NARCHI BULLETIN

SJH, Issue 4, May 2019

REACHING THE UNREACHED

NARCHI

Delhi Branch

Baby Born "Too Small, Too Soon": How to manage?

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Room No. 001, Department of Obstetrics & Gynaecology,
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Department of Obstetrics & Gynaecology,
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& Safdarjung Hospital, New Delhi-110029
Email: narchidelhisjh@gmail.com

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President's Message

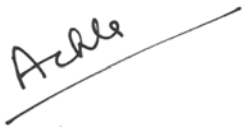
Greetings to my NARCHI family,

I welcome you all as we welcome summers and beat the heat with coolers and wish all of you to stay healthy and hydrated. First of all my heartful thanks to all the members for appreciating the annual conference of NARCHI Delhi Branch held at Hotel Eros, Nehru Place. I appreciate your efforts in taking time out of your hectic schedule to join us.

I am happy that the work of NARCHI is being recognized and appreciated by all the members which further inspire us to work harder.

We are all set to host the World Conference of NARCHI 2020 for which we require your blessings and cooperation to make it a grand success.

We look forward to see you all on 6th June, at our upcoming CME on "Baby born too small; too soon" at Safdarjung Hospital.



Dr Achla Batra

"We ourselves feel that what we are doing is just a drop in the ocean.
But the ocean would be less because of that missing drop."
– Mother Teresa

Vice President's Message

Dear Friends,

While you are enjoying mangoes in summer heat, we bring to you this issue on the challenging problems: Preterm labor and fetal growth restriction. We talk about the management of mothers with conditions that lead to delivery of babies while they still may be too small.

Let's come to some conclusions in this issue!

Happy holidays!

Dr Saritha Shamsunder

"Faith is taking the first step even when you don't see the whole staircase."
– Martin Luther King, Jr.

Secretary's Message

Greetings from NARCHI Delhi Branch !

We meet you again through this bulletin after the 25th Annual NARCHI Delhi Conference Souvenir issue. I thank you all from the bottom of my heart for making the silver jubilee NARCHI Delhi conference a huge thumping success. It gives me immense pleasure to introduce this fourth quarterly issue of NARCHI Delhi bulletin dedicated to ***"Baby born too small, too soon: How To manage?"***. Once again I congratulate our dedicated editorial team for bringing out this issue on such a vital topic which is cause of concern to both practitioners and academicians.

India contributes to 12.8 million of the 32.4 million global burden of SGA infants of which nearly 12.5 million infants are born preterm. SGA is an important global problem with consequences for child survival and development, and an even more critical problem for countries in South Asia, especially India. A generational change is needed to address this issue of 'low-birthweight- born too small and preterm- born too soon'. The risk factors for adverse outcomes, and the interventions that are effective in preventing adverse outcomes of both these conditions has been beautifully addressed in this issue in an evidence based approach.

In continuum with our motto of 'Reaching the Unreached' we have been organizing health camps, public forums and CMEs on important aspects of mother and child health. In addition to this, the first of its kind endeavor which we introduced in our tenure is the involvement of nursing personnel in the Annual Conference. There was a separate dedicated Nursing CME for the nursing students involving faculty from nursing colleges as well as gynecologists and pediatricians. It got a special mention and appreciation from Dr Dinesh Baswal, Deputy Commissioner, Maternal Health, Ministry of Health & Family Welfare, Government of India.

We intend to continue our efforts which will help provide a framework for working toward improved health outcomes for mothers and children and their families. You all must be aware by now, that we are eyeing at bringing forth another wonderful conference for all of you "**NARCHI World Conference 2020**" under the able leadership of our beloved president, Dr Achla Batra. I humbly seek suggestions, cooperation and involvement of all the NARCHI members from all across Delhi and NCR to make this endevour successful. Also, the ICMCH (Indian College of Maternal and Child Health) convocation will be held during the world congress. So, the interested practitioners and institute faculties who wish to apply for fellowship of can do so and contact the NARCHI Delhi secretariat for the needful.

I wish happy reading to all NARCHI members.

Dr Monika Gupta

Editor's Message

Greetings from the editorial board!

It seems like long time no see, but here we are back after 3 months with our next issue.

The first session of the Annual NARCHI conference held in February was on a very crucial topic, preterm labour and foetal growth restriction. The topic was highly appreciated by the delegates, however, due to it being on a working day morning many who wanted to attend could not make it. So we decided to dedicate this issue to the same topic **"Baby born too small, too soon: How to manage?"**

There has been a lot of research going on in the management of preterm labour and pregnancy with foetal growth restriction. The concern regarding long term neurodevelopmental effects of antenatal corticosteroids have challenged its use in the late preterm fetuses. And, even with the availability of different groups of drug for tocolysis, beta sympathomimetics are gaining popularity again.

We have made an effort to equip our readers with the latest evidence based recommendations. This issue covers preterm birth from the prediction & prevention to management that includes recent developments in tocolytic and antenatal corticosteroid therapy. It also touches briefly the management of foetal growth restriction along with basics and interpretation of Doppler study of uterine and foetal vessels.

Please do give your feedback and watch out for the quiz. Send your responses to **narchidelhisjh@gmail.com.**

Hope you enjoy reading it as much as we enjoyed assembling it for you.

Dr Jyotsna Suri
jyotsnasuri@gmail.com

Dr Rekha Bharti
rekhabharti@gmail.com

First Row: Dr Jyotsna Suri & Dr Rekha Bharti (The Editors)
Second Row: Dr Monu Singh (Assistant Editor), **Dr Sarita Singh** (Co-Editor), **Dr Megha Mittal** (Assistant Editor)

Preterm Birth: Prediction and prevention

Nidhi Thakur[1], Renu Arora[2]
[1]Research Officer, [2]Consultant & Professor, Obstetrics & Gynaecology
Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi

Preterm birth refers to a delivery that occurs before 37 weeks of gestation. In India, the preterm birth rate is 13.6% which is 18.5% of global live births. Major morbidities associated with preterm birth include respiratory distress syndrome, necrotizing enterocolitis, retinopathy of prematurity and intraventicular haemorrhage. Long term problems include cerebral palsy, neurodevelopmental delay, deafness, visual impairment and chronic lung disease. The prevalence of long term disability is associated with gestational age and ranges from 14 to 23%. Identification of risk factors for PTB before conception or early in pregnancy will lead to interventions that help prevent these.

Risk Assessment

History of spontaneous preterm birth- A history of PTB is the major risk factor for preterm birth, and recurrences often occur at the same gestational age. The Preterm Prediction study observed that recurrence rate of PTB at <35 weeks was 15.2% compared to 3.3% in nulliparous. This risk is increased with a history of more than one PTB. It ranges from 32% with previous 2 preterm deliveries to 21% for previous 1 term/1 preterm delivery.

Cervical surgery- Cold knife conization and loop electrosurgical excision procedures for treatment of cervical intraepithelial neoplasia have been associated with increased risks for late miscarriage and PTB.

Uterine malformation- In women with congenital uterine malformations, the risk for PTB depends upon the specific abnormality. Unification malformations like septate uterus and bicornuate uterus have highest risk of miscarriage and PTB. Women with fibroids may also be at slightly increased risk for pregnancy loss and PTB. A large fibroid (≥5 to 6 cm), multiple fibroids and submucosal fibroid appear to be the most important risk factors for PTB.

Artificial reproductive techniques- Pregnancies conceived by assisted reproduction are at higher risk for PTB, even in the absence of multifetal gestation. The increased risk may be due to baseline maternal factors related to subfertility and/or factors related to assisted reproduction procedures.

Multifetal gestation- It accounts for only 2 to 3% of all births but 17% of births before 37 weeks and 23% before 32 weeks of gestation, making it one of the very important risk factors for PTB.

Early pregnancy bleeding- It is often due to decidual haemorrhage which results in release of tissue factor that can trigger local thrombin formation. Decidual thrombin production has been associated with subsequent induced PTB due to preeclampsia, abruption as well as foetal growth restriction.

Short cervix- There is an inverse relationship between cervical length measured by transvaginal ultrasound at 16 to 24 weeks and gestational age of delivery. Short cervical length is commonly defined as length less than 25 mm. Several studies have shown that the risk of preterm delivery is greater in high risk women with CL<25 mm and the risk increases exponentially with decreasing CL. The incidence of PTB <34 weeks is 19 to 76% in women with CL <25 mm as compared to 7 to 23% with CL >25 mm.

Infection- Preterm deliveries resulting from preterm uterine contractions or PPROM are likely to be a result of inflammatory/infectious process. Approximately 85% pregnancies which result in early preterm labour (<28weeks) have histological evidence of inflammation and chorioamnionitis.

Asymptomatic bacteriuria- It complicates 2-10% of all the pregnancies. In a 1998 review, Villar et al found that antibiotic treatment of asymptomatic bacteriuria reduced the incidence of PTB and LBW. However this finding was not replicated by 2007 meta-analysis. It showed that the treatment of asymptomatic bacteriuria clearly and substantially decreases the incidence of pyelonephritis and low birth weight but significance with PTB was not established.

Genetic factors- Genetic polymorphisms appear to contribute to a woman's likelihood of PTB. PTBs are more prevalent in some pedigrees and racial groups. In women who were born preterm themselves and in women with a first-degree female relative who had a PTB are more likely to have PTB.

Social, Demographic and Behavioural risk factors-

There is an established association between PTB and extremes of age (<16 years and >35 years). Physiologic immaturity and socioeconomic factors may increase risk for adolescent mothers; a higher prevalence of preexisting chronic diseases and obesity may increase risk for older mothers. Women with short stature appear to be at increased risk for preterm birth while taller women appear to be at a decreased risk.

Modifiable risk factors- A short interpregnancy interval (<6 months), low prepregnancy BMI, poor weight gain in pregnancy, maternal smoking and drug abuse are all associated with PTB.

Chronic medical disorders- Chronic maternal medical disorders can be associated with maternal or foetal complications necessitating medically induced PTB as well as an increased risk for spontaneous PTB. Examples include women with hypertension, renal insufficiency, type 1 diabetes mellitus, and some autoimmune diseases.

Occupational physical activity- A meta-analysis reported that PTB is associated with standing and walking at work for more than 3 hours per day, lifting and carrying >5 kg weight, lifting and carrying specially in the third trimester, and having a job that required physical effort or physical exertion. A large European case-control study noted employed women are at higher risk of PTB if they worked longer than 42 hours/week, stood more than six hours/day, or had low job satisfaction.

Predicting the Risk Factors of Preterm Labour

At the first antenatal visit, a PTB risk assessment may be performed in order to triage women into 'high risk' so that they can be managed accordingly.

Identify asymptomatic women at risk- At first visit assessment of clinical risk factors is done by obtaining a detailed medical history, reviewing aspects of all previous pregnancies, and determining their candidacy for prophylactic interventions, such as progesterone supplementation, cervical cerclage, or both.

Biomarkers- Cervicovaginal fetal fibronectin (FFN) can be a useful biomarker for predicting PTB within 7 to 14 days in women with contractions and mild cervical dilation (symptomatic women). The Preterm Prediction study evaluated FFN at 24 to 28 weeks and demonstrated its Negative Predictive Value (NPV) of >96%. However, PPV is <30%. Several studies have evaluated the predictive ability of combined cervical screening and FFN testing. In symptomatic women, with cervical length <15 mm & a positive fibronection test (>50 ng/ml), the sensitivity for predicting of PTB have been shown to be >70% while maintaining NPV >98%.

