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MOGS MEDIA

Vol. 1 Preterm Birth

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President's Message

Dear friends,

Thank you for bestowing your faith in me and giving me the privilege of leading this fantastic organization, the Mumbai Obstetric and Gynaecological society, MOGS. Times have suddenly changed and we have to adapt to them. In this era of COVID19 and social distancing which will affect all of us for quite a long period of time,we have to keep ourselves abreast with all the latest information by digital means.

It gives me great pleasure to bring to you the first E-newsletter of the year 2020, **'MOGS MEDIA'**. This a series of focussed newsletters where we will be bringing to you an important subject discussed in detail with all the latest updates which will be relevant to you in your daily practise. This first issue is on the very common problem of Preterm birth and how we can best manage it. The editor Dr Pratik Tambe and all the contributors have made a lot of effort to bring you concise and precise information and we are thankful to them .

I really look forward to interacting with you on many different platforms this year-through newsletters, webinars, Facebook events, small group meetings and many more, till the situation of the pandemic settles down and we can have larger conferences again.

Thank you once again for all your support over the years and look forward to a wonderful year at MOGS.

Stay safe, stay healthy.
Best wishes.

"The only way to make sense out of change is to plunge into it, move with it, and join the dance."

— Alan Wilson Watts

Dr Rishma Dhillon Pai
President MOGS.

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Editors' message

Dear MOGS members,

It is with great pride that we bring you this first issue of the MOGS Media newsletter. The MOGS Media newsletter will be themed on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists.

This issue is centred around the issues surrounding the difficult topic of **“Preterm Birth”** and highlights the current evidence on this subject. We have chosen articles which highlight practical management tips, current guidelines and emerging areas of patient benefit.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative.

We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

Dr Pratik Tambe
Dr Madhuri Mehendale
Dr Mansi Medhekar
(Editors)

MOGS MEDIA NEWSLETTER

Vol 1 : Preterm Birth

Prediction of Preterm Labour

Dr Riddhi Desai

In prediction, lies the power to avert any undue medical condition. This, has been the centering thought and the driving force of modern medicine.

Preterm delivery has been defined by WHO as, babies born alive before 37 weeks of pregnancy are completed. It has been researched over the years and yet,prediction of labour whether at term or preterm remains elusive. The prevalence of preterm labour (PTL)is estimated to be 5–18% of all deliveries worldwide and is the leading cause of perinatal morbidity and mortality[1]. It reflects the need to re-evaluate quality of antenatal surveillance. Prognostication of PTLallows for targeted and timely interventions, thus reducing health, psychological and economic impact it causes.

Tests for prediction of PTL

PTLhas multifactorial aetiology and hence, no single test has shown strong evidence regarding their efficacy. Since there are no standard parameters, in practice we use a combination of tests, namely, identifying women at risk by clinical symptoms and signs, monitor cervical length by ultrasound or digital examination and screening for biochemical markers such as fetal fibronectin. The efficacy of these tests differs according to the purpose of the prediction, i.ewhether it is used in asymptomatic high-risk women or symptomatic women in threatened PTL, singleton or multiple gestation.

1. Risk Assessment[2-5]

Identification of therisk factors helps highlight the high-risk asymptomatic women, who can benefit from pre-emptive measure such as progesterone supplementation or cervical cerclage. Risk assessment in symptomatic women can help initiate precautionary measures including tocolysis, antenatal corticosteroid or magnesium sulphate administration or transfer to tertiary centres. Pre-conceptional counselling regarding these factors may also help to further reduce the risk. The various risk factors are summarised in **Table 1.** Numerous risk scoring systemshave been proposed, but their ability to identify women at increased risk or subsequently prevent PTL, have not been validated by large clinical trials. Risk factor assessment alone is unreliable, and over 50% of pregnancies that deliver preterm will fail to be identified.

Table 1 Risk factors for preterm delivery

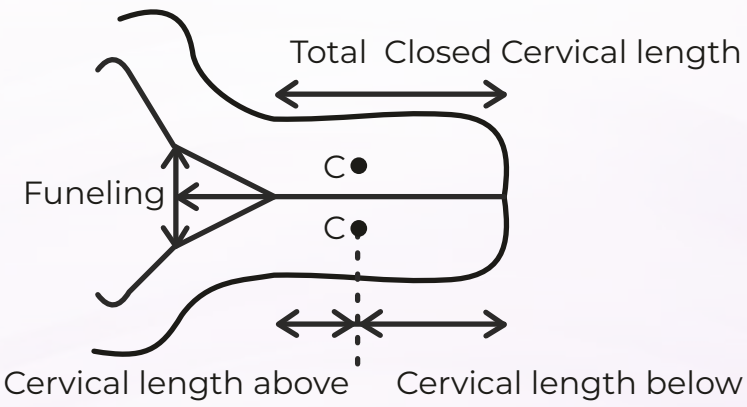
Maternal characteristics	Reproductive history	Current pregnancy characteristics
Family history of preterm birth Low socio-economic status Maternal age (low and high) Ethnicity Infections (genitourinary or extra genital) Uterine anomalies Periodontal disease History of cervical excisional procedures/surgery LEEP/conization) Stress Depression Tobacco use Low body mass index	Prior preterm birth Prior stillbirth/ Pregnancy loss >16 weeks GA Induced abortion Cervical insufficiency	Vaginal bleeding Use of assisted reproductive technologies Multiple gestation Polyhydramnios Short cervical length

