO supports corticosteroids in multiple pregnancies.[4,23]

Antibiotics

Women with spontaneous preterm labour and intact membranes are at high risk of Group B Streptococcus infection (GBS), so the acute use of antibiotics could eradicate the infection, prolong the pregnancy and improve neonatal outcome, but at the same time leaves the foetus in a hostile inflammatory environment.

The RCOG does not recommend routine prophylaxis in this situation as there is evidence that antibiotics given under these circumstances increase the risk to their offspring of functional impairment and cerebral palsy. The ORACLE II randomized controlled trial was the most important study showing lack of effectiveness of antibiotic therapy in preterm labor.[24] WHO too does not recommend routine use of antibiotics in preterm labour with intact membranes.[23]

CDC 2010 provided an algorithm (Fig 2 & 3) in collaboration with ACOG regarding use of intrapartum antibiotics against group B streptococcus (GBS) in preterm labour as GBS is the leading cause of infectious morbidity and mortality among newborns.[25]

Magnesium sulphate ($MgSO_4$)

Evidences suggest that $MgSO_4$ if administered before 32 weeks of gestation when delivery is anticipated reduces the risk and severity of cerebral palsy in surviving infant.[26] ACOG and WHO endorse this recommendation.[23,25] NICE guidelines consider intravenous

$MgSO_4$ between 30^{+0} and 33^{+6} weeks of pregnancy who would have preterm birth within 24 hours.[11] Dose is 4gm IV over 20 minutes, then 1 g/hour until delivery or for 24 hours, whichever came first.

CONCLUSION

Better prevention and proper treatment of preterm labour helps reducing adverse neonatal and infant outcome and improve survival and quality of life. This field needs lot of researches. The ultimate goal of management of preterm labour should not merely be prolonging pregnancy but to improve neonatal outcome and to reduce morbidity and mortality.

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Do the difficult things while they are easy and do the great things while they are small. A journey of a thousand miles must begin with a single step.

- Lao Tzu

Cervical Cerclage for preventing Preterm Labour: An overview

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INTRODUCTION

One predominant factor of preterm delivery is cervical insufficiency, characterized by acute, painless cervical dilatation in the absence of uterine activity. The use of cervical cerclage in the prevention of preterm delivery was described by Shirodkar in 1955 and then by McDonald two years later. It is not clear why dilatation and effacement of the cervix occurs prematurely, but it is thought that the forced mechanical closure of an 'incompetent' cervix with a suture maintains the cervical length as well as the mucus plug – both of which have a role in preventing labour.

Cervical cerclage may be performed prophylactically in the first trimester when the clinical history suggests risk of mid-trimester loss or when cervical resistance studies confirm low cervical resistance. It may also be performed when there is evidence of a short cervix (<25 mm) or cervical shortening on ultrasound. More rarely, a rescue cervical suture may be inserted when the patient presents with a cervix that is already dilated with the membranes bulging into the vagina but no signs of labour, infection or heavy vaginal bleeding.

Placement of vaginal cerclage is the most commonly performed treatment for cervical insufficiency. However, abdominal cerclage can be considered in some conditions where cervical cerclage cannot be performed vaginally or will not be effective even though it is a more morbid procedure than transvaginal cerclage.

TRANSABDOMINAL CERCLAGE

Timing and indications

Transabdominal cerclage placement can be performed prior to conception (interval) or in early pregnancy.[1] Common conditions where abdominal cerclage can be considered are

1. Women with cervical insufficiency who have failed two or more previous transvaginal cerclages
2. When a transvaginal cerclage is technically impossible to perform due to extreme shortening, scarring, or laceration of the cervix

However, there are no studies comparing the outcome of transabdominal and transvaginal cerclage in similar populations of patients.

The preconception placement ensures optimum exposure and there is less risk of excessive bleeding and injury to the pregnancy. Placement after the first trimester is a problem due to large size of the uterus which makes the procedure difficult. Different studies reported that live birth rates were similar whether abdominal cerclage was performed before or during pregnancy [2]

Techniques of placement

Techniques include open transabdominal, laparoscopic and robotic approach. The rates of third trimester delivery and live birth after abdominal cerclage via laparoscopy were high and comparable to those via laparotomy.[3] Robotic assisted abdominal cerclage has now been performed successfully in nonpregnant and pregnant women [4,5]

Complications

Delivery needs to be planned and It is suggested to have elective cesarean delivery at 37 to 39 weeks of gestation. The mersilene band can be removed at cesarean delivery, or left in place if future pregnancies are planned. Infection and erosion of the cerclage into the vagina and complications from prolonged retention of vaginally placed cerclages, years after placement can occur in case of failure to remove it.[6-8] Considering the complications, an abdominal cerclage probably should be removed when child bearing is complete, even though this entails an additional surgical procedure.