A test (PreTRM Test) for two serum proteins, insulin-like growth factor-binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG), became available for clinical use to predict preterm birth in 2017. In a study to predict spontaneous preterm delivery in asymptomatic pregnant women, the test had sensitivity and specificity of 75% and 74%, respectively.

A 2011 systematic review of other 30 available biomarkers concluded that none of the other biomarkers were clinically useful for predicting PTB in asymptomatic women.

Cervical screening- **Measurement of cervical length between 16 and 24 weeks gestation has been shown to be a sensitive predictor of PTB in both low and high risk women.** Transvaginal cervical ultrasonography has been shown to be a reliable way to assess the length of the cervix. Unlike the transabdominal approach, transvaginal cervical ultrasonography is not affected by maternal obesity, position of the cervix, and shadowing from the foetal presenting part.

Prevention of Preterm Labour

Cervical cerclage (Surgical cerclage): Indications for Cervical Cerclage in women with singleton pregnancies are based on either obstetrics history or ultrasound finding of short cervix.

With three or more previous PTB and/or 2nd trimester losses, cerclage typically are placed at around 12–14 weeks of gestation, obstetric history based or history indicated cerclage. Other indication of surgical cerclage is ultrasound indicated i.e. patients with previous history of spontaneous preterm birth and short cervical length (<25 mm) in present pregnancy. Most of such patients can be safely monitored with serial transvaginal ultrasound examinations only. Surveillance should begin at 16 weeks and is done every fortnightly till end of 24 weeks of gestation. Cerclage is recommended for women who have short cervical length (<25 mm) with or without the presence of funnelling. Cerclage is associated with significant reduction in preterm births, as well as improvements in neonatal morbidity and mortality. In contrast to this, for women in the low-risk population with incidental finding of cervical length <25 mm detected between

16 to 24 weeks of gestation, cerclage has not been associated with a significant reduction in preterm birth and is not recommended.

Procedure- Surgical approaches include transvaginal and transabdominal cervical cerclage. The standard transvaginal methods currently used include McDonald and Shirodkar techniques. In the McDonald procedure, a simple purse-string suture of nonabsorbable material is inserted at the cervicovaginal junction. The Shirodkar procedure involves the dissection of the vesicocervical mucosa in an attempt to place the suture as close to the cervical internal os as might otherwise be possible. The bladder and rectum are dissected from the cervix in a cephalad manner, the suture is placed and tied, and mucosa is replaced over the knot.

Transabdominal cerclage generally is reserved for patients in whom cerclage is indicated but cannot be placed because of anatomical limitations (eg, after a trachelectomy). Transabdominal cerclage can be accomplished through open laparotomy or laparoscopy depending on physician experience. Abdominal cerclage procedures usually are performed in the late first trimester or early second trimester (10–14 weeks of gestation) or in the nonpregnant state. The stitch can be left in place between pregnancies with subsequent caesarean delivery. In cases of previous history indicated unsuccessful cerclage by vaginal route that resulted in pregnancy loss, transabdominal encirclage can be applied. For women with prior unsuccessful ultrasound indicated cerclage, vaginal cerclage at 12 to 14 weeks of gestation in the next pregnancy is indicated.

In patients with no complications, transvaginal McDonald cerclage removal is recommended at 36–37 weeks of gestation. In cases of a planned vaginal delivery, intentional deferral of cerclage removal until the time of labour is not recommended. For patients who elect caesarean delivery at or beyond 39 weeks of gestation, cerclage removal at the time of caesarean may be performed.

Progesterone therapy (Medical cerclage): Progesterone is a hormone responsible for maintaining uterine quiescence during pregnancy and may modulate cytokine and contraction associated protein expression and activity. A systematic review and metaanalysis performed in 2012 reported that antenatal vaginal progesterone for women at high risk of PTB with CL<25 mm was associated with significant reduction in PTB rate (12% vs 22%). For women with no previous history of PTB (low risk) who develop a short cervix, progesterone supplementation can prolong gestation. A 2018 systematic review and meta-analysis of randomized trials (including OPPTIMUM) found that vaginal progesterone supplementation reduced the risk of preterm birth and neonatal morbidity and mortality in singleton gestations with midtrimester cervical length ≤25 mm even in low risk women.

Two trials in which women with a short cervical length were randomly assigned to weekly intramuscular hydroxyprogesterone caproate (250 mg or 500 mg) or placebo till 36 weeks reported that treatment with hydroxyprogesterone caproate did not reduce the risk of preterm birth. Vaginal progesterone clearly inhibits cervical ripening; the effect of hydroxyprogesterone caproate on cervical ripening is less clear.

However, Society of Maternal Fetal Medicine and UpTodate recommends hydroxyprogesterone caproate 250 mg weekly administered intramuscularly for women with a history of spontaneous preterm birth and natural progesterone 100 mg daily administered vaginally for women with a short cervix (≤20 mm), based on the outcomes reported in the trials.

No evidence exists to support the addition of an alternative form of progesterone to the current progesterone treatment (adding a vaginal form to an intramuscular form).

Maintenance therapy: The use of progesterone in women who remain undelivered after an episode of threatened preterm labour is investigational and it is not routinely recommended.

Conclusion

It is recommended that in women with a previous preterm birth, progesterones are started in the second trimester (16 to 20 weeks) and continued till 36 weeks of gestation. Serial TVS is done to follow their cervical length once in 2 weeks and more frequently (once a week) if CL is between 25 to 30 mm until 24 weeks of gestation, and consider cerclage if cervical length is <25 mm. While in low risk cases with singleton gestation without a prior preterm birth history with an incidentally finding of short cervical length <20 mm before or at 24 weeks of gestation in present pregnancy, vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women.

A first-trimester urine culture should be performed on all pregnant women, and regular antenatal screening is recommended for women at high risk for

asymptomatic bacteriuria. Preconception identification and optimization of chronic medical diseases, such as diabetes and hypertension, can improve maternal health and pregnancy outcome.

Suggested Reading

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Preterm Labour: Diagnosis and management

Taru Gupta[1], Divya[2]
[1]Professor, [2]Assistant Professor, Obstetrics & Gynaecology, ESI-PGIMSR Basaidarapur, New Delhi

Preterm birth (i.e., before 37 weeks of pregnancy) is the one of the biggest cause of neonatal mortality and morbidity. Babies born preterm have high rates of early and late neonatal mortality and the risk of mortality increases as gestational age at birth decreases. The most important long-term consequence of prematurity is neurodevelopmental disability.

Accurate identification of women in true preterm labour allows appropriate application of interventions that can improve neonatal outcome: antenatal corticosteroid therapy, group B streptococcal infection prophylaxis, magnesium sulfate for neuroprotection, and transfer to a facility with an appropriate level of newborn care.

Terminology Used to Describe Preterm Labour

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.

Threatened Preterm labour: Frequent uterine contractions without effacement or dilation of the cervix.

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. The diagnostic test is either transvaginal ultrasound of cervical canal length <15 mm or positive foetal fibronectin, >50 ng/ml.

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

Advanced preterm labour: Cervix dilated more than 3 cm and effaced 80% or more.

Diagnosis of preterm labour pains: Presence of uterine contractions, four or more in 20 minutes or eight or more in 1 hour, each lasting for more than 40 seconds with progressive dilatation and effacement of cervix. (Dilatation more than one cm and effacement more than 80%).

History

- Medical and surgical causes of pain should be ruled out
- Duration, character, intensity and interval of pain, progressive in nature
- Associated with show or LPV
- High risk factor for PTL- previous h/o of polyhydroamnios, PTL, twin pregnancy, mullerian anomaly
- Any indication for termination of pregnancy

Examination

- General physical exam including vital assessment, orodental hygiene, respiratory and cardiovascular system (r/o heart disease) for any contradictions to tocolyis.
- P/A Uterine height, presentation, contraction, amount of liquor, estimated baby weight.
- Before per speculum exam, bed side test for PTL (Foetal fibronectin), if available, can be done. Foetal fibronectin (FFN), a glycoprotein found in the chorioamniotic membranes, decidua and cytotrophoblast is elevated in cervicovaginal secretions of women between 22 weeks-33 weeks likely to have Preterm delivery. If the test is negative, no need of tocolysis or corticosteroids.
- P/S examination (P/V examination if not assessed by P/S)– to assess cervical dilatation, effacement, status of membranes.
- P/V not to be repeated in labour room unnecessarily.

Management of Established PTL

- Patient should be admitted to labour room
- Reassurance & counselling regarding risk of preterm labour
- Prognosis of preterm baby to be explained in written
- Maintain adequate hydration
- Pulse, BP, Temperature charting
- Monitoring of uterine contraction

Send Investigations

- Hb, TLC, DLC
- ABO Rh
- C Reactive Protein- if associated with ruptured membranes
- Urine for routine and culture sensitivity
- High vaginal swab culture & sensitivity
- Routine antenatal investigations (HIV, VDRL, HBsAg, Blood Sugar)
- FHR monitoring- CTG Tracing
- USG - Fetal growth, morphology, estimated foetal weight, amount of liquor, placental location and grade, cervical length, internal os diameter, presence of funnelling.

Indications for Termination of Pregnancy

Features of chorioamniotis: Maternal tachycardia (p>100/ min); Fever (>100^0 F); Uterine tenderness; Foul odour of amniotic fluid; TLC raised; CRP positive & Foetal tachycardia.

Other indications of termination: Adequate lung maturity; GCA in foetus; Severe FGR; Severe placental insufficiency; Abruption or IUFD

Role of antenatal corticosteroids- Accelerate fetal organ maturation.

1. Single course of corticosteroids are recommended for pregnant women between 24+0/7 weeks and 33 6/7 weeks who are at risk of preterm delivery within 7 days, including those with ruptured membranes and multiple gestation.
2. Administration of steroids may be considered in pregnant women between 34+0/7 weeks and 36 6/7 weeks who are at risk of preterm delivery within 7 days and who have not received previous course of antenatal corticosteroids.
3. A single repeat course of ACS should be considered in women who are less than 34+0/7 weeks who are at risk of preterm delivery within 7 days and whose prior course of antenatal corticosteroids was administered more than 14 days previously.
4. *Injection betamethasone or dexamethasone, 4 doses, im, 6 mg 12 hourly apart are recommended*. As betamethasone preparations in India contain only betamethasone phosphate which is short acting.
5. Treatment with ACS for less than 24 hours is also associated with significant reduction in neonatal morbidity and mortality.
6. 1st dose should be administered even if ability to give 2nd dose is unlikely.
7. Benefit of ACS is greatest at 2- 7 days after initial dose.

Tocolysis for 48 hours for delaying delivery for maximum effect of steroids (optimum benefit of steroid begins 24 hours after therapy and lasts for seven days. Tocolysis is not recommended beyond 34 weeks of gestation & is generally not recommended before 24 weeks.

Nifedipine: Initial oral dose is 20 mg, followed by 10-20 mg 3-4 times daily, adjusted according to uterine activity for upto 48 hours. Main adverse effects include flushing, palpitations, nausea and vomiting and hypotension. Nifedipine is contraindicated in cardiac disease, it should be used with caution in diabetes or multiple pregnancy, owing to risk of pulmonary oedema. The oral route of administration, low costs and a possible efficacy in reducing neonatal morbidity favour the use of CCBs.

Oxytocin Antagonist/ Atosiban: Atosiban is a nonapeptide, desamino-oxytocin analogue, and a competitive vasopressin/oxytocin receptor antagonist (VOTra). It inhibits the oxytocin-mediated release of inositol trisphosphate from the myometrial cell membrane. As a result, 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 occur. In addition, atosiban suppresses oxytocin-mediated release of PGE and PGF from the deciduas.