2. Monitoring of Cervical Length (CL)[6-9]

Cervical shortening can in few cases be physiological or occurs due to multifetal gestations, infections or subclinical contractions. Cervical insufficiency is structural weakness of cervix associated with an increase in mid-trimester loss.

Transvaginal ultrasound (TVS) has become the gold standard and is superior to digital examination and transabdominal ultrasound. This is because the TVS technique of measuring cervical length (Figure 1) is standardised with good reproducibility and minimal interobserver variation.

Figure 1 Schematic representation of transvaginal ultrasonographiccervical measurements



The landmarks to be visualised during the measurement of cervix are the bladder, internal and external OS and the cervical canal. Additional features like the presence of funnelling, amniotic sludge or dilatation of the internal or external OS are to be noted. The dynamic changes can be assessed by taking the measurement over 5 mins. Serial assessment of CL at appropriate interval has proven to be a better than a single measurement.

There is conflicting evidence over the most beneficial time for measurement of CL. The earlier, short cervix is found, the greater the risk of PTL. CL<25mm(10th centile) for 24 weeks gestational age, increased the risk of PTLby 6-fold. CL<15 mm in symptomatic women with threatened PTL was found to be a sensitive predictor. CL assessed in mid-trimester asymptomatic twin pregnancies has been found to be a poor predictor. It is unclear, whether CL surveillance is equivalent to clinical assessment of the need for elective cerclage in those at risk of preterm delivery.

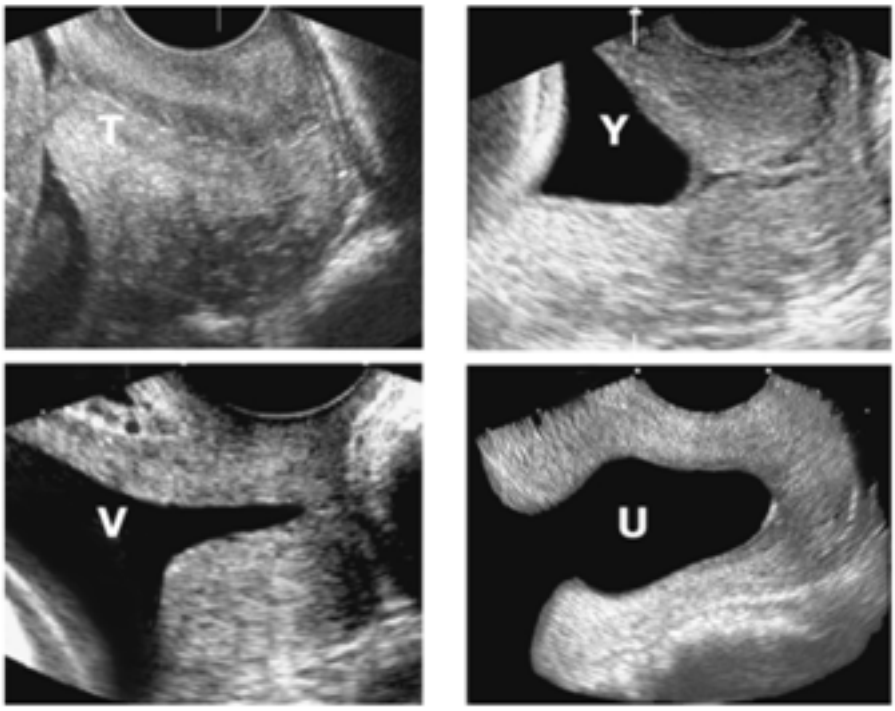
Cervical factors scoring has also been proposed where, a combined score of CL <2cms in TVS, Cervical score <1.5 on digital cervical exam, has proven to be a good indicator for preterm delivery.

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

CL as a single test cannot be reliably utilised to predict PTL due to limitations in ultrasound availability and operator expertise. In combination with risk assessment, it may prove to be the best possible indicator for therapeutic intervention.