In the event of a fetal loss in the first trimester, cervical dilation and evacuation of the uterus can be safely performed without removal of the transabdominal cerclage and for a second trimester pregnancy loss, dilation and evacuation (D&E) can be accomplished successfully in some cases with the cerclage in situ.[9] For a successful outcome, the technical skills and experience of the operator are important.

Therefore, considering the pros and cons transabdominal cerclage has been advocated for women who failed transvaginal procedures in previous pregnancies.

TRANSCERVICAL EMERGENCY CERCLAGE

Timings and Indications

Emergency (salvage/rescue) cervical cerclage refers to placement of a cerclage in the setting of significant cervical dilatation and/or effacement prior to 28 weeks' gestation and in the absence of labor.

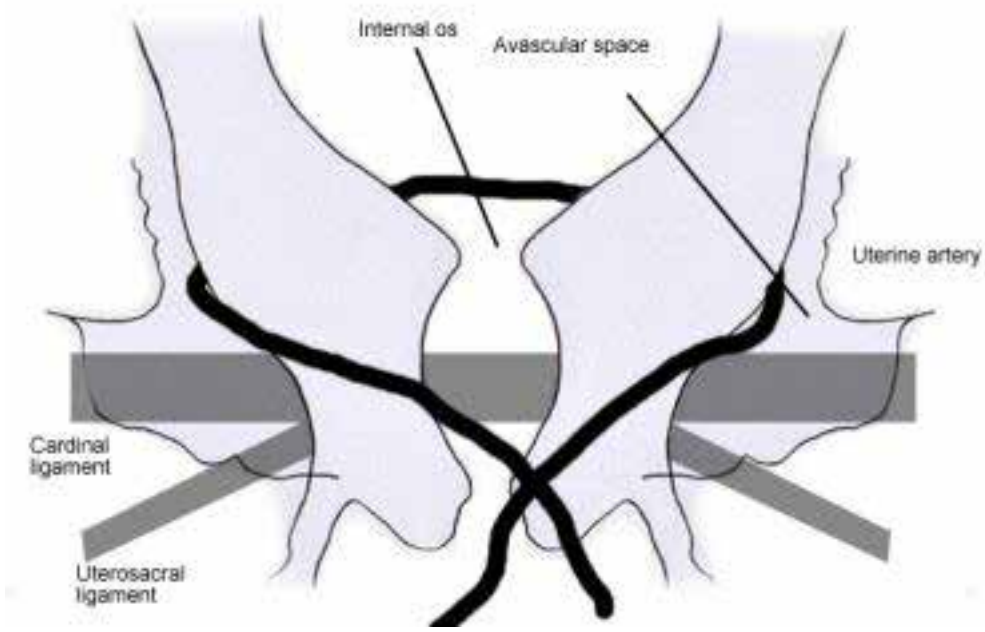

Figure 1: Position of abdominal cerclage

Women with sonographic evidence of cervical shortening and/or funneling may benefit from emergency cervical cerclage, although the data in this regard is controversial with few studies suggesting improvement in perinatal outcome.[10,11] However, there are some contradictory studies which suggest that cerclage does not prevent preterm delivery in women at high-risk for preterm birth on the basis of cervical shortening.[12,13] Moreover a higher rate of preterm PROM was observed in women who received a cerclage as compared with those without cerclage.[13] Further studies are awaited to clarify this issue.

Contraindications

There are some absolute contraindications to emergency cerclage like chorioamnionitis, ruptured membranes and bleeding. What may be considered relative contraindications are factors such as placenta previa, mucopurulent cervical discharge with membrane opacification, fetal membranes prolapsing through the os, and/or intrauterine fetal growth restriction (IUGR).

Many would not recommend emergent cervical cerclage placement beyond the limit of fetal viability (i.e. 24 weeks' gestation), because the potential for harm outweighs the potential benefit. However, ACOG supports cervical cerclage placement up to 28 weeks' gestation.

Complications

Bulging membranes into the cervix, avoiding inadequate placement of the cerclage in a superficial portion of the cervix, and the risk of iatrogenic rupture of the membranes during the operative procedure make emergency cerclage difficult for surgeons and poses challenges such as uterine contraction, laceration of the cervix, or even hysterorrhexis after cerclage.