The onset of uterus relaxation following atosiban is rapid, uterine contractions being significantly reduced within 10 minutes to achieve stable uterine quiescence.

Each vial of 5 ml solution contains 37.5 mg atosiban (as acetate). Each ml of solution contains 7.5 mg atosiban

Atosiban is administered intravenously in three successive stages: an initial bolus dose (6.75 mg)/0.9 ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 micrograms/min) for three hours, followed by a lower dose (subsequent infusion 100 micrograms/min) up to 45 hours.

Magnesium sulphate for foetal neuroprotection: Consider intravenous magnesium sulfate for neuroprotection of the baby for women between 28 and 32 weeks of pregnancy who are either in established preterm labour or having a planned preterm birth within 24 hours.

Give a 4 g 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).

For women on magnesium sulfate (magsulf), monitor for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate and deep tendon (for example, patellar) reflexes. If a woman has or develops oliguria or other signs of renal failure: monitor more frequently for magnesium toxicity and think about reducing the dose of magnesium sulfate.

Long term inutero exposure to magsulf is associated with fetal & neonatal bone demineralization and fractures.

Management of Labour

First stage: Bed rest to prevent premature rupture of membrane and avoid repeated digital examination, P/V to be repeated only when indicated. FHR monitoring is done by CTG/intermittent auscultation.

Second Stage: Vacuum is contraindicated, if required forceps may be used for instrumental delivery.

If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding: consider milking the cord and clamp the cord as soon as possible. Otherwise delay cord clamping of preterm babies by 30-60 seconds if the mother and baby are stable. Position the baby at or below the level of the placenta before clamping the cord. Senior Paediatrician should be available. Inform paediatrician for making surfactant available if required.

Management of Threatened Labour

NICE guidelines 2016 advised against using combination of transvaginal ultrasound and fetal fibronectin for diagnosis of preterm labour.

It is suggested that if a woman is less than 29+6 weeks gestation and is in suspected preterm labour, she should receive treatment for preterm labour (admission, tocolysis, antenatal corticosteroids and magsulf if indicated). For women with more than 30+0 weeks gestation, transvaginal USG should be done and only women who have cervical length ≤15 mm should receive treatment for preterm labour.

If it is not feasible to do cervical length measurement, fetal fibronectin is done and if value is >50 ng/ml, treatment for preterm labour should be started.

However, *Society of Maternal and Fetal Medicine recommends* that all women between 23+0 to 33+6 weeks of gestation presenting with symptoms of preterm labor (PTL) should be evaluated for cervical length (CL) on transvaginal USG, if CL is >30 mm, FFN is not advocated, no treatment is required and woman is kept under observation. If CL is 20-29 mm, FFN is done if positive treatment for PTL should be started. In women with CL <20 mm, treatment for PTL is given without performing FFN.

The sample for FFN should be obtained before transvaginal sonography to avoid false positive report.

Management of P-PROM

Preterm prelabour rupture of membranes (PPROM) complicates up to 3% of pregnancies and is associated with 30–40% of preterm births. PPROM can result in significant neonatal morbidity and mortality, primarily from prematurity, sepsis and pulmonary hypoplasia. In addition, there are maternal risks associated with chorioamnionitis.

The diagnosis of spontaneous rupture of the membranes is achieved by maternal history followed by a sterile speculum examination.

If, on speculum examination, no amniotic fluid is observed, clinicians should consider performing an insulin like growth factor binding protein 1 (IGFBP1) or placental alpha microglobulin-1 (PAMG-1) test of vaginal fluid to guide further management.

Following the diagnosis of PPROM, an antibiotic (preferable erythromycin 250 mg 6 hourly) should be given for 10 days or until the woman is in established labour (whichever is sooner), with consideration of corticosteroids and magnesium sulphate. *Do not give amoxyclav as it is reported to be associated with increased risk of necrotizing entrocolitis in the baby*.

A combination of clinical assessment, maternal blood tests (reactive protein and white cell count) and foetal heart rate should be used to diagnose chorioamnionitis in women with PPROM; these parameters should not be used in isolation.

Women whose pregnancy is complicated by PPROM and who have no contraindications to continuing the pregnancy should be offered expectant management, as this is associated with better outcomes compared with early birth.

Late Preterm (34+0/7–36+6/7 weeks of gestation)

Antibiotics to prolong latency are not recommended, termination of pregnancy after counseling patient

Preterm (24 0/7–33 6/7 weeks of gestation)
Expectant management, Antibiotics recommended for prolonging the latency if there are no contraindications

Single-course corticosteroids, GBS prophylaxis as indicated

Less than 24 weeks of gestation
Patient counselling for expectant management or induction of labor, antibiotics may be considered as early as 20+0/7 weeks of gestation

GBS prophylaxis, Tocolysis, magnesium sulfate and corticosteroids are not recommended before viability

Termination of pregnancy: *If foetal and maternal condition is stable, in all cases of PPROM pregnancy should be terminated at 34+0 weeks gestation or at diagnosis if pregnancy is ≥34+0 weeks.*

Suggested Reading

1. ACOG Committee Opinion August 2017, https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co713.pdf. (last accessed 15th May 2019)
2. ACOG Practice Bulletin. Management of Preterm Labor. Number 171, October 2016
3. NICE guideline. Preterm labour and birth. November 2015. https://www.nice.org.uk/guidance/ng25/resources/preterm-labour-and-birth-pdf-1837333576645. (last accessed 15th May 2019)
4. Green Top Guidelines, Peer review draft. Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes. June 2018. https://www.rcog.org.uk/globalassets/documents/guidelines/consultation-documents/preterm-prelabour-rupture-of-membranes-draft-peer-review.pdf. (last accessed 15th May 2019)
5. SMFM Preterm Birth Toolkit. https://www.smfm.org/publications/231-smfm-preterm-birth-toolkit. (last accessed 15th May 2019)
6. Tsatsaris V, Carbonne B, Cabrol D. Atosiban for preterm labour. Drugs. 2004;64(4):375-82.

SOCIETY OF FETAL MEDICINE

Society of Fetal Medicine

Upcoming Events (2018 - 2019)

19th December 2018
Second Quarterly Meeting (2018-2019)
of the Delhi Chapter of Society of Fetal Medicine
Ayurvigyan Auditorium, R&R Hospital
DhaulaKuan, New Delhi
For details contact
Col. (Dr.)Reema Bhatt at +91 9205646811
Email: reemakamalbhatt@yahoo.co.in)

22nd December 2018
Quarterly Meeting (2018-2019of the
Ludhiana Chapter of the Society of Fetal Medicine
Christian Medical College & Hospital, Ludhiana
For details contact
Dr. Naveen Pereira at +91 9815100244
(Email: dr.naveenpereira@rediffmail.com)

6th January 2019
Inaugural CME of the SFM Aurangabad Chapter
For details contact
Dr. Bimal Sahani at +91 9823550582
Email: sonoscan@rediffmail.com)

27th January 2019
SFM North Kerala Chapter Meeting in
association with Thrissur Gynae Society, Thrissur, Kerala
For details contact
Dr. Ambady Ramakrishnan at +919745005767
Email: ambady1950@yahoo.co.in)

9th -10th February 2019
Trifeto CME of SFM and Trichy OBGYN Society
For details contact
Dr. MalathiG Prasad at +91 8220435777
Email: malathi_prasad@hotmail.com)

23rd - 24th February 2019
SFM Ultrasound Update Hyderabad
For details contact
Dr. TLN Praveen at +91 9949638959
Email: tlnpraveen@googlemail.com)

9th - 10th March 2019
Inaugural Meeting of the SFM Amritsar Chapter
Radisson Blu Hotel, Amritsar, Punjab
For details contact
Dr. Vikram Gulati at +91 9781138888
Dr. Amandeep at +91 9872454954
(Email: vngulati@rediffmail.com).

31st March 2019
SFM CME on Fetal Anomalies Evaluation in
association with Mirzapur OBGYN Society
For details contact - Dr. Meena Vishwakarma
Email: drmeena67@gmail.com)

21st April 2019
CME 2019 of Chhattisgarh Chapter
of Society of Fetal Medicine, Raipur, Chhattisgarh
For details contact
Dr. Harshad Ruprela at +91 9769612561
Email: drharshadruprela@gmail.com)

28th April 2019
Third Quarterly Meeting (2018-2019)
of the Delhi Chapter of the Society of Fetal Medicine
Lecture Theater, AIIMS, New Delhi
For details contact Dr. Krishna Gopal at +91 9818624184
Dr. Aparna Sharma at +91 9711824415
(Email: dablookg@yahoo.co.in, kaparnasharma@gmail.com).

12th May 2019
SFM CME in association with Bhopal OBGYN Society
For details contact
Mr. Deepak Dixit at +91 7771010949
(Email: deepak.n@lifecell.in)

18th - 19th May 2019
Inaugural Meeting of the SFM Jammu Chapter
For details contact
Dr. Arshad Bhat at +91 9419185948
(Email: arshadbhat14@gmail.com).

1st - 2nd June 2019
SFM Shimla Meeting
For details contact
Dr. Vivek Kashyap at +91 9811116050
Email: drvkashyap@yahoo.com).

26th - 28th July 2019
SFM Basic Fetal Intervention and Invasive
Procedures Workshop, Hyderabad
For details contact
Dr. TLN Praveen at +91 9949638959
Email: tlnpraveen@googlemail.com)

23rd - 25th August 2019
FetalCardiocon2019
Annual Fetal Cardiology Conference
of the SFM, New Delhi
For details contact
Vishal Mittal at +91 9312227181
Email: sfmsecretariat2017@gmail.com)

8th - 11th September 2019
ISPD 2019, 23rd International Conference on
Prenatal Diagnosis and Therapy, Singapore
For details contact
Vishal Mittal at +91 9312227181
Email: sfmsecretariat2017@gmail.com)

12th - 16th October 2019
ISUOG World Congress, Berlin, Germany
For details contact
Vishal Mittal at +91 9312227181
Email: sfmsecretariat2017@gmail.com)

22nd - 24th November 2019
SFM Fetocon 2019 and Mahabaleshwar
Retreat, Mahabaleshwar, Maharashtra
For details contact
Dr. Chandrashekhar Kenjale at +91 9823238430
Email: cskenjale@gmail.com)

21st - 22nd December 2019
SFM Nagercoil and Kanyakumari
Fetal Medicine CME,Nagercoil, Tamil Nadu
For details contact
Dr. Selvapriya at +91 9443721809
(Email: selvapriya239@gmail.com)

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secretariat at +91 9312227181
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Events Held Under Aegis of NARCHI