Finding of cervical funnelling on TVS in combination with short cervix, has also been found to enhance the sensitivity of prediction of PTL. It is defined as dilation of the internal os of the cervix, with protrusion of the amniotic membrane 5 mm or more into the endocervical canal. It indicates early cervical ripening. This has been described in terms of the shapes observed on ultrasound: first a 'T'-shape before any dilation occurs; then a 'Y'-shape whilst some closed length of cervix remains; as effacement continues, the canal opens almost to the externalos, and the cervix appears as a 'V'; finally it appears as a 'U' as dilation progresses. Since the exact technique of determining funnelling has interobserver variability it is not a very reliable stand-alone test for prediction. **(Figure 2)**

Figure 2 Ultrasound images of the shapes of cervical funnelling



3. Fetal Fibronectin[10,11]

It is a glycoprotein found in the cervicovaginal secretion beyond 16 - 20 weeks gestation and after 34 weeks gestation. If found beyond 20 weeks gestation or elevated levels (> 50 ng/mL), it may suggest a disruption of the choriodecidual interface and is a predictor ofPTL.

It is the only test that is currently FDA approved and has a negative predictive value. A negative fetal fibronectin indicates a low probability of delivery within 7 to 14 days, even in the presence of contractions. This may prevent unnecessary hospitalization and medical intervention.

Routine screening for fetal fibronectin is not advised. It may be a valuable screening tool when women are reporting signs and symptoms ofPTLsuch as contraction or increased vaginal discharge. Ultrasonographic cervical length assessment and fetal fibronectin appear to be similar in predictive ability, and the combination of both in a high-risk population maybe of value.

4. Other tests[12-14]

Biological fluids including whole blood/serum/plasma, urine, saliva, amniotic fluid, and cervico vaginal fluid (CVF), are rich sources of proteins and have been studied for a suitable bedside test for predicting PTL.

Phosphorylated insulin-like growth factor binding protein-1 (PIGFBP-1) is secreted by decidual cells and leaks into cervical secretions when fetal membranes detach from decidua. It has a high negative predictive value, but poor positive predictive value.

Placental alpha-macroglobulin-1 (PAMG-1) is a glycoprotein synthesised in the decidua and found in high concentrations in the amniotic fluid. It has use in prediction ofpreterm rupture of the membranes and maybe it may be useful in PTL in symptomatic women with intact membranes.

New markers, Plasma concentrations of the N-acylethanolamines (NAEs) N-arachidonoylethanolamine (AEA), N-oleoylethanolamide (OEA) and N-palmitoylethanolamide (PEA), may have potential in the future.

Salivary estriol and progesterone, biomarkers related to inflammation, placentalproteins/hormones, angiogenesis, coagulation, proteomics and genetics, bacterial vaginosis testing in recent studies have not been promising as a predictor test.

Conclusions

The quest for finding a single accurate diagnostic predictor of PTL continues. 'One size fits all' cannot be applied be applied to these tests, customization and combination of tests can improve the utility of these tests. Summary of FIGO recommendations[15] and tests is given in Table 2 and 3.

Table 2 Summary of FIGO recommendations for prediction of PTL

1. Identification of symptomatic patients
2. Take into consideration new risk factors (age, medically assisted technologies for pregnancy, fetal male sex, psychosocial stress, previous cesarean section, etc.).
3. Before undertaking any therapeutic strategy, careful identification of women at risk for, so as to detect manageable conditions and fetal and/or maternal contraindications.
4. Combined use of cervical length measurements and biochemical markers, improves identification of symptomatic patients at risk for imminent spontaneous PTL
5. Of the available biochemical tests, that based on fetal fibronectin (fFN) has been the best characterized. However, the value of this test, like that of phosphorylated insulin-like growth factor protein-1 (phIGFBP-1) and cervical length measurement alone, may be limited only to their negative predictive value (NPV), given its poor positive predictive value (PPV).

6. While a CL< 1.5 cm and >3.0 cm has high predictive value. FIGO recommends the use of transvaginal ultrasound to measure CL in patients with symptoms of PTL
7. In patients in whom the CL is 1.5 cm- 3.0 cm, it may be recommended for a biomarker test with the highest combination of NPV and PPV to be run shortly after a vaginal examination. According to recent literature, this test seems to be that based on placental alpha-microglobulin-1 (PAMG-1; PartoSure).
8. Use of steroids should be reduced by adequate PTL risk assessment and by avoidance of early elective cesarean section. CL measurement, in combination with PAMG-1 testing can help to determine which women are at low risk of delivery within 7 days, and perhaps allow more judicious use of antenatal treatments.

Table 3 Summary of predictive tests

Test	Singleton Pregnancy		Multiple Pregnancy	
	Asymptomatic High Risk	Symptomatic threatened Preterm Labour	Asymptomatic High Risk	Symptomatic threatened Preterm Labour
Cervical length	+	+	+	
Fetal Fibronectin	+	+	+	+
Cervical length + Fetal fibronectin	++	++	+	

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Spontaneous Preterm Birth in Singleton ART Pregnancies

Dr Garima Sharma

Preterm birth (gestation of <37 weeks) is a global public health problem with more than one-third of neonatal deaths being directly attributable to it. Earlier, it was believed that ART increases the chance of preterm births mainly due to multifetal gestation.Elective single embryo transfer reduces the incidence of multiple pregnancy but does not reduce the risk of preterm delivery associated with in vitro fertilization (IVF).