In cases of prolapsing membranes into os, trendelenburg position, filling the bladder, placement of a 30-mL Foley catheter or moistened sponge forceps into the cervical os and/or therapeutic amniocentesis has been used in the past to reduce the fetal membranes prior to cerclage placement, with variable success.

Preoperative amniocentesis in asymptomatic parturient with cervical incompetence should not be regarded as an absolute prerequisite for emergency cerclage placement even though Romero et al showed that microbial invasion of the amniotic fluid can be expected in more than 50% of patients with cervical dilatation >2 cm between 14 and 24 weeks' gestation.[14]

EVIDENCE REVIEW

Both transvaginal and transabdominal cervical cerclage offers select patients with cervical insufficiency improved rates of neonatal survival. The transvaginal placement of a cervical cerclage has less morbidity than the transabdominal approach with a comparable neonatal survival rate.[15] Liddiard et al found that there was little difference in the gestation at delivery between the elective and emergency cerclage groups and no statistical difference between live-birth rate, mean birth weight, Apgars at 1 minute and neonatal unit admission.[16]

Evidence from retrospective and nonrandomized prospective trials shows that rescue cervical cerclage may prolong pregnancy by an average of 4-5 weeks, with a 2-fold reduction in the chance of preterm birth before 34 weeks. A higher chance of failure is expected if cervical dilatation exceeds 4 cm or if membranes are bulging into the vagina.[17]

CONCLUSION

It is difficult to predict those who may require emergency cervical cerclage although multiple pregnancies are at risk. Emergency cerclage has a very high complication rate and is associated with a high loss rate but a large randomized controlled trial (RCT) is required to determine whether this intervention actually prolongs pregnancy.

There is one school of thought which feels that such an RCT would be unethical as it would deprive patients of standard therapy, others argue that it is wrong for us to continue to think that emergency cerclage has ever been proven to be beneficial in a rigorous, scientific fashion. In the absence of sufficient evidence demonstrating a benefit, emergency cervical cerclage should be used judiciously and only after extensive and comprehensive patient counseling. Till then the decision for an emergency cerclage should be individualized after comprehensive counseling by a senior obstetrician.

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1. **Effectiveness of the contemporary treatment of preterm labor: a comparison with a historical cohort.**

   Wagner P, Sonek J, Abele H, Sarah L, Hoopmann M, Brucker S, Wu Q, Kagan KO.

   Arch Gynecol Obstet. 2017. doi: 10.1007/s00404-017-4389-6. [Epub ahead of print]

OBJECTIVE: To compare the effectiveness of contemporary treatment of preterm labor to a historical cohort.

STUDY DESIGN: Retrospective matched case-control study to compare the outcomes of patients that were treated for preterm labor at the University Hospital of Tuebingen, Germany in 2014/2015 (current treatment cohort) and 2006/2007 (historical cohort). The study included women with singleton gestations who were admitted with the diagnosis of preterm labor between 24 + 0 and 34 + 0 weeks' gestation and a cervical length of ≤15 mm. Women in the historical cohort were hospitalized until either 34 weeks' gestation or until complete cessation of uterine contractions. They were treated with intravenous beta-mimetics continuously, received antibiotics based on the vaginal culture and corticosteroids regardless of cervical length measurement. Bed rest was always recommended. The current treatment cohort was tocolyzed with an oral calcium channel blocker for approximately 3 days followed by vaginal progesterone until 34 weeks' gestation. Corticosteroids were given only if the cervical length is ≤15 mm. Bed rest was not recommended.

RESULTS: The study population consisted of 110 pregnancies, 55 in the historical cohort and 55 in the current treatment cohort. At the time of admission, mean gestational age in both groups was 29.3 and 29.7 weeks. In the historical and current treatment cohort the length of the hospitalization was 24.0 and 5.5 days and tocolysis was given for 19.5 and 3.4 days, respectively. In the historical cohort, mean gestational age at delivery was 35.6 weeks. In 63.6% cases delivery occurred prior to 37 weeks. In the current treatment group mean gestational age at the delivery was 37.0 weeks and 36.4% were delivered prior to 37 weeks.

CONCLUSION: Short-term hospitalization and tocolysis followed by vaginal progesterone for maintenance tocolysis is more effective than a protocol which includes long-term hospital stay, beta-mimetics, antibiotics, and bed rest.

2. **The effects of nifedipine and atosiban on perinatal brain injury: a secondary analysis of the APOSTEL III trial.**

   Nijman TAJ, Goedhart MM, Naaktgeboren CN, de Haan TR, Vijlbrief DC, Mol BW, Benders MJN, Franx A, Oudijk MA.