1. A Health Camp was organized on 3rd February, 2019 in Shastri Nagar near Kashmiri gate metro station. Talk on "Health Education for Females" was given by Dr Susheela Gupta.
2. An Awareness Program on endometriosis was held at Kasturba hospital by Dr Shivani Aggarwal on 6th February, 2019.
3. Forum of Obstetricians and Gynecologists of South Delhi in association with Milan Fertility Center organised a CME on 15th February, 2019 at Park Inn by Radisson, Vikram Hotel.
4. A Cancer Awareness Camp was organised at Sardar Vallabh Bhai Patel Hospital by Dr Anita Rajhoria. Around 100 women were counselled and made aware about the importance of screening of common gynecological cancers.
5. A Lecture on Menstrual Health & Hygiene was delivered by Dr Mamta Mittal on 15th February, 2019 at North Delhi Modern School for students of class 6th to class 8th.
6. The mega event, 25th Annual Conference of NARCHI, Delhi Branch was organized on 23rd and 24th February at Hotel Eros, Nehru Place. There were three pre conference workshops on "Vulval Disorders from Adolescent to Menopause" at Safdarjung Hospital, "Basic Infertility" at Max Superspeciality Hospital, Saket and "Fetal Medicine: common fetal problems" at Sir Gangaram Hospital. The conference was followed by two post conference workshops, "Critical care and neonatal resuscitation" and "PPH- Hands on Surgical Skills" at Hotel Eros. A CME for Nurses was also organized on 24th February at Hotel Eros as a part of annual conference.
7. "Thalassemia Welfare Dinner" and cultural evening was organized on 23rd February at Hotel Eros, Nehru Place as part of silver jubilee celebration of NARCHI Delhi.
8. A workshop on "Obstetric Critical Care" was conducted for undergraduate students from five states under MEDSICON conference on 3rd March, 2019 at Safdarjung Hospital.
9. An Awareness Programme on "Hepatitis in Pregnancy" was conducted in Kasturba Hospital by Dr Shivani Aggarwal. A presentation was made regarding the disease burden, types of hepatitis, impact on mother and foetus, the consequences, and prevention/treatment etc.
10. A talk on "Cervical Cancer Awareness and Prevention" was organised at Sri Aurobindo college on 27th March 2019. Dr Saritha Shamsunder, Dr Anita Sabharwal and Dr Priyanka had a very interactive session with students and teachers of the college.
11. A CME on Integerated Antepartum Management and Breast Feeding and role of breast pump was conducted on 13th April, 2019 at Eros Hotel Ballroom. Informative lectures on Breast Feeding and role of breast pump were delivered by Dr Vatsala Dhadwal and Dr Gaurav Jawa. This was followed by Baisakhi celebrations.
12. A CME on Breast and Cervical Cancer was held on 25th April, 2019 at Hotel City Park, Pitampura. Dr Jyoti Bhaskar addressed various issues in treating premalignant cervical lesions, Dr Shashi Lata Kabra brushed upon the breast symptoms and Dr Susheela Gupta asserted the need for protein supplement.
13. For the skill training of budding Obstetricians, NARCHI DELHI in association with Johnson and Johnson organized a "Basic Knot & Suture and Endosuturing Training" on 4th & 5th May 2019 at VMMC & Safdarjung Hospital. The sessions were conducted in a state of art skill training bus named as "Johnson & Johnson Institute on wheels".
14. A Thalassemia awareness camp was organised at Sardar Vallabh Bhai Patel Hospital by Dr Anita Rajhoria in Commemoration of World Thalassemia on 9th May, 2019.
15. A CME was conducted at Madhuban Hotel, GK1, Delhi on 11th May under aegis of NARCHI and FOGsd. Dr Aradhana Kalra delivered lecture on Endometriosis and Infertility. Dr Aparna Sharma spoke on Challenges in the management of the iso-immunized pregnancies.
16. A Cervical Cancer Screening Camp was organized in RCC Sangam Vihar by Dr Kusum Chopra on 19th May, 2019 in collaboration with Rajiv Gandhi Cancer Hospital.

Events held under aegis of NARCHI


Health Camp at Shastri Nagar


Awareness program at Kasturba Hospital


CME at Milan Hospital


Cancer awareness Camp at SVBP Hospital


Dr Mamta Mittal on Menstrual Health


MEDSICON Critical Care Workshop


Awareness Programme: Hepatitis in pregnancy


Cervical Cancer Awareness and Prevention


CME: Integerated Antepartum Management and Breast Feeding


CME on Breast and Cervical Cancer


Basic Knot & Suture and Endosuturing Training

Johnson & Johnson Institute on wheels at SJH


Thalassemia awareness camp SVBP Hospital


CME: Endometriosis and Infertility

Cervical Cancer Screening Camp, Sangam Vihar

Glimpses of 25th Annual NARCHI Dell



Preconference Workshop: Vulval disorders from adolescent to menopause at Safdarjung Hospital



Preconference Workshop Fetal Medicine: Common Fetal Problems, organized by Sir Gangaram Hospital



Preconference Workshop: Basic Infertility, organized by Max Superspeciality Hospital, Saket



Post Conference Workshop: Critical care and neonatal resuscitation at Hotel Eros



Post Conference Workshop: PPH- hands on surgical skills at Hotel Eros

hi Branch Conference February 2019

Conference: Registration, Nurses CME and Valedictory

Conference: Inaugration, Souvenir Release, Felicitating Patron Dr Urmil Sharma


Conference: Felicitating Patrons Dr S N Mukherjee, Dr Kamal Bachshee and Dr Aruna Batra


Light Moments at Annual NARCHI Conference


Gala dinner for the Welfare of Thalassemics & Cultural Evening

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An Update on Tocolysis in Preterm Birth

Jyoti Bhaskar
Senior Consultant Obstetrics and Gynaecology, Max Superspeciality Hospital, Vaishali, Uttar Pradesh

Preterm birth complications are the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths. India tops the list of 10 nations contributing 60% of the world's premature deliveries– with the maximum number of preterm births with 3,519,100 of them, almost 24% of the total number.

Though prevention of a preterm birth is the primary focus, it is essential to improve neonatal outcomes once the preterm labour is diagnosed. To be able to implement the evidence based methods to decrease neonatal morbidity and mortality, tocolysis plays a significant role.

Should All Women Presenting with Preterm Labour be Offered Tocolysis?

Identifying those women with preterm labour who will actually go on to preterm delivery is very difficult but essential. Preterm labour may resolve spontaneously in up to 30% of cases and about 50% of pregnant women deliver without tocolysis near term. Less than 10% of women deliver within 7 days of an initial diagnosis of preterm labour and hence, it is essential to identify these women as only they will benefit from tocolysis.

Interventions to reduce the likelihood of delivery should be reserved for women with preterm labour at a gestational age at which a delay in delivery will provide benefit to the newborn. Because tocolytic therapy generally is effective for up to 48 hours, only women with fetuses that would benefit from a 48-hour delay in delivery should receive tocolytic treatment.

Recommendations of Various International Societies

According to European Association of Perinatal Medicine 2017, tocolysis is indicated at the onset of regular preterm contractions, not fewer than 4 contractions within 20 minutes and dynamic cervical changes (shortening/expansion of the cervix) between 22 + 0 and 36 + 6 weeks of pregnancy.

ACOG 2016 (Management of preterm labour. Practice Bulletin No. 171) recommends tocolysis in the case of regular preterm contractions and cervical dilation of ≥ 2 cm between 24 to 34 weeks of gestation but consider its use before 23 weeks based on individual circumstances.

NICE 2015 guidelines recommend tocolysis to women between 24 to 34 weeks of pregnancy who are suspected or diagnosed to have preterm labour and have intact membranes. In women less than 29+6 weeks of gestation diagnosis is based on clinical assessment (regular, painful contractions and cervical shortening/opening verified by vaginal examination, but not ≥ 4 cm). In those 30 weeks or more, the diagnosis is made by transvaginal cervical length measurement of less than 15 mm **or** positive fibronectin test (concentration more than 50 ng/ml) in cases where ultrasound is not possible but not both.

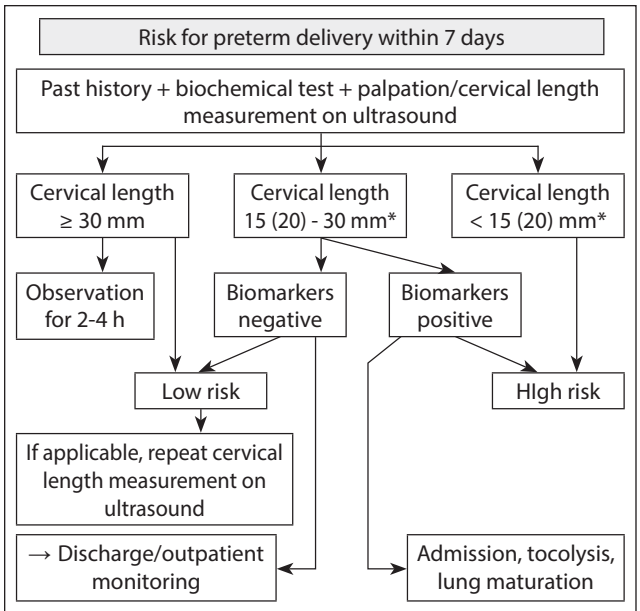
There is consensus between various guidelines that tocolysis should be administered to women with preterm labour who are between 24 to 34 weeks of gestation or have documented cervical length shortening along with contractions.

No evidence exists to support the use of prophylactic tocolytic therapy, home uterine activity monitoring, cerclage, or narcotics to prevent preterm delivery in women with contractions but no cervical change.

Recent Update

In a subgroup analysis of the APOSTEL-I study, the combination of cervical length measurement on ultrasound and the determination of foetal fibronectin proved to be cost-effective through the reduction in inpatient admissions, tocolysis and induction of foetal lung maturation.

It is currently being discussed whether, in addition to cervical length measurement on ultrasound, the additional determination of a biomarker such as fibronectin significantly improves the prediction of preterm delivery and thus should be included in the clinical management in the event of threatened preterm delivery.



Cut-off 15 or 20 mm is due to differences in recommendations.

What are Contraindications to Tocolysis Therapy?

Tocolysis is contraindicated when the maternal/fetal risks of prolonging pregnancy or the risks associated with these drugs are greater than the risks associated with preterm birth. Established contraindications to labour inhibition include: *Intrauterine fetal demise; Lethal fetal anomaly; Nonreassuring fetal status; Preeclampsia with severe features or eclampsia; Maternal hemorrhage with hemodynamic instability; Intraamniotic infection; Preterm prelabor rupture of membranes & Medical contraindications to the tocolytic drug*.

What is the Aim of Giving Tocolytic Drugs to Women in Preterm Labour?

There is no evidence exists that tocolytic therapy has any direct favourable effect on neonatal outcomes or that any prolongation of pregnancy afforded by tocolytics actually translates into statistically significant neonatal benefit.

According to the current view, the objective of tocolysis is

- The prolongation of the pregnancy by at least 48 hours to ensure completion of induction of lung maturation using corticosteroids
- To enable an in-utero transfer of the pregnant woman to a perinatal centre with a neonatal intensive care unit.
- And to complete foetal neuroprotection using magnesium sulphate in < 32 weeks of pregnancy.

These measures are evidence-based methods to decrease neonatal morbidity and mortality.

ACOG also recommends tocolytics to prevent preterm labour when it is safe to do so and when there are underlying, self-limited conditions that can cause labour, such as pyelonephritis or abdominal surgery, and are unlikely to cause recurrent preterm labour.

What Factors Should be Considered while Choosing a Tocolytic?

The following criteria should be taken into account:

- Approved or off-label use
- Tocolytic effectiveness to prolong the pregnancy by at least 48 hours
- Rate of maternal adverse effects/complications
- Rate of foetal adverse effects/complications
- Early, late, long-term morbidity
- Practicability (e.g. mode of application), need for monitoring
- Costs, cost effectiveness

What are The Tocolytic Drugs Available and Is There Any Ideal Tocolytic?

Most Effective Tocolytic Drugs include Calcium channel blockers, Atosiban, Cox Inhibitors, and Beta Sympathomimmetics.

Calcium Channel Blockers

Mechanism of Action: Calcium channel blockers directly block the influx of calcium ions through the cell membrane and increase calcium efflux from the cell. The resulting decrease in intracellular free calcium inhibits calcium-dependent myosin light-chain kinase phosphorylation, leading to myometrial relaxation.