Recent evidence

An elevated risk of preterm birth following ART has also been found for singleton pregnancies compared with non-ART singleton pregnancies[1]. Both singleton and multiple pregnancies resulting from assisted reproductive technologies have been shown to be at increased risk for a variety of obstetric complications, which may warrant the need for early delivery. However, the extent to which this is attributed to spontaneous preterm labour or to iatrogenic indications has not been determined.

A meta-analysis of cohort studies was conducted with an aim to quantify the risk of spontaneous PTB (sPTB) in singleton pregnancies resulting from IVF or ICSI treatment as compared with that in spontaneously conceived pregnancy.[2]

Out of a total sample size of 61,677 births, 8,044 singletons were conceived after IVF/ICSI and 53,633 conceived spontaneously. A data analysis showed significant increase in the incidence of sPTB < 37 weeks in singleton IVF/ICSI pregnancies compared with those conceived spontaneously (810/8,044 (10.1%) vs 2,932/53,633 (5.5%); odds ratio (OR), 1.75; 95% CI, 1.50-2.03; I2 =39%). A subgroup analysis of studies matching for maternal age and parity confirmed the finding (OR, 1.63; 95% CI, 1.30-2.05; I2=33%).

Analysis of the secondary outcomes (sPTB < 34 and < 32 weeks, preterm prelabour rupture of membranes, stillbirth, perinatal mortality, neonatal sepsis, respiratory distress syndrome and gastrointestinal morbidity) showed a significant increase in the incidence of sPTB < 34 weeks in pregnancies conceived after IVF/ICSI compared with those conceived spontaneously (37/1,012 (3.6%) vs 24/1,107 (2.2%); OR, 1.78; 95% CI, 1.03-3.08; I2=6%).The meta-analysis concluded that the risk of sPTB in singleton ART pregnancies is significantly greater than that in spontaneously conceived singletons.

Pathophysiology

Various theories have been hypothesized to explain increased risk of spontaneous preterm births in singleton ART pregnancies:

First-trimester combined screening in IVF/ICSI pregnancies following fresh embryo transfer shows increased concentrations of free -human chorionic gonadotropin and a reduced concentration of pregnancy-associated plasma protein.[3] These biomarkers indicate abnormal placentation and possibly anomalous outcomes like spontaneous preterm births in IVF/ICSI pregnancies.

Higher risk of placental insufficiency in IVF / ICSI pregnancies leads to fetal hypoxemia or chronic placental inflammation and this may contribute to sPTBin this, group.[4] Therefore, it is believed that placental development plays a key role in the pathogenesis of sPTB in IVF/ICSI pregnancies.

Virtually all IVF/ ICSI cycles involve controlled ovarian hyperstimulation with injectable gonadotropins, therefore the resulting pregnancies are associated with multiple corpora lutea. Relaxin, a peptide hormone is produced by the corpus luteum of pregnancy which stimulates procollagenase (MMP-1) and prostromelysin-1 (MMP-3) production while decreases the production of tissue inhibitor of metalloproteinase-1 (TIMP-1).As a result of these changes relaxin hormone acts as a potent stimulator of collagen breakdown.

The increased relaxin levels observed in gonadotropin-stimulated pregnancies do not fall after the first trimester and persist for the duration of pregnancy.Collagen breakdown plays an important role in the increased elasticity necessary for cervical effacement and dilatation during labour and this may explain increased risk of spontaneous preterm births in IVF/ICSI pregnancies.[5]

Although other luteal products are also important, relaxin provides a plausible link between excess luteal function and premature cervical change and hence preterm delivery. Also, relaxin levels are more closely linked to the number of corpora lutea than to the presence of twins or triplets, therefore all pregnancies resulting from gonadotropin stimulation would be at risk, not just multiple pregnancies.[6]

Women conceiving after IVF/ICSI are a special population of pregnant women. They are generally older than women conceiving spontaneously due to long years of infertility. Infertility itself is a known risk factor for preterm birth.

The different causes (endometriosis, adenomyosis, polycystic ovary syndrome, uterine fibroids) and unexplained infertility share inflammatory pathways, hormonal aberrations, decidual senescence and vascular abnormalities, thereby predisposing infertile women to high risk of spontaneous preterm births.[7]

There is substantial evidence that very preterm birth is connected to vanishing of one gestational sac.[8]

Extended culture upto Day 5 as seen in blastocyst transfers may cause potential genetic or epigenetic effects on the trophectoderm cells, leading to impaired implantation and placentation forming the basis for a higher risk of preterm birth. This theory is supported by several animal studies that show effects of extended embryo culture environment on blastocyst quality and gene expression.[9]

Pregnancies from frozen thawed embryo transfer cycles may have a more natural uterine environment which is favourable for early placentation and embryogenesis, whereas ovarian stimulation in fresh cycles alter endometrial angiogenesis and implantation and therefore increased risk of spontaneous preterm birth.[10]

Another explanation put forward for better results in pregnancies subsequent to frozen ET is that the physical effects of freezing and thawing embryos may filter out weaker embryos and allow only good quality ones to survive, resulting in better fetal growth.