   Ultrasound Obstet Gynecol. **2017**. *doi: 10.1002/uog.17512. [Epub ahead of print]*

OBJECTIVE: Brain injury in prematurely born neonates is strongly associated with poor neurodevelopmental outcome. The aim of our study is to evaluate if nifedipine reduces overall brain injury compared to atosiban in women with threatened preterm birth.

METHODS: We performed a secondary analysis of the APOSTEL III-trial (Dutch Clinical Trial Registry, number NTR2947). This was a randomized clinical trial that allocated women with threatened preterm labor between 25-34 weeks of gestation to nifedipine or atosiban. For this secondary analysis, we included women delivering at ≤ 32 weeks of gestational age in the two main contributing centers. The primary outcome was the presence of brain injury. Brain injury was defined as the existence of abnormalities on ultrasound investigation, it was divided into mild and severe brain injury. To evaluate type and severity of brain injury, all neonatal ultrasounds made during neonatal intensive care admission and medium care admission were analyzed. A sensitivity analysis assessing differences in baseline or known risk factors for brain injury, was performed to test the robustness of our results.

RESULTS: We studied 117 neonates, born from 102 women, of which 51 neonates had been exposed to nifedipine and 66 to atosiban. Brain injury was observed in 22 neonates (43.1%) in the nifedipine group and in 37 (56.1%) neonates in the atosiban (OR 0.60; 95% CI: 0.29-1.24). Mild brain injury was comparable between nifedipine (33.3%) and atosiban (48.5%, OR 0.53; 95% CI 0.25-1.13). Severe brain injury was also comparable between the groups, 9.8% for nifedipine and 7.6% for atosiban (OR 1.33; 95% CI 0.36-4.85). Intraventricular hemorrhage (≥ grade I) was most frequently seen; 18 neonates (35.3%) in the nifedipine group versus 25 neonates (37.9%) in the atosiban group (OR 0.90; 95% CI 0.42-1.91). The sensitivity analysis, with adjustment for maternal age and gestational age at randomization, showed no statistical difference of brain injury (OR 0.58; 95% CI 0.27-1.27).

CONCLUSION: In children born before 32 weeks after the use of tocolytics, the prevalence of brain injury was high. No significant differences were found between nifedipine and atosiban in terms of overall brain injury. However, as this study was a secondary analysis of the APOSTEL III trial, it was underpowered for brain injury, as the latter was not the primary outcome of APOSTEL III.

3. **The placental factor in spontaneous preterm birth in twin vs. singleton pregnancies.**

   Weiner E, Dekalo A, Feldstein O, Barber E, Schreiber L, Bar J, Kovo M.

   Eur J Obstet Gynecol Reprod Biol. 2017;214:1-5. doi: 10.1016/j.ejogrb.2017.04.035. [Epub ahead of print]

OBJECTIVE: The association between infection and inflammatory response in singleton preterm birth (PTB) is well established, yet, less is known about PTB in twins. We aimed to compare the placental component and pregnancy outcome in pregnancies complicated with PTB of singletons vs. twin deliveries. We hypothesized that due to different underlying mechanisms, placental inflammatory lesions will be more prevalent in placentas derived from singleton pregnancies than twins.

STUDY DESIGN: Labor characteristics, neonatal outcome and placental histopathology reports of spontaneous PTB at 24-33$^{6}/_{7}$ weeks, from 1/2008-12/2015, were reviewed. The observations were compared between dichorionic-diamniotic twin deliveries (twins group) and singleton deliveries (singleton group) matched for gestational age. Excluded from the study medically indicated deliveries, due to preeclampsia or fetal growth restriction, and monochorionic twins. Placental lesions were classified to maternal vascular supply lesions, fetal vascular supply lesions, and maternal (MIR) and fetal (FIR) inflammatory

responses. Composite neonatal outcome was defined as one or more of early complications: respiratory distress, necrotizing enterocolitis, sepsis, blood transfusion, ventilation, seizures, intra-ventricular hemorrhage, hypoglycemia, phototherapy, or death.