Efficacy: Most trials of calcium channel blockers for inhibition of acute preterm labor have used nifedipine. In a 2014 systematic review and meta-analysis of randomized trials of calcium channel blockers compared with placebo/no treatment for preterm labor, use of a calcium channel blocker reduced the risk of delivery within 48 hours, but there was no

statistical reduction in this outcome compared with other classes of tocolytics. However, calcium channel blockers showed statistical benefits over beta-agonists with respect to prolongation of pregnancy, serious neonatal morbidities and maternal adverse effects.

Dosage of Nifedipine: According to NICE 2015 guidelines, initially 20 mg oral, followed by 10–20 mg three to four times daily (6-8 hrly), depending on uterine activity. (No more than 160 mg/24 hrs). Higher doses are recommended by ACOG 2016: 30 mg nifedipine initially, then 10–20 mg every 4-6 hrly.

Adverse Effects: Dose-dependent adverse effects such as flushing, headaches, dizziness, palpitations, tachycardia and hypotension may occur. The rate of serious maternal adverse effects is 0.9% and is significantly higher than after atosiban; the rate of treatment discontinuation as a result of marked hypotension is < 0.5%.

Caution: Contraindicated in women with known hypersensitivity to the drugs, hypotension, or preload-dependent cardiac lesions. It should be used with caution in women with heart failure with reduced ejection fraction. The daily dosages should not exceed 150 mg in women with multiple pregnancies, receiving intramuscular corticosteroid administration and high volume replacement. It should not be used concomitantly with Magnesium sulphate as it could result in respiratory depression.

Conclusion for Clinical Practice: Drug is not approved as tocolytic, has simple application mode and low cost. Tocolytic efficacy is high and equieffective to beta sympathomimetics and atosiban. Rate of maternal adverse effects is low, has no negative effects on the foetus/newborn and no negative long-term effects on the child. *It is recommended as first-line tocolytic by: NICE 2015, WHO 2015, French guideline 2017*.

Atosiban

Mechanism of action: Atosiban was specifically developed as a tocolytic and is a modified form of oxytocin that competitively blocks uterine oxytocin receptors (selective oxytocin receptor antagonist), therefore halting uterine contractions.

Efficacy: APOSTEL-III study, is a randomised, controlled study (n = 510) on pregnant women with regular preterm contractions, a cervical length of ≤ 10 mm or a cervical length of 11–30 mm and a positive fibronectin test comparing nifedipine with atosiban. No significant differences were seen between nifedipine and atosiban with regard to prolongation of pregnancy by ≥ 48 hours (68% vs. 66%) and by 7 days (51% vs. 45%), no significant differences with regard to perinatal mortality (5% vs. 2%) and neonatal morbidity (14% vs. 15%). Another randomised study from Germany (n =105)[7] compared beta agonist to atosiban. On fenoterol, adverse cardiovascular effects were observed in 78% of cases and on atosiban in only 4% of cases (treatment discontinuation rate 9% versus 0).

Dosage: Atosiban is given intravenously in three successive stages: Initial intravenous injection of 6.75mg in 0.9ml slowly injected over one minute. This is followed by continuous infusion at a rate of 24 ml/hr for up to 3 hours. The infusion rate is then reduced to 8ml/hr for up to 45 hours. Total duration of the treatment should not exceed more than 48 hours. Further cycles of treatment can be used should contractions recur, and no more than three retreatments are recommended during a pregnancy.

Common side effects: The main side effects are hypersensitivity and injection site reactions. Adverse maternal cardiovascular effects have not been reported.

Conclusion for Clinical Practice: It is approved in India (not in the USA). The tocolytic efficacy is comparable to beta sympathomimetics and nifedipine, has few, adverse effects for mother and child. There are no specific contraindications apart from hypersensitivity to the drug. However, intravenous application and immobilisation is necessary and drug cost is high. It is recommended as a first-line tocolytic, or suitable tocolytic in the case of pre-existing metabolic and cardiovascular diseases in the mother and in the case of contraindications to nifedipine and indomethacin.

Cox Inhibitors

Mechanism of Action: Cyclooxygenase (COX, or prostaglandin synthase) is the enzyme responsible for conversion of arachidonic acid to prostaglandins, which are critical in parturition. Nonspecific cyclooxygenase inhibitors reduce prostaglandin production by inhibition of both COX 1 and 2.

Efficacy: A network meta-analysis from 2012 which included 18 studies (1980–2007) showed that COX inhibitors were the most effective tocolytics for prolonging pregnancy by 48 hours in comparison to placebo (OR 5.39; 95% CI 2.14–12.34)– with concomitantly the lowest rate of maternal adverse effects and good neonatal outcome.

In comparative trials, indomethacin reduced the risk

of birth within 48 hours of initiation of treatment compared with any beta-agonist and appeared to be as effective as nifedipine.

Dosage: Initial dosage 50–100 mg oral or rectal, followed by 25–50 mg every 4–6 h for 48 hrs. Fetal blood concentrations are 50 percent of maternal values, but the half-life in the neonate is substantially longer than that in the mother.

To avoid premature closure of the ductus arteriosus, it is recommended to administer COX inhibitors only up to the 32nd week of pregnancy for 48 hours. Prior to 32 weeks of pregnancy, an echocardiographic examination of the foetal ductus arteriosus with assessment of the tricuspid valve (tricuspid regurgitation) is recommended if treatment lasts > 48 hours. According to the recommendations of the European Association of Perinatal Medicine 2017, the amount of amniotic fluid should be checked prior to starting therapy and after 48–72 h as indomethacin, results in oligohydramnios in 5–15% of cases, and even in up to 70% of cases in the case of use for more than 72 h.

Indomethacin should only be given if there is a normal amount of amniotic fluid and if oligohydramnios occurs, it should be discontinued or at least the dose should be reduced.

Side Effects: Maternal- nausea, esophageal reflux, gastritis, and emesis, are seen in approximately 4% of women. Fetal- Primary concerns are constriction of the ductus arteriosus and oligohydramnios.

Contraindications: Platelet dysfunction or bleeding diathesis, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin).

Conclusion for Clinical Practice: It is off-label use tocolytic, has easy application, and is cost-effective. But can be used only until 32 weeks of pregnancy for 48 hours. Indications of increased neonatal morbidity (severe intraventricular bleeding, necrotising enterocolitis, periventricular leucomalacia): inform paediatrician of administration.

Varying recommendations (controversial data, to some extent): *Not recommended/insufficient data*: Cochrane Review 2015, Hammers et al. 2015, Nijman et al. 2016. *WHO Recommendations 2015. Recommended with restrictions*: Navathe and Berghella 2016, European recommendations 2017, *Recommended*: among others: 2009 meta-analysis, 2012 network meta-analysis, ACOG Practice Bulletin 2016.

Beta Sympathomimmetics

Mechanism of action: Beta-agonists, such as ritodrine, reduce the sensitivity to calcium, and total intracellular calcium concentrations, thereby causing myometrial relaxation.

Efficacy: According to a 2012 network meta-analysis, beta sympathomimetics are indeed effective in prolonging pregnancy for 48 hours, but significantly less effective than calcium channel blockers and indomethacin and also have the highest rate of maternal adverse effects of all tocolytics in comparison to placebo.

The beta-2 receptor agonist Terbutaline is now NOT recommended for use in PTL due to these serious side effects (U.S. Food and Drug Administration, 2011). However, terbutaline is still used for emergency treatment of intrapartum uterine hyperstimulation to aid resuscitation of a fetal bradycardia.

Conclusion for Clinical Practice: It is approved for tocolysis and effective for prolonging the pregnancy by 48 h. It has unfavourable adverse effect profile of all tocolytics and the highest therapy discontinuation rate (Adverse effects 3.8 times higher in comparison to other tocolytics and the therapy discontinuation rate is between 6 and 38%). There are no teratogenic effects but they cross the placental barrier and can therefore lead to foetal tachycardia (in up to 28% of cases), as well as neonatal hyperinsulinaemia/hypoglycaemia. Need immobilisation of the pregnant woman in the case of parenteral use and intensive monitoring is needed (e.g. ECG, laboratory testing), close circulatory monitoring is necessary.

In current guidelines, beta sympathomimetics are no longer recommended for tocolysis. However, recently published multicentric studies from India and Korea have reported beta sympathomimetics to be still the most popular tocolysis used as firstline. Jaju et al also found significant improvement in mean latency period, prolongation of delivery beyond 48-hours and perinatal outcomes amongst patients on isoxsuprine versus other pharmacological agents.

Less Effective Tocolytic Drugs

Magnesium Sulfate

Efficacy: The data on magnesium sulphate as a tocolytic are controversial. In a 2014 systematic review of randomized trials comparing magnesium sulfate with no treatment/placebo control, magnesium sulfate administration did **not** result in a statistical reduction

in birth <48 hours after trial entry (RR 0.56, 95% CI 0.27-1.14; three trials, 182 women) or improvement in neonatal and maternal outcomes. Magnesium sulfate causes fewer minor maternal side effects than beta-agonists, but the risk of major adverse risk events is comparable

Current Recommendation: Except in the U.S., magnesium sulphate is **no longer recommended for tocolysis** in current reviews and guidelines.

Magnesium sulfate reduces the severity and risk of cerebral palsy in surviving infants if administered when birth is anticipated before 32 weeks of gestation. Hence it has a role in neuroprotection. If tocolysis is indicated because of persistent preterm labor in a patient receiving magnesium sulfate for neuroprotection, the most effective tocolytic with the most favorable side-effect profile should be used.

Nitrous Oxide Donors

The transdermal application of nitroglycerin (patches, 10 mg/24 h) was considered for some years to be a new, innovative method for tocolysis since it is effective, has few side effects, is easy to apply and cost-efficient.

Efficacy: In a 2014 meta-analysis of randomized trials that compared glyceryl trinitrate by any route with placebo (three trails), beta-adrenergic receptor agonists (nine trials), and nifedipine (one trial), use of glyceryl trinitrate did **not** significantly prolong pregnancy by ≥48 hours, reduce preterm birth, or result in improved neonatal outcomes compared with any of the comparators.

Conclusion for Clinical Practice: It is not approved for tocolysis (off-label use) but is more effective in comparison to beta sympathomimetics with regard to prolongation of pregnancy by 48 hours. The possibly decreased acceptance is due to high rate of headaches. There is inadequate data, **no recommendation in international guidelines.**

Overview of Tocolytics

Should tocolytics be used after acute therapy for maintenance?

Maintenance therapy with tocolytics is ineffective for preventing preterm birth and improving neonatal outcomes and is not recommended for this purpose. A meta-analysis has not shown any differences between magnesium sulfate maintenance therapy and either placebo or beta-adrenergic receptor agonists in preventing preterm birth after an initial treated episode of threatened preterm labour.

Because of the lack of efficacy and potential maternal risk, the FDA states that oral terbutaline should not be used at all to treat preterm labour. When compared with placebo, maintenance tocolysis with nifedipine does not appear to confer a reduction in preterm birth or improvement in neonatal outcomes. Atosiban is the only tocolytic that has demonstrated superiority as maintenance therapy over placebo in prolonging pregnancy.

Are tocolytics indicated and safe to administer in multiple gestations?

The use of tocolytics to inhibit preterm labour in multiple gestations has been associated with a greater risk of maternal complications, such as pulmonary edema. In addition, prophylactic tocolytics have not been shown to reduce the risk of preterm birth or improve neonatal outcomes in women with multiple gestations.