Implications for clinical practice and future research

A recent meta-analysis by Cavorettoet al shows that singleton pregnancies conceived after IVF/ICSI are at a higher risk of sPTBin comparison to spontaneous conception. Screening for sPTB in IVF/ICSI pregnancies is advisable in order to apply preventive strategies. The paucity of available data on the etiological differentiation of PTB in IVF/ICSI is critical and should stimulate researchers to present these outcomes in the future.

Further research on different subgroups of ART pregnancy is required to establish the etiology of sPTB (infertility, assisted reproductionand abnormal placental function). It is strongly recommended that clear classification of core outcomes of PTB, primarily distinguishing between spontaneous and iatrogenic forms of PTB should be done.

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Prophylactic Cervical Cerclage

Dr Rohan Palshetkar

Cervical insufficiency

Cervical insufficiency is the inability to retain a pregnancy in the absence of contractions or labor. It is a clinical diagnosis characterised by recurrent painless cervical dilation and spontaneous mid trimester loss of a viable foetus. It is usually a clinical retrospective diagnosis after a poor obstetric outcome.

With an increase in fertility treatments, the rate of multiple pregnancies is on the rise. Multiple gestation pregnancies are associated with a higher incidence of maternal and neonatal complications. Spontaneous preterm birth is one of these complications. It is usually associated with short cervical length which is an indicator of preterm delivery. Several methods have been proposed to reduce the incidence of preterm labour.

Other treatments

Conflicting opinions exist regarding the effectiveness of bed rest. Vaginal progesterone has been shown to be beneficial in high-risk singleton pregnancies. However, in multiple pregnancies, the rate of preterm delivery remained unchanged following the use of vaginal progesterone.[1],[2] A cervical pessary has been proposed as a means of preventing preterm delivery. The pessary insertion is a non-invasive, easy procedure that does not require anaesthesia. However, its efficacy is controversial and under investigation.

Transabdominal cerclage

Transabdominal cervical cerclage (TAC) was first described in 1965 and has been proposed in cases where vaginal cerclage is difficult to perform mainly due to anatomical difficulties. Transabdominal cerclage is applicable in cases of shortened or absent cervix or radical trachelectomy[3] and may be used in cases of failed vaginal cerclage.[4]

Vaginal cerclage

Important drawbacks are, however, associated with transabdominal cerclage. These include an increased intraoperative risk, due to the position of the abdominal suture, extended hospital stay and increased risk of infection.[5] Even though the abdominal approach is beneficial, as the suture can be placed higher on the cervix, the patient must undergo one laparotomy or laparoscopy for placement of the cerclage and a second operation for cesarean delivery.[3]

Vaginal cervical cerclage was introduced by Shirodkar and MacDonald in the 1950s. A suture is used in order to reinforce the cervix during pregnancy, ultimately increasing the mechanical strength of the cervix and avoiding dilatation and premature delivery.

Ultrasound indicated cerclage and rescue cerclage

Multiple pregnancies often show cervical shortening. It has been proposed that bi-weekly ultrasound monitoring of the cervical length in multifetal pregnancies is an option and once the cervix is shortened to ≤ 25 mm to proceed to ultrasound-indicated cervical cerclage. However, it has been shown that ultrasound examination, even of twin pregnancies, shows dynamic, rapid changes of the cervical length in pregnancies delivered preterm, compared to those delivered at term.

All of the above indicate that the obstetrician should not rely only on ultrasound monitoring of the cervix in multiple pregnancies, as the progress of the cervical length in such pregnancies is unpredictable. Moreover, the application of emergency cerclage did not show a good outcome in the majority of twin pregnancies as reported by Gupta et al. Of the 11 applications of emergency cerclage in twin pregnancies, only two showed a good outcome (18%).[6]

This low success rate of emergency cervical cerclage further supports the need for a prophylactic elective cervical cerclage. One must take the decision to proceed to elective cervical cerclage instead of expectant wait and emergency/rescue cervical cerclage if indicated. The literature so far indicates that emergency cervical cerclage does prolong the pregnancy but shows a high level of chorioamnionitis and preterm premature rupture of the membranes.

Prophylactic cerclage

The beneficial effect of prophylactic cerclage in multiple pregnancies was made apparent more than two decades ago. In 1999, Elimian et al showed that prophylactic cerclage in triplet pregnancies reduced the incidence of extremely low birth weight neonates and the majority of pregnancies delivered after 31 weeks gestation.[7]

One of the advantages of a prophylactic cerclage, that patients do not have to be in complete bed rest and the associated psychological and socioeconomic issues are avoided. Therefore, a prophylactic cerclage maybe should be considered in indicated cases.