RESULTS: The twins group (n=72) was characterized by higher maternal BMI (p=0.009), and higher rates of assisted reproductive techniques (56.2% vs. 17.8%, p<0.001) and cesarean deliveries (75.3% vs. 32.8%, p<0.001) as compared to the singleton group (n=72). Placentas from the singleton group were characterized by higher rate of MIR, 58.9% vs. 19.2%, (p<0.001), FIR, 31.5% vs. 3.4%, (p<0.001), retro-placental hemorrhage, 26% vs. 8.9% (p<0.001), and vascular lesions related to maternal malperfusion, 28.8% vs. 9.6%, (p<0.001), as compared to placentas from the twins group. Higher rate of neonatal sepsis was observed in the singleton group as compared to the twins group, 24.7% vs. 4.1%, p<0.001, respectively. By logistic regression analyses retro-placental hemorrhage, placental maternal vascular malperfusion lesions, MIR, FIR and neonatal sepsis were found to be independently associated with singleton PTB: aOR 3.4, 95% CI 2.1-6.9, p<0.001, aOR=3.1, 95% CI 1.8-7.2, p<0.001, aOR=2.9, 95% CI 1.4-7.8, p<0.001, aOR=4.9, 95% CI 2.3-6.9, p<0.001, and aOR=4.8, 95% CI 2.3-6.7, p<0.001 respectively.

CONCLUSION: Placentas from singleton PTBs are characterized by higher rate of inflammatory and malperfusion lesions. The lack of these findings in twins PTBs suggests different factors that participate in the development of preterm birth in twins, such as over-distension of the uterus and up regulation of oxytocin receptors.

4. **Analysis of transcriptional activities of angiogenic biomarkers during intrauterine complications leading to preterm birth.**

   Rabajdová M, Dudič R, Urban P, Dudičová V, Urdzík P, Mareková M.

   Eur Rev Med Pharmacol Sci. 2017;21(7):1433-1442.

OBJECTIVE: Pre-eclampsia, growth retardation and preterm delivery are the most common reasons leading to increased maternal and perinatal mortality. The increased expression of hypoxia induced factors, such as HIF-1, triggers the overexpression of anti-angiogenic genes. The aim of this study was to determine the transcriptional activity of individual pro- and anti-angiogenic markers (VEGF, HIF-1, sEng, Flt-1, PlGF-1) in maternal blood samples from patients with spontaneous preterm labor, preterm labor in combination with pre-eclampsia and fetal growth restriction in comparison with physiologically terminated pregnancies.

PATIENTS AND METHODS: The transcriptional activity of specific genes was detected from the blood of patients using the chromatin immunoprecipitation capture method coupled with quantitative real-time PCR.

RESULTS: The maximum differences in mRNA levels of PlGF-1 and VEGF-A were detected in two groups: the group of normal-term birth with complications and the group of preterm labor with complications (both significantly lower than the control, $p < 0.001$). In contrast, a marked increase of mRNA levels was found in the same groups of patients for the HIF-1, endoglin and Flt-1 genes ($p < 0.001$).

CONCLUSIONS: According to our results, we can conclude that increased oxidative stress, increasing the expression levels of anti-angiogenic genes and reduction of the transcriptional activity of pro-angiogenic genes can provide additional information during diagnostics of pathological complications of labor.

5. **Prediction of spontaneous preterm delivery in asymptomatic twin pregnancies using cervical length and granulocyte elastase.**

   Tanaka K, Yamada K, Matsushima M, Izawa T, Furukawa S, Kobayashi Y, Iwashita M.

   Taiwan J Obstet Gynecol. 2017 Apr;56(2):188-191. doi: 10.1016/j.tjog.2016.07.014.

OBJECTIVE: The purpose of this study was to evaluate sonographic cervical length (CL) and granulocyte elastase (GE) in cervical secretion as predictors of preterm delivery in asymptomatic twin pregnancies.

MATERIALS AND METHODS: This study prospectively enrolled asymptomatic twin pregnancies with CL < 25 mm at 22-29 weeks of gestation. All women were hospitalized for preterm labor, and the cervical secretion was obtained for GE testing on admission. The results of CL measurement and GE testing were reviewed, and the relationship between each variables and preterm delivery prior to 34 weeks of gestation was assessed.

RESULTS: Overall, we included 54 women with twin pregnancies, of which 12 (22.2%) had preterm deliveries prior to 34 weeks of gestation. A CL of <20 mm was significantly associated with preterm delivery with an odds ratio of 4.88 (95% confidence limit, 1.15-20.73). GE was not an independent predictive marker for preterm delivery. We also performed a subgroup analysis on the combination of CL and GE for predicting preterm delivery. Among the patients with GE(-), CL < 20 mm markedly increased the risk of preterm delivery with an odds ratio of 10.89 (95% confidence limit, 1.40-77.10). CL was not associated with preterm delivery among those with GE(+). Those with negative GE and shorter CL demonstrated the shortest duration of pregnancy after admission.