Adequate data does not exist to specifically demonstrate benefit from the use of antenatal corticosteroids in multiple gestations. However, because of the

Tocolytics	Approved	Prolongation of pregnancy* by 48 h	Adverse effects - mother	Adverse effects - child	Mode of application	Amount of monitoring needed	Drug costs
Beta sympathomimetics (continuous i.v.)	+	++	+++	++	i.v.	high	moderate
Indomethacin	-	++(+)	(+)	+(+)	rectal/oral	low	very low
Atosiban	+	++	(+)	-	i.v.	low	high
Magnesium sulphate	-	Controversially dose-dependent	Dose-dependent ++	++	i.v.	moderate	moderate
Calcium channel blockers (nifedepine)	-	++(+)	+	(+)	oral	low	very low
No donors	-	++	++	-	transdermal	low	low

clear benefit attributable to the use of antenatal corticosteroids in singleton gestations, most experts recommend their use in preterm multiple gestations.

Is there any role of other pharmacological and non pharmacological methods in management of preterm labour?

Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with preterm labour and intact membranes as there is no evidence-based role for antibiotic therapy in the prevention of prematurity in patients with acute preterm labour.

Progesterone supplementation- Women in acute preterm labour do not benefit from progesterone supplementation.

Bed rest and hydration have not been shown to be effective for the prevention of preterm birth and should not be routinely recommended.

Summary

Despite insufficient and controversial data, tocolysis is and remains an indispensable measure in everyday obstetrical practice. They should be given to women between 24 to 34 weeks of pregnancy and only when preterm contractions are associated with cervical changes for not more than 48 hrs.

Tocolytic agents have not been proven to reduce perinatal or neonatal mortality. The only aim of tocolysis is to allow administration of antenatal steroids and magnesium sulphate for neuroprotection (< 32 weeks) and in utero transfer to a tertiary care centre.

To date, there is no "ideal" tocolytic. Nifedipine and atosiban are suitable tocolytics with regard to efficacy, adverse effect profile and effects on the child. Indomethacin is a potent tocolytic with anti-inflammatory effects and a low rate of maternal adverse effects and should be justified, especially in early preterm delivery. Beta sympathomimetics although not recommended by International Society Guidelines due to the high rate of maternal and foetal adverse effects are again gaining popularity in India. Magnesium sulphate should not be used as a tocolytic due to the controversial study results and the adverse effect profile at a high dose.

Maintenance treatment with tocolytic drugs or repeat tocolytic treatment does not appear to improve perinatal outcome and therefore is not recommended. Use of multiple tocolytic agents should be avoided due to the risk of increasing adverse effects. Particular caution should be exercised if tocolytics are considered in multiple gestations due to the increased risk of 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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Antenatal Corticosteroids: Evidence based approach

Rekha Bharti[1], Jyotsna Suri[2]
[1]Associate Professor, [2]Professor, Obstetrics & Gynaecology, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi

Antenatal corticosteroids therapy administered to women at risk for preterm delivery reduces the incidence and severity of respiratory distress syndrome, need for mechanical ventilation, intraventricular hemorrhage, necrotizing enterocolitis and neonatal mortality.

The first paper on the benefits of antenatal corticosteroid was published more than four decades ago, but till date research is ongoing on the long term neurodevelopmental effects on the foetus and also to find out the upper limit of pregnancy gestation where the benefits of administering corticosteroids outweigh the adverse effects on the foetus. Cochrane review 2017 reaffirmed the use of a single course of antenatal corticosteroids to accelerate foetal lung maturation in women at risk of preterm birth. However, recent evidence supports the use of single repeat course of corticosteroids in a selected group of pregnant women.

Choice of Corticosteroid and Dose

Betamethasone and dexamethasone are preferred over other steroids because they are less extensively metabolized by the placental enzyme 11 beta-hydroxysteroid dehydrogenase type 2. Both are equally effective for accelerating foetal lung maturity and have comparable safety profile, however, use of betamethasone requires fewer injections than dexamethasone.

Dose: Betamethasone, two doses of 12 mg given intramuscularly 24 hours apart or Dexamethasone four doses of 6 mg given intramuscularly 12 hours apart. A nonsulfite-containing preparation of dexamethasone should be used as the sulfite preservative (NNF60211) may be neurotoxic in newborns.

1 ml of betamethasone is a combination of 3 mg of betamethasone sodium phosphate and 3 mg of betamethasone acetate. Betamethasone sodium phosphate is soluble so is rapidly absorbed, while betamethasone acetate is only slightly soluble and, therefore, provides sustained activity. Its biological half-life is 35 to 54 hours.

Dexamethasone is available as dexamethasone sodium phosphate, which has a rapid onset and short duration of action. Therefore, the dosing frequency for dexamethasone is shorter than that for betamethasone. It is less costly and more widely available than betamethasone.

The combination of Betamethasone acetate + phosphate, which require only two doses at 12 hour interval, is not available in India. ***The salt available 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.

At the above doses, 75 to 80 percent of available corticosteroid receptors are occupied, which provides maximum corticosteroid receptor-mediated response in foetal target tissues. These doses result in cord blood glucocorticoid levels in the range seen with physiologic stress in the preterm neonate.

Effect of Administering Higher Dose or Shortening Dosing Interval

Higher dose: Giving corticosteroids above the recommended dose has no advantage as the steroid receptors are not available for the extra drug administered and also the higher levels of corticosteroids will suppress the steroid receptors by homologous down-regulation.

Shorter dosing interval: Obstetricians often reduce the dosing interval of antenatal corticosteroids in order to complete the course before delivery. However, safety and efficacy of such regimen is not clear. The steroids receptors may not be available if the drug is administered early and also one study has shown increased risk of necrotizing enterocolitis with a shorter dosing interval.

Mechanism of Action of Antenatal Corticosteroids

Corticosteroids administered to pregnant women accelerate development of type 1 and type 2 pneumocytes, leading to structural and biochemical

changes that improve lung volume, compliance and gas exchange. Type 2 pneumocytes also increase surfactant production. Corticosteroids facilitate surfactant release and absorption of alveolar fluid after birth. They also improve the capillary stability, therefore reduce incidence of intraventricular hemorrhage and necrotizing enterocolitis.

Rationale for Repeating Steroid Course in Selected Women

It is observed in the cell culture models that although cytostructural maturation persists after withdrawal of steroids, the surfactant production is reversible. A placebo-controlled randomized trial also reported benefits of rescue course of betamethasone. The respiratory compliance was increased in babies delivering at less than 34 weeks gestation when rescue course of betamethasone was administered.

Although, these findings were not consistent in other trials, The American College of Obstetricians and Gynecologists opine that "a single repeat course of antenatal corticosteroids should be considered in women who are less than 34+0 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. Rescue course of corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario" [43].

Gestational Age at Administration of Corticosteroids

Lower limit: For the effect of corticosteroids lungs need to have reached a stage of development that is responsive to corticosteroids. Corticosteroids can be administered after 22+0 weeks gestation in women who are at increased risk of preterm delivery within the next one to seven days. However, administration of antenatal steroids at 22+0 to 22+6 weeks of gestation should only be done if woman gives consent for neonatal intervention and after counseling regarding the risk of major morbidity in the offspring.

Upper limit: There is no controversy regarding administration of antenatal corticosteroids till 34 weeks of gestation. Beyond 34+0 weeks of gestation the data on the efficacy of antenatal corticosteroids is inconsistent and long term safety is also questionable.

Following are the recommendations of various international societies:

According to the operational guidelines June 2014, released by Ministry of Health and Family Welfare, Govt. of India, single course of injection of Dexamethasone is to be administered to women with preterm labour (between 24 and 34 weeks of gestation) at all levels of health facilities in the public as well as the private sector.

According to the *Society for Maternal-Fetal Medicine Specialists*, women with 34+0 to 36+6 weeks gestation who are at risk of preterm birth within seven days should receive a two-dose course of antenatal betamethasone. For these women with symptoms of preterm labor, cervical dilation should be ≥3 cm or effacement ≥75 percent and tocolysis should not be used to delay delivery for completion of the course of steroids. For women with potential medical/obstetric indications for early delivery, steroids should not be administered until a definite plan for delivery has been made.

The American College of Obstetricians and Gynecologists recommends administration of betamethasone for women with a singleton pregnancy at 34+0 to 36+6 weeks of gestation at imminent risk of preterm birth within 7 days, with the following caveats: Antenatal corticosteroid should not be administered to women with chorioamnionitis. Tocolysis should not be used to delay delivery in women with symptoms of preterm labor to allow completion of corticosteroids course. Medically/obstetrically indicated preterm delivery should not be postponed for steroid administration. Antenatal corticosteroids should not be administered if the patient has already received a course of corticosteroids. Newborns should be monitored for hypoglycemia.

The NICE guideline (NG25) on preterm labor and birth suggests considering maternal corticosteroids for women between 34+0 and 35+6 weeks of gestation who are in suspected, diagnosed, or established preterm labor, are having a planned preterm birth, or have preterm prelabor rupture of membranes.

However, some authors have cautioned against universal adoption of antenatal corticosteroids for pregnancies at risk of preterm birth at 34+0 to 36+6 weeks of gestation because it is unclear whether the short-term benefits (reduction in transient tachypnea of the newborn) clearly outweigh the risks (neonatal hypoglycemia, unknown long-term neurodevelopmental outcome and metabolic risks).

Efficacy of Anatenatal Corticosteroids before Elective Caesarean Delivery at 37+0 to 39+6 Weeks of Gestation

A 2018 meta-analysis of four randomized trials of antenatal corticosteroids (betamethasone or dexamethasone) administered 48 hours before planned cesarean delivery at ≥37 weeks of gestation found reductions in neonatal respiratory morbidity compared with placebo or no treatment: transient tachypnea of the newborn (2.3 versus 5.4 percent; RR 0.43, 95% CI 0.29-0.65), respiratory distress syndrome (RDS; 2.6 versus 5.4 percent; RR 0.48, 95% CI 0.27-0.87), and admission to the NICU for respiratory morbidity (2.3 versus 5.1 percent; RR 0.45, 95% CI 0.22-0.90). A trend toward reduction in need for mechanical ventilation was also noted. Neonatal hypoglycemia and long-term outcomes in offspring were not reported.

What is The Harm in Administering Antenatal Corticosteroids after 34+0 Weeks of Gestation?

Antenatal steroids may have effect on the neurodevelopment outcomes of the foetuses exposed to corticosteroids beyond 34+0 weeks of gestation. This is due to the fact that exponential brain growth occurs after 34 weeks gestation. The foetus brain grows by 35%, cortical volume increases by 50%, and 25% of cerebellar development occurs after 34 weeks of gestation. Therefore, exposure to exogenous betamethasone or dexamethasone during this time period is likely to have greater adverse consequences on brain development than at any other period of development.

Also, disruption of the normal foetal environment at this critical time may lead to changes in development of the neuroendocrine system, life-long effects on endocrine, behavioral, emotional, and cognitive function, and increased risks for development of a wide range or metabolic, cardiovascular, and brain disorders in later life.

It is observed that in newborns, postnatal systemic glucocorticoid therapy contributes to neurodevelopmental impairment, especially cerebral palsy.

Although in near term foetuses also endogenous cortisol surge occurs that is responsible for preparation of parturition. But, the high levels of 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) in the foetal brain help to protect it from the effects of the physiological rise in endogenous cortisol, but do not protect it from maternally administered betamethasone or dexamethasone due to the resistance of these drugs to metabolism by 11β-HSD-2. Therefore, these steroids lead to supraphysiological activation of glucocorticoid receptors in the foetal brain near term.

The ASTECS trial compared administration of betamethasone 48 hours before planned cesarean delivery at ≥37 weeks with usual care. When follow-up was performed at 8 to 15 years of age, schools were more likely to perceive steroid-exposed children to be in the lowest achievement group compared with the control group. However, objective testing of academic ability was not performed as part of the trial and results from national standardized assessments did not show statistical differences between the scores for each group.