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Progesterone Supplementation for Prevention of Preterm Birth

Dr Mansi Medhekar

Preterm birth(PTB) is one of the most common complications during pregnancy and is an important cause neonatal mortality and morbidities, including long term consequences such as cerebral palsy and developmental disability.

The most effective prevention strategy is prediction of risk factors. Most predictive risk factors of PTB include a previous history of PTB and short cervical length. Relatively less predictive risk factors include – multiple pregnancy, smoking, uterine anomaly and history of curettage and cervical conization.

Progesterone supplementation therapy is one of the few proven effective methods to prevent PTB in high risk women.The efficacy of progesterone supplementation for prevention of PTB depends primarily on appropriate patient selection.

In 2003, 2 randomized, double-blind, placebo-controlled trials demonstrated that progesterone supplement therapy can prevent PTB in women with past history of PTB. Many following studies were carried out and now the American Congress of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend the usage of progesterone to prevent PTB in certain pregnant women — those with history of spontaneous PTB, such as preterm labour and premature rupture of membranes, and those with short CL during the mid-trimester.[1]

Type, routes, dose, and interval of administration

Type	Route	Dose	Interval
17 alpha hydroxyprogesterone caproate	Intramuscular	250mg	weekly
Natural micronized progesterone	Vaginal suppository	100,200,400mg	daily
	Vaginal gel	90mg	daily
	Oral capsule	100,200,400mg	daily

It has not been fully elucidated whether which progesterone therapy is better with regard to the efficacy of preventing PTB, cost-effectiveness or side effects. The choice of drug would depend upon the availability, affordability, practitioner's preference and patient's choice.

Clinical scenarios

Pregnancies likely to benefit from progesterone supplementation

- In women who have had a previous spontaneous preterm singleton birth and
- In women with a short cervix on ultrasound examination in the current pregnancy.

Pregnancies where the benefit of progesterone supplementation is unclear

The benefit of progesterone supplementation in women at high risk of preterm birth, but without a short cervix or a prior history of singleton spontaneous preterm birth, is not supported by strong evidence.

Singleton pregnancy with spontaneous twin preterm birth in prior pregnancy

A prior spontaneous preterm birth is a risk factor for a subsequent spontaneous preterm birth whether the initial preterm delivery was a singleton or a twin pregnancy.[2,3] No study has specifically evaluated whether progesterone supplementation decreases the risk of a preterm birth of a singleton after a previous spontaneous preterm birth of twins, but a benefit is plausible.

After cerclage

In women with short cervix without prior history of spontaneous preterm, if cerclage is performed for short cervix, adjuvant treatment with progesterone has not shown any significant benefit. However, in practice many obstetricians do prefer to supplement these women with vaginal progesterone.

After preterm prelabour rupture of membranes

Beginning progesterone supplementation is not beneficial in women who develop preterm prelabour rupture of membranes (PPROM) in the current pregnancy. By contrast, women with a history of preterm birth due to PPROM appear to benefit from progesterone supplementation in subsequent pregnancies.[4]

Maintenance therapy after threatened preterm labour

Use of progesterone in women who remain undelivered after an episode of threatened preterm labour is investigational, although most practitioners routinely prescribe progesterone supplementation for maintenance tocolysis.[5]

Multiple gestation

Progesterone is not effective in unselected multiple gestations. One reason may be that the pathogenesis of preterm labour and delivery in multiples is different from that in singletons and less impacted by changes in progesterone.[6]

Uterine anomaly or assisted reproductive technology

Women with some uterine anomalies and those who conceive with assisted reproductive technology appear to be at increased risk of preterm birth. The effectiveness of progesterone therapy for prevention of spontaneous preterm birth in these women is unknown.

Recommendations for progesterone supplementation to prevent pretermbirth[7]

Indication	Progesterone supplementation indicated?	Management
Singleton pregnancy Prior spontaneous PTBNormal cervical length	Yes	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks of gestation and continuing through 36 weeks of gestation or until delivery and monitor cervical length. Natural micronized progesterone administered vaginally is a reasonable alternative.Short (≤25 mm) cervix →
Singleton pregnancy, prior spontaneous twin PTB Normal cervical length	Possibly	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks of gestation and continuing through 36 weeks of gestation or until delivery and monitor cervical length. Natural micronised progesterone administered vaginallyis a reasonable alternative. Short (≤25 mm) cervix → consider performing
Singleton pregnancy No prior spontaneous PTB Short cervix (≤20 mm)	Yes	Micronised Progesterone 200 mg vaginally each night from time of diagnosis through 36 weeks of gestation. Other options include 8 percent vaginal gel containing 90 mg micronized progesterone per dose.
Multiple pregnancy (twins or triplets) without prior PTB Normal cervical length	No	No progesterone ,no cerclage

Twins, prior PTB	Possibly	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks of gestation and continuing through 36 weeks of gestation or until delivery and monitor cervical length. Natural micronized progesterone administered vaginally is a reasonable alternative
Twins, short cervix	Possibly	Vaginal progesterone, no cerclage
Preterm premature rupture of membranes	No	
Undelivered after an episode of preterm labour	No	

Summary and recommendations

Progesterone supplement therapy is effective in prevention of PTB. However, its efficacy varies depending on the indication and type, administration route, and dose of progesterone.