CONCLUSION: The combination of sonographic CL and GE of cervical secretion is useful to predict the risk of preterm delivery in asymptomatic twin pregnancies.

6. **Cesarean delivery in the second stage of labor and the risk of subsequent premature birth.**

   Wood SL, Tang S, Crawford S.

   Am J Obstet Gynecol. 2017 Apr 4. pii: S0002-9378(17)30417-9. doi: 10.1016/j.ajog.2017.03.006. [Epub ahead of print]

BACKGROUND: Cesarean delivery is being increasingly used by obstetricians for indicated deliveries in the second stage of labor. Unplanned extension of the uterine incision involving the cervix often occurs with these surgeries. Therefore, we hypothesized that cesarean delivery in the second stage of labor may increase the rate of subsequent spontaneous premature birth.

OBJECTIVE: We sought to determine if cesarean delivery in the late first stage of labor or in the second stage of labor increases the risk of a subsequent spontaneous preterm birth.

STUDY DESIGN: We conducted a retrospective cohort study of matched first and second births from a large Canadian perinatal database. The primary outcomes were spontaneous premature birth <37 and <32 weeks of gestation in the second birth. The exposure was stage of labor and cervical dilation at the time of the first cesarean delivery. The protocol and analysis plan was registered prior to obtaining data at Open Science Foundation.

RESULTS: In total, 189,021 paired first and second births were identified. The risk of spontaneous preterm delivery <37 and <32 weeks of gestation in the second birth was increased when the first birth was by cesarean delivery in the second stage of labor (relative risk, 1.57; 95% confidence interval, 1.43-1.73 and relative risk, 2.12; 95% confidence interval, 1.67-2.68, respectively). The risk of perinatal death in the second birth, excluding congenital anomalies, was also correspondingly increased (relative risk, 1.44; 95% confidence interval, 1.05-1.96).

CONCLUSION: Cesarean delivery in second stage of labor was associated with a 2-fold increase in the risk of spontaneous preterm birth <32 weeks of gestation in a subsequent birth. This information may inform management of operative delivery in the second stage.

7. **Association between CACNA1C gene polymorphisms and ritodrine-induced adverse events in preterm labor patients.**

   Baek MY, Hwang HS, Park JY, Chung JE, Lee KE, Lee GY, Seong JW, Yee J, Kim YJ, Gwak HS.

   Eur J Clin Pharmacol. 2017 Apr 8. doi: 10.1007/s00228-017-2222-6. [Epub ahead of print]

OBJECTIVE: As a tocolytic agent, ritodrine has been used in European and Asian countries but has lost popularity due

to safety concerns. This study aimed to investigate the relationship between adverse drug events caused by ritodrine and the CACNA1C polymorphisms in preterm labor patients.

METHODS: Data were collected from medical records including maternal age, gestational age, body mass index, dilation score, effacement score, modified Bishop score, maximum infusion rate, and adverse drug events. Five single-nucleotide polymorphisms of the CACNA1C gene (rs10774053, rs215994, rs215976, rs2239128, and rs2041135) were analyzed.

RESULTS: One hundred eighty-six patients were included, 33 of whom had adverse drug events. A allele carriers of rs10774053 showed about 0.293-fold lower adverse drug events than GG genotype carriers (p = 0.012, absolute risk reduction = 16.5%) after adjusting for other confounding variables; the number needed to genotype for preventing one patient with GG genotype from suffering higher incidence of adverse drug events was calculated to be 14.6. Increase in maximum infusion rate of 1 mL/h was associated with a 1.03-fold (95% CI 1.01~1.06, p = 0.005) increased risk of adverse drug events. None of the patients with a CC genotype of rs215994 had adverse drug events, whereas 22.1% of the T allele carriers had adverse drug events.

CONCLUSION: This study showed that CACNA1C gene polymorphisms could alter the probability of adverse drug event risk when ritodrine is used in preterm labor.

8. **The QUIPP app: a safe alternative to a treat-all strategy for threatened preterm labour.**

   Watson HA, Carter J, Seed PT, Tribe RM, Shennan AH.

   Ultrasound Obstet Gynecol. 2017 Apr 24. doi: 10.1002/uog.17499. [Epub ahead of print]

OBJECTIVES: To evaluate the impact of a treat-all policy (advocated by NICE) compared to the QUIPP app (predictive model combining history of spontaneous preterm birth gestation and quantitative fetal fibronectin) for women in threatened preterm labour at <30 weeks gestation.