Anticipated Maternal and Foetal Effects of Antenatal Corticosteroids

Maternal effects: Transient hyperglycemia occurs in many women, the effect starts 12 hours after the first dose and last for upto five days. Therefore, screening for gestational diabetes should either be done before administration of corticosteroids or should be postponed by at least 5 days after last dose of steroid. Also, in women with diabetes, hyperglycemia can be severe if not closely monitored and treated.

The total leukocyte count increases by approximately 30% within 24 hours after betamethasone injection, and the lymphocyte count significantly decreases. These changes return to baseline within three days, but may complicate the diagnosis of infection.

Foetal effects: foetal heart rate and behavioural changes in foetus are frequent after corticosteroid administration but return to baseline by 4-7 days. The most consistent FHR finding is a decrease in variability on days two and three after steroid administration. Reduced foetal breathing and body movements can result in a lower BPP score or NR-NST. However, this is not a consistent finding. NST and BPP should be carefully evaluated in women receiving corticosteroids.

The changes in the foetal heart pattern and BPP are due to either a direct physiologic response of the brain to corticosteroids or an indirect result of a transient increase in foetal vascular resistance and blood pressure.

Doppler flow studies- A transient improvement in

umbilical artery end-diastolic flow (EDF) after antenatal corticosteroid administration has been described in 63-71% of patients. The improvement began eight hours after the first dose of betamethasone and last for 1 to 10 days (median 3 days). However, this finding has not been reciprocated in other studies. Preterm foetuses with severe early-onset growth restriction and absent or reversed EDF do not have a consistent cardiovascular response to maternal betamethasone administration. Some exhibit transient improvement of EDF, while others do not. The later group is at risk of foetal acidosis.

Special Population

Obesity: No change in dose is recommended in obese women receiving antenatal corticosteroids. *Multifoetal gestation*- No change in dosing schedule is required. *Hypertension*- Betamethasone has low mineralocorticoid activity compared with other corticosteroids and does not aggravate hypertension. *Diabetes*- Antenatal corticosteroid therapy should be administered to women with diabetes when indicated. *Preterm premature rupture of membranes*- Antenatal corticosteroid administration improves neonatal outcome in pregnancies complicated by preterm premature rupture of membranes and does not increase the risk of neonatal or maternal infection.

Indian Scenario

The data on efficacy and safety of antenatal corticosteroid is mainly from the high income countries. A multifaceted intervention trial (ACT) designed to increase the use of antenatal corticosteroids in low-income and middle-income countries published in the Lancet journal, February 2015, reported increased neonatal and perinatal mortality in the late preterm and early term foetuses exposed to antenatal corticosteroids. The study also observed increased infectious morbidity in steroid exposed mother and the babies. However, one of the limitations of the study was that instead of gestational age, baby weighing less than 5 percentile were taken as a proxy for preterm birth.

Summary

Antenatal corticosteroids should be administered to women at 23+0 to 33+6 weeks gestation, who are at high risk of spontaneous or induced preterm delivery within 7 days. The use of antenatal corticosteroids in women at gestation 22+0 to 22+6 weeks should be after consultation with the foetal medicine specialist and neonatologist. This should be done after proper counseling and informed consent from the woman and family.

Although administration of corticosteroids before preterm births between 34 and 37 weeks of gestation has been reported to have potential benefits, till more data on safety of antenatal corticosteroids in Indian population is available administration of antenatal corticosteroids in women at ≥34+0 weeks gestation should be done after counseling and informed consent.

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"Always remember, you are braver than you believe,
stronger than you seem and smarter than you think."
– A. A. Milne

Doppler in FGR: Basics and interpretation

Sumitra Bachani[1], Kuldeep Singh[2]
[1]Senior Specialist, VMMC & Safdarjung Hospital, [2]Consultant Ultrasonologist, Dr Kuldeep Singh Clinic, East of Kailash

Foetal growth restriction (FGR) is an obstetrical entity with the greatest variation in clinical practice regarding diagnosis, monitoring and recommended gestational age at delivery. The first aim in the clinical management of FGR is to distinguish 'true' FGR from constitutionally small for gestational age (SGA) foetuses as the former are at a higher risk of stillbirth and adverse outcomes. The second aim is to identify whether there is risk of in utero foetal hypoxia or death that may recommend delivery prior to term.

Identification of 'Foetal Growth Restriction' Versus '(constitutional) Small for Gestational Age'

A growth restricted foetus is the one which fails to achieve its genetically established growth potential. It is associated with abnormal Doppler suggesting foetal adaptation to undernutrition/hypoxia, signs of placental disease and a higher risk of preeclampsia. SGA foetuses do not present the aforementioned changes and display perinatal outcomes similar to those of normally grown foetuses.

All guidelines recommend that Effective foetal weight (EFW) <10th centile is an appropriate definition of FGR, with additional parameters to confirm pathological growth restriction including either one or all three namely uterine artery PI (Pulsatility Index) >95th centile, abnormal umbilical artery PI (>95th centile), abnormal Cerebroplacental ratio (CPR) (<5th centile).

Aside from the clinically relevant distinction between FGR and SGA, FGR is presented under two different phenotypes when the onset is early or late in gestation. Late onset FGR develops at or beyond 32 weeks gestation and early onset FGR develops before 32 weeks. Being early or late-onset determines differences in the severity of placental disease, as well as in the foetal adaptive response and deterioration. Thus, foetuses with late onset disease do not present the sequence of Doppler deterioration described for early-onset FGR (Table 1).

Doppler ultrasound is also widely used in the management of pregnancy complicated by Foetal growth restriction. The most common Doppler indices used are S/D ratio, RI (resistance index) and PI (pulsatility index). S/D ratio is peak systolic frequency shift (S) to end-diastolic frequency shift (D) ratio; RI is S-D/S and PI is S-D/A (A is Average frequency shift value over the cardiac cycle).

Table 1: Early and late onset FGR

Early onset	Late onset
Challenge: management	Challenge: diagnosis
Prevalence: 1% to 2%	Prevalence: 3% to 5%
Severe placental disease: UA Doppler abnormal, high association with PE	Mild placental disease: UA Doppler normal, low association with PE
Severe hypoxia ++: systemic cardiovascular adaptation	Mild hypoxia: central cardiovascular adaptation
High mortality and morbidity	Lower mortality (but common cause of late stillbirth)

Factors Affecting the Doppler Indices

Gestational age- As the pregnancy advances there is decline in the impedance to foeto-placental blood flow, therefore end-diastolic velocity (D) increases. This is reflected as decline in S/D ratio and RI.

Foetal breathing movements and foetal body movements- Changes in intrathoracic pressure and central hemodynamics occuring during foetal breathing, and foetal body movements generated Doppler signals can interfere with the study of umbilical artery Doppler. Therefore, Doppler should be done during cycles of foetal apnoea and when the baby is not moving.

Location of the cord studied- The doppler indices are higher at the foetal than at the placental end of the cord. For PW Doppler, whenever possible a mid-level free floating loop or foetal end of the cord should be studied.

Angle of insonation- As we use ratios, the Doppler indices are independent of angle of insonation. However, it is preferable to keep the angle of insonation as close to zero as possible as the axis of the blood vessel affects the Doppler frequency shift and therefore the size of the waveform. The higher is the angle, the smaller is the waveform.

Wall filter setting- The wall filter removes signals generated by the vascular wall but a higher filter setting also removes low frequency umbilical artery flow signals during the end diastole. Therefore, the wall filter should be kept as low as achievable for the specific ultrasound device.

How Does Doppler Correlate with Foetal Condition?

Uterine artery- After 26 week gestation uterine artery S/D ratio should be <2.7 (Fig 1). If the end-diastolic flow does not increase throughout pregnancy or a small uterine artery notch is detected at the end of systole, the foetus is at high risk for developing FGR. Absent or reversed diastolic blood flow is ominous finding and may precede foetal death or signal a high risk of abnormal foetal neurologic outcome.

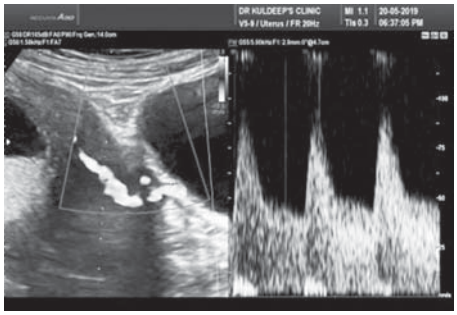

Fig 1: Uterine artery flow pattern

Umbilical artery- The UA Doppler (Fig 2) is the only measure that has both diagnostic and prognostic role in the management of FGR. The maternal and foetal conditions that lead to abnormal angiogenesis and obliteration of terminal villi lead to increased resistance to the blood flow. This is reflected in the umbilical artery Doppler indices as decreased end diastolic flow measured as increase in S/D ratio, RI and PI. When 30% of the villous vasculature ceases to function, an increase in umbilical artery resistance leading to reduced end-diastolic flow is consistently seen. It is a weak predictor of adverse foetal outcome. With more terminal villi getting affected the diastolic flow through umbilical artery further decreases and there is either absence or reversal of diastolic blood flow through umbilical artery. When 60 to 70 percent of the villous vasculature is obliterated, umbilical artery diastolic flow is absent or reversed. This indicates poor foetal prognosis.

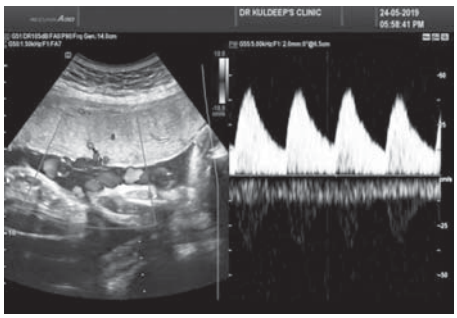

Fig 2: Umbilical artery flow

Middle cerebral artery (MCA)- Due to reduction in the nutritional and respiratory support, the foetus undergoes adaptive changes initially by preferential preserving the foetal growth over placental growth, followed by deceleration of the foetal growth rate. There is redistribution of blood flow to the more vital organs like brain, heart, adrenals, and placenta at the expense of flow to muscles, viscera, skin, and other organs. This leads to decreased resistance to blood flow through MCA, "Brain Sparing (Fig 3). The brain as such receives continuous forward flow throughout the cardiac cycle and FGR is associated with further increased end-diastolic velocities and decreased S/D ratios in the middle cerebral arteries.

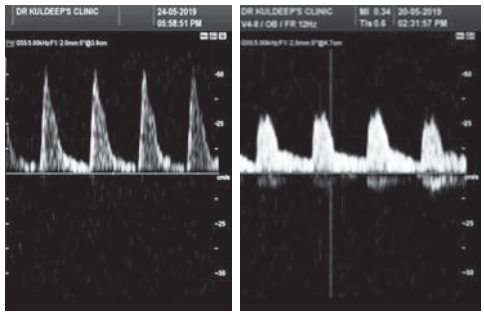

Fig 3: MCA normal low diastolic velocity (left), Brain sparing high diastolic velocity (right)

There is an association between abnormal MCA-PI and adverse perinatal and neurological outcome, but it is unclear whether delivering before term could add any benefit. MCA is particularly valuable for the identification and prediction of adverse outcome among late-onset FGR, independently of the UA Doppler, which is often normal in these foetuses. RCOG guidelines recommend measurement of MCA indices at >32 weeks in FGR even with normal umbilical artery Doppler, whereas ACOG guidelines suggest measurement of MCA Doppler only in cases of abnormal UA doppler.