For singleton pregnant women with history of spontaneous PTB, including preterm labour and premature rupture of membranes, weekly injection of 250 mg of 17 -OHPC, as well as daily administration of vaginal micronized progesterone suppository (100 or 200 mg) are effective in preventing recurrent PTB, but the preventative effects of vaginal progesterone gel or oral progesterone capsules currently lack evidence.

For singleton pregnant women with CL <25 mm during mid trimester, daily administration of vaginal micronized progesterone suppository (100 or 200 mg) or gel (90 mg every day) is effective in preventing PTB, but the preventative effect of 17 -OHPC therapy lack evidence.

In women with twin pregnancy, an injection of 17 -OHPC nor an administration of vaginal micronized progesterone suppository or gel could prevent PTB. Yet, for twin pregnant women with short CL, vaginal progesterone supplement therapy may be effective for reducing the rate of PTB and improving the neonatal outcome.

As a maintenance therapy after the inhibition of preterm labour, 17 -OHPC cannot prevent PTB but can extend the gestational age and increase the birth weight.

Both vaginal and oral micronized progesterone treatment can prevent PTB <37 weeks of gestation, extend the gestational age, and increase the birth weight. Yet the exact role of progesterone as a maintenance therapy after the inhibition of preterm labour remains much to be discovered.

In cases of premature rupture of membranes, there lacks evidence on the effect of progesterone supplement therapy in preventing PTB.

The progesterone supplement therapy generally begins at 16 to 24 weeks of gestation and ends at 34 to 36 weeks of gestation.

No evidence currently exists on which progesterone supplement therapy can maximize the preventative effects while minimizing the side effects.

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Atosiban: An Advance In Tocolytics

Dr Madhuri Mehendale

Preterm birth is strongly associated with neonatal death and long-term neurological morbidity. The purpose of tocolytic drug administration is to postpone threatening preterm delivery for at least 48 hours to allow the maximal effect of antenatal corticosteroids and maternal transportation to a center with specialized neonatal care facilities.

Oxytocin has long been ascribed an important role in the initiation of term and preterm labor. Among several pathophysiological processes ongoing with the initiation of preterm labor, the most important is an earlier increase in the concentration of oxytocin receptors in the myometrium. Oxytocin stimulates myometrial contractions through a number of signaling pathways. Therefore, oxytocin receptors are commonly used as targets for the development of tocolytics, and the only drugs developed specifically for the management of preterm labor are oxytocin receptor antagonists.

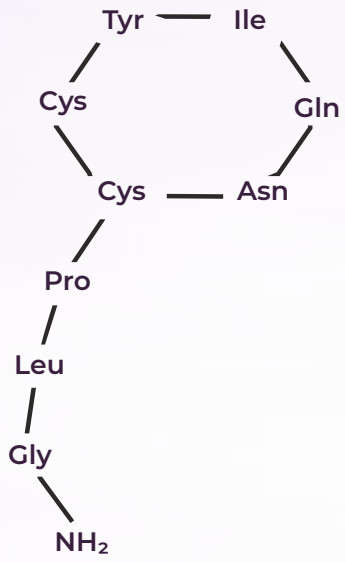
Atosiban, a chemically synthesized Nona peptide of oxytocin, is a competitive antagonist of oxytocin at uterine oxytocin receptors and has been developed as a new tocolytic therapy in the treatment of preterm labor. It acts in a dose-dependent manner with no evidence of tachyphylaxis.

Physical and chemical properties:

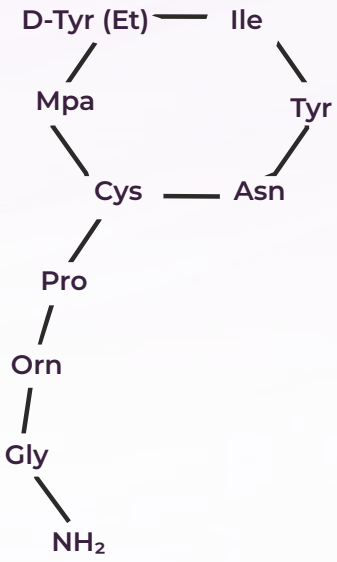
It is a white to off-white, highly hygroscopic, freeze-dried amorphous powder which is soluble in water. Storage is to be done at 2-8 degrees centigrade. Protection from light is advised.