METHODS: We conducted a subanalysis of prospectively collected data of pregnant women presenting with symptoms of preterm labour from the EQUIPP (REC Ref. 10/H0806/68) and PETRA (REC Ref. 14/LO/1988) research database. Women between 24 and 34 weeks of gestation in suspected labour at a tertiary inner-city hospital (abdominal pain or tightenings) were identified. Each episode was retrospectively assigned a risk of birth within 7 days using the QUIPP app. A primary outcome of delivery within 7 days was used to model the accuracy of the QUIPP app compared with a treat-all policy.

RESULTS: With a risk threshold of 5% (of delivery within 7 days) to treat, 9/9 women would have been correctly treated giving a sensitivity of 100% (one-sided 97.5% CI 0.664) and a negative predictive value PV of 100% (CI 98.9 to 100%). The positive predictive value was 30% (95% CI 4.3 to 49.1%) before 30 weeks and 20% (CI 11.9 to 54.3%) between 30 and 34 weeks. If this 5% threshold had been used to triage women between 24 and 29+6 weeks, 89% of admissions (168) could have been safely avoided compared to 0% with a treat-all strategy. No true cases would have been missed as none of the women who were given a risk less than 10% delivered within 7 days.

CONCLUSION: For women in threatened preterm labour, the QUIPP app can accurately guide management at risk thresholds of 1%, 5% and 10%, allowing outpatient management for the vast majority. A treat-all approach, would have protected none, exposed 188 mothers and babies to unnecessary hospitalisation and steroids, and increased the burden on networks and transport services due to unnecessary in-utero transfers. Prediction should be used before 30 weeks to determine management until there is evidence that such high levels of unnecessary intervention do less harm than the rare false negatives.

9. **Home uterine monitoring for detecting preterm labour.**

   Urquhart C, Currell R, Harlow F, Callow L.

   Cochrane Database Syst Rev. 2017 Feb 15;2:CD006172. doi: 10.1002/14651858. CD006172.pub4.

BACKGROUND: To reduce the morbidity and mortality associated with preterm birth, home uterine activity monitoring aims for early detection of increased contraction frequency, and early intervention with tocolytic drugs to inhibit labour and prolong pregnancy. However, the effectiveness of such monitoring is disputed.

OBJECTIVES: To determine whether home uterine activity monitoring is effective in improving the outcomes for women and their infants considered to be at high risk of preterm birth, when compared with care that does not include home uterine activity monitoring.

SEARCH METHODS: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2016), CENTRAL (Cochrane Library 2016, Issue 5), MEDLINE (1966 to 28 June 2016), Embase (1974 to 28 June 2016), CINAHL (1982 to 28 June 2016), and scanned reference lists of retrieved studies.

SELECTION CRITERIA: Randomised control trials of home uterine activity monitoring, with or without patient education programmes, for women at risk of preterm birth, compared with care that does not include home uterine activity monitoring.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion and risks of bias, extracted data and checked them for accuracy. We did not attempt to contact authors to resolve queries. We assessed the evidence using the GRADE approach.

RESULTS: There were 15 included studies (6008 enrolled participants); 13 studies contributed data. Women using home uterine monitoring were less likely to experience preterm birth at less than 34 weeks (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.62 to 0.99; three studies, 1596 women; fixed-effect analysis) (GRADE high). This difference was not evident when we carried out a sensitivity analysis, restricting the analysis to studies at low risk of bias based on study quality (RR 0.75, 95% CI 0.57 to 1.00; one study, 1292 women). There was no difference in the rate of perinatal mortality (RR 1.22, 95% CI 0.86 to 1.72; two studies, 2589 babies) (GRADE low).There was no difference in the number of preterm births at less than 37 weeks (average RR 0.85, CI 0.72 to 1.01; eight studies, 4834 women; random-effects, Tau2 = 0.03, I2 = 68%) (GRADE very low). Infants born to women using home uterine monitoring were less likely to be admitted to neonatal intensive care unit (average RR 0.77, 95% CI 0.62 to 0.96; five studies, 2367 babies; random-effects, Tau2 = 0.02, I2 = 32%) (GRADE moderate). This difference was not maintained when we restricted the analysis to studies at low risk of bias (RR 0.86, 95% CI 0.74 to 1.01; one study, 1292 babies). Women using home uterine monitoring made more unscheduled antenatal visits (mean difference (MD) 0.48, 95% CI 0.31 to 0.64; two studies, 1994 women) (GRADE moderate). Women using home uterine monitoring were also more likely to have prophylactic tocolytic drug therapy (average RR 1.21, 95% CI 1.01 to 1.45; seven studies, 4316 women; random-effects, Tau2 = 0.03, I2= 62%), but this difference was no longer evident when we restricted the analysis to studies at low risk of bias (average RR 1.22, 95% CI 0.90 to 1.65; three studies, 3749 women; random-effects, Tau2 = 0.05, I2 = 76%) (GRADE low). The number of antenatal hospital admissions did not differ between home groups (RR 0.91, 95% CI 0.74 to 1.11; three studies, 1494 women (GRADE low)). We found no data on maternal anxiety or acceptability.