Cerebroplacental ratio- The cerebroplacental Doppler ratio (CPR) is the middle cerebral artery pulsatility index (or resistance index) divided by the umbilical artery pulsatility index (or resistance index). A low CPR indicates foetal blood flow redistribution (brain sparing) and is predictive of adverse neonatal outcome. In late-onset FGR foetuses, abnormal CPR is present before

delivery in 20% to 25% of the cases, and it is associated with a higher risk of adverse perinatal outcome after labour induction. Fetuses with abnormal MCA-PI have sixfold increased risk of emergency cesarean section for foetal distress when compared with SGA fetuses with normal MCA-PI.

Aortic isthmus (AoI) Doppler (Fig 4): This vessel reflects the balance between the impedance of the brain and systemic vascular system. Reverse Aortic isthmus (AoI) flow is a sign of advanced deterioration, and a further step in the sequence starting with the UA and MCA Doppler. AoI has a strong association with both adverse perinatal outcome and neurological deficit in the infant. However, longitudinal studies show that the AoI precedes ductus venosus (DV) abnormalities by 1 week, and consequently, it is not as good as DV to predict the short-term risk of stillbirth.

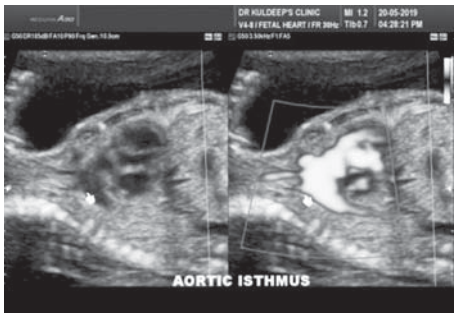

Fig 4: Site for Aortic Isthmus Doppler

Ductus venosus (DV)- The flow in venous circulation is forward and uniform in normal foetuses (Fig 5). With the progressively increasing umbilical arterial resistance, foetal cardiac performance becomes impaired and central venous pressure increases, resulting in reduced diastolic flow in the DV and other large veins. Vasodilatation of the DV helps in diverting nutrient and oxygen rich blood to the heart but enhances retrograde transmission of atrial pressure. The DV RI increases with loss of the 'a' wave, an absent or reversed ductus venous a-wave indicates cardiovascular instability and can be a sign of impending acidemia and death. Absent or reversed flow in the DV (absent or reversed a wave) or pulsatile umbilical venous flow, generally occur approximately two weeks after changes are observed in the arterial circulation.

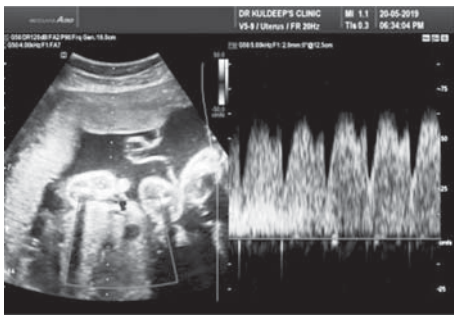

Fig 5: Ductus Venosus Flow Pattern

On the basis of available evidence, it is not known whether delivery should be recommended as soon as the DV PI becomes abnormal or whether delivery should be deferred until the DV A-wave becomes absent/reversed.

The use of venous Doppler is still investigational however, obstetricians are using this to avoid very preterm delivery (<32 weeks) in foetuses with AREDF in the umbilical artery with reassuring foetal surveillance testing.

Conclusion

Certain Doppler indices have diagnostic value while some indices predict the prognosis and neonatal outcomes. Doppler parameters combined with antenatal foetal surveillance testing can be used to avoid unnecessary preterm termination of pregnancies complicated by FGR.

Suggested Reading

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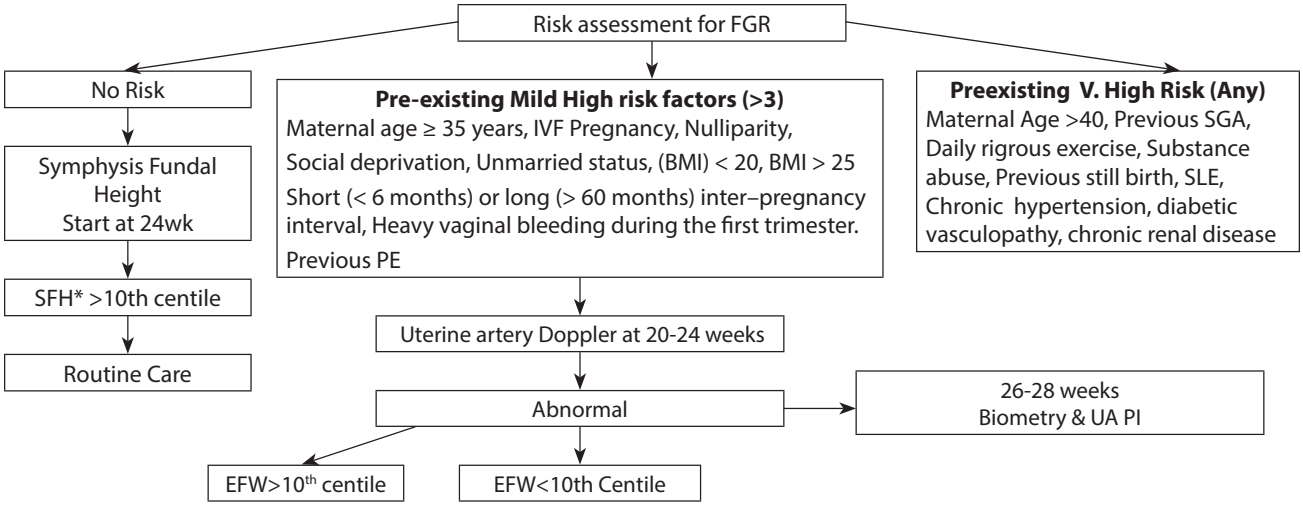
Algorithm: Management of FGR fetus

Achla Batra[1], Sarita Singh[2]
[1]Consultant & Professor, [2]Senior Specialist, Obstetrics & Gynaecology
Vardhman mahavir Medical College & Safdarjung Hospital, New Delhi

Definitions

Fetal Growth Restriction (FGR) A fetus that has not reached its growth potential. Small for gestational age (SGA)
Estimated fetal weight/birthweight <10th centile
Severe FGR SGA <3rd centile is often used as a proxy for severe FGR
Early FGR <32 weeks gestation
Late FGR >32 weeks gestation



Clinical Suspicious of FGR by SFH <10th Centile do USG Biometery, if EFW <10th Centile do UA and MCA Velocimetery

Ensure dating
Anatomic evaluations of fetus and placenta
if soft marker, structural defect or severe FGR<24 week- Aneuploidy screen
If history suggestive of infection, usg markers of infection present – Infection screen

Umbilical Artery Doppler velocimetery & MCA Doppler

Normal UA Doppler	UA PI >95 Centile EDF Present	UA PI >95 Centile EDF Absent	UA PI >95 Centile REDF
Repeat UA Doppler 2weekly	Repeat UA and MCA Doppler weekly	Admit ,Doppler UA ,MCA biweekly	Admit, Doppler UA, MCA &DV daily
Biometery AFI 2 weekly	Biometery 2 weekly	CTG, AFI biweekly	CTG Daily
Deliver at 37 wk MCA PI <5th centile	CTG, AFI weakly	Cortcosteroids	Cortico steroids
Earlier after 34 weeks if static growth over 3 weeks	Cortcosteroids if <34 weeks	Magsulf <32 weeks	Magsulf<32 weeks
No concurrent finding delivered 38 to 39 weeks	Deliver at 37 weeks	Deliver at 34 weeks	Deliver at 32 weeks
	Earlier if CTG abnormality or static growth	Earlier if CTG abnormal	Earlierif - CTG abnormal - Reversal in DV

Note: *Symphysio Fundal Height

NB

In early onset FGR MCA Doppler not used for timing delivery, In late onset FGR MCA RI <5th centile or CPR <1 guides delivery

Suggested Reading

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"Don't stand unmoving outside the door of a crying baby whose only desire is to touch you. Go to your baby. Go to your baby a million times. Demonstrate that people can be trusted, that the environment can be trusted, that we live in a benign universe."

– Peggy O'Mara

Quiz Time

1. Measurement of cervical length should be done between 16 and 24 weeks gestation in

a. High risk women
b. Low risk women
c. Both a & b
d. None of the above

2. In women with ≥ 3 previous PTB and 2nd trimester losses, history indicated cerclage are placed at around

a. 12–14 weeks
b. 14-16 weeks
c. 16-18 weeks
d. 18-20 weeks

3. Ultrasound indicated cerclage are indicated in women with previous history of spontaneous preterm birth and short cervical length of _____ in present pregnancy

a. <25 mm
b. <15 mm
c. <30mm
d. <10 mm

4. According to Society of maternal and fetal medicine, in women with preterm labor, FFN should be done if cervical length is

a. >30 mm
b. 20-29 mm
c. 20 mm.
d. All of above

5. Betamethasone available in India contains

a. Betamethasone sodium phosphate and betamethasone acetate in 1:1 ratio
b. Only betamethasone acetate
c. Only betamethasone sodium phosphate
d. Betamethasone sodium phosphate and betamethasone acetate in 1:2 ratio

6. A single repeat course of antenatal corticosteroids is recommended in women who fulfill following criteria

a. <34+0 weeks of gestation
b. have an imminent risk of preterm delivery within the next 7 days
c. whose prior course of antenatal corticosteroids was administered > 14 days previously
d. All of the above

7. The dose of dexamethasone in women with risk of preterm birth within next 7 days is

a. 6 mg 6 hourly for 4 doses
b. 6 mg 12 hourly for 4 doses
c. !2 mg 12 hourly for 2 doses
d. 12 mg at 24 hours interval for 2 doses

8. WHO recommended first line choice for tocolysis is

a. Isoxsuprine
b. Nifedipine
c. Atosiben
d. All of the above

9. Foetal growth restriction is defined as effective foetal weight of

a. <10 percentile
b. <5 percentile
c. <3 percentile
d. None of the above

10. In a woman with FGR and umbilical artery PI >95 centile with positive EDF, foetal biometry should be done

a. Every 2 weeks
b. Every week
c. Twice a week
d. Every 3 weeks

Answers of the November issue quiz: 1 (iii), 2 (iv), 3 (ii), 4 (iii), 5 (iii), 6 (iii), 7 (i), 8 (i), 9 (iii), 10 (i).

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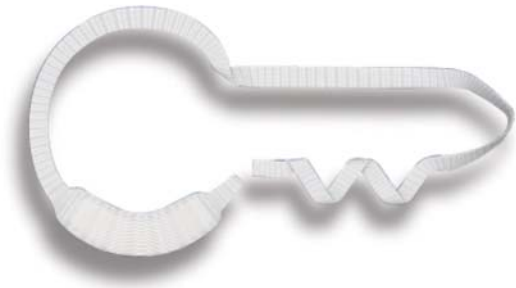

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1. Propess prescribing information dated June 2016

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- inaccurate time period of consumption

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- 2nd Test between 24 and 28 weeks of gestation
- 3rd Test around 32 - 34 weeks of gestation

Diagnosis (In pregnancy)	2-hour plasma glucose[3]
Normal	< 120 mg/dl
Gestational glucose intolerance	120 - 139 mg/dl
Gestational Diabetes Mellitus (GDM)	140 - 199 mg/dl
Diabetes	≥ 200 mg/dl

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