CONCLUSIONS: Home uterine monitoring may result in fewer admissions to a neonatal intensive care unit but in more unscheduled antenatal visits and tocolytic treatment; the level of evidence is generally low to moderate. Important group differences were not evident when we undertook sensitivity analysis using only trials at low risk of bias. There is no impact on maternal and perinatal outcomes such as perinatal mortality or incidence of preterm birth.

Brain Teasers

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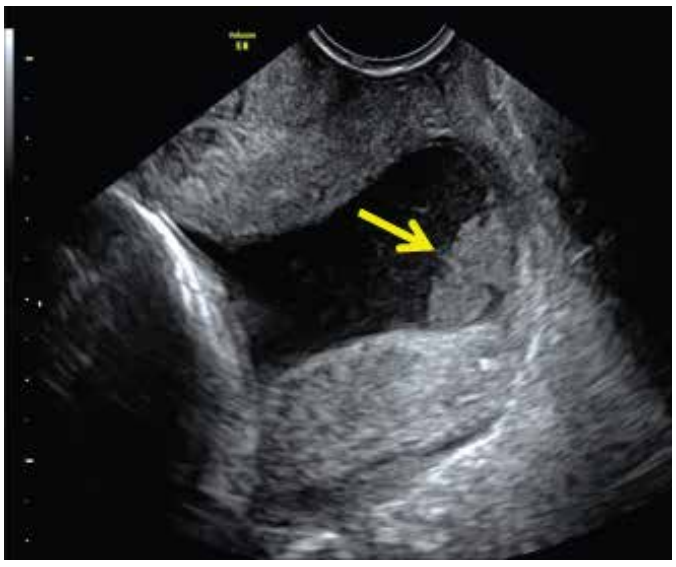
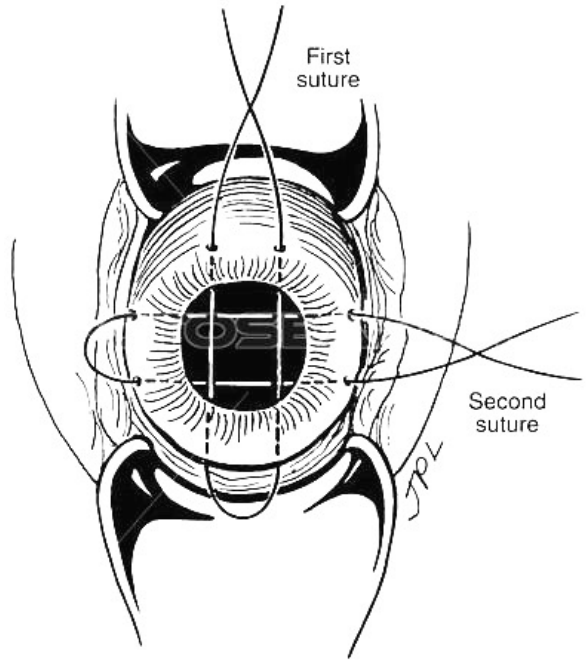
Chairperson Quiz committee FOGSI (2015-2017)

Q. 1. In this transvaginal USG , what does the arrow indicates?



Q. 2. Name the type of circlage operation?



Q. 3. An immunochromatic test detecting Placental Alpha-Microglobulin- 1 (PAMG-1) is used in diagnosis of

a. Preterm labor
b. Preterm premature rupture of membrane
c. Eclampsia
d. Placenta previa

Q. 4. Which of the following is not used as predictor of preterm labor

a. Fetal fibronectin
b. TVS measurement of cervical length
c. FMS- like tyrosine kinase receptor-1
d. Increase phosphorylated IGF-1

Q. 5. In setting of Pretem Premature rupture of membranes (PPROM), if given, Co- Amoxiclav is associated with increased risk of …….

ANSWERS TO BRAIN TEASERS – MAY ISSUE

1. Strawberry cervix seen in trichomonas Vaginalis
2. Leukoplakia or hyperkeratosis
3. Cryotherapy is not the method of choice for HSIL
4. CIN I preceded by HSIL & AGC cytology
5. 1- 1.5%