Molecular formula: $C_{43}H_{67}N_{11}O_{12}S_2$

It resembles oxytocin ($C_{43}H_{66}N_{12}O_{12}S_2$) with the modifications at **1, 2, 4** and **8** positions. The N-terminus of the cysteine residue is deaminated to form **3**-mercaptopropanic acid at position **1**, at position **2** L-tyrosine is modified to D-tyrosine with an ethoxy group replacing the phenol, threonine replaces glutamine at position **4** and ornithine replaces leucine at position **8**.



Oxytocin



Atosiban

Mechanism of action

Oxytocin acts on the genesis of uterine contractions through two separate pathways. First, by binding to its receptors on the smooth muscle cell membranes, it increases the intracellular concentration of calcium through the inositol triphosphate (IP3) pathway and via activation of calcium channels. Secondly, it induces prostaglandin secretion in the decidua and fetal membranes via the diacylglycerol pathway. A paracrine effect causes these prostaglandins to act on uterine smooth muscle cells and cause muscle contraction.

Atosiban binds to membrane-bound oxytocin receptors on the myometrium and prevents oxytocin-stimulated increases in inositol triphosphate production. This ultimately prevents the release of stored calcium from the sarcoplasmic reticulum and the subsequent opening of voltage-gated calcium channels. This block of cytosolic calcium increase prevents contractions of the uterine muscle, decreasing the frequency of contractions and inducing uterine quiescence.

Atosiban has more recently been found to act as a biased ligand at oxytocin receptors. It acts as an antagonist of Gq coupling, explaining the inhibition of the inositol triphosphate pathway thought to be responsible for the effect on uterine contraction, but acts as an agonist of Gi coupling. This agonism produces a pro-inflammatory effect in the human amnion, activating pro-inflammatory signal transducer NF-κB. It is thought that this reduces Atosiban's effectiveness compared to agents that do not produce inflammation as inflammatory mediators are known to play a role in the induction of labour.

Pharmacokinetics: In women receiving 300 µg/min by intravenous infusion for 6-12 hours, average steady-state concentrations of 442 ng/mL were reached within one hour. Steady-state concentrations increase proportionally to the dosage of the drug.

Atosiban has a mean volume of distribution of 41.8 L. It crosses the placenta and, at a dose of 300 µg/min, maternal/fetal concentration ratio of 0.12 is found. Drug concentrations in the fetal circulation do not increase with longer infusion rates, suggesting that the drug does not accumulate in the fetus. Atosiban is 46-48% bound to plasma proteins in pregnant women. It is not known to partition into red blood cells. Differences in the free fraction of the drug between the maternal and fetal compartments are unknown.

It is metabolized to two metabolites created through the cleavage of the peptide bond between ornithine and proline, which is thought to be facilitated by prior cleavage of the disulfide bridge. The larger fragment remains active as an antagonist of oxytocin receptors but is ten times less potent than the parent molecule. At a dosage of 300 µg/min, the ratio of parent molecule to the primary metabolite is observed to be 1.4 at the second hour and 2.8 at the end of the infusion. Small amounts of Atosiban are also found in the urine, with 50 times the amount appearing as the large fragment metabolite of oxytocin. The amount of drug excreted in the feces is not known. It has a mean clearance rate of 41.8 L/h.

Pharmacodynamics:

Atosiban decreases the frequency and tone of uterine contractions. The onset of uterine relaxation is rapid. Contractions significantly reduce within 10 minutes to achieve stable uterine quiescence (<= 4 contractions per hour) for 12 hours.

Indications:

Atosiban is indicated for use in delaying imminent preterm birth in pregnant adult women with:

- Regular uterine contractions of at least 30 seconds duration at a rate of at least four contractions per 30 minutes.
- Cervical dilation of 1-3 cm (0-3cm for nulliparas) and effacement of at least 50%
- Gestational age of 24-33 weeks
- A normal fetal heart rate

According to RCOG guidelines, Atosiban is the preferred agent for tocolysis and is licenced to be used.

Recently, Atosiban has also been used in Artificial Reproductive Technology during Embryo Transfer. Atosiban treatment before embryo transfer is effective in the priming of the uterus for implantation. It improves uterine receptivity by:

- Reducing uterine contractions
- Reduction in intrauterine PGF2 production
- Improving uterine blood supply: it preferentially relaxes uterine arteries, which increases uterine perfusion

Dosage: Initially, 6.75 mg bolus (as 7.5 mg/mL solution) over 1 min is given, immediately followed by continuous infusion (as 0.75 mg/mL solution) of 0.3 mg/min for 3 hours, then 0.1 mg/min for up to 45 hours. The total duration of treatment should be ≤48 hours. The maximum dose that can be given is 330.75 mg in 48 hours.

Step	Regimen	No. of Vials	Atosiban Dose in ml	Atosiban Dose in mg	Atosiban Dose in minuite	Drip rate		Time
						With 500 ml infusion bottle	With 100 ml infusion bottle	
1	Intial bolus IV injection over 1 min.	1	0.9 ml	6.75 mg	6.75 mg given over 1 min	Bolus Injection	Bolus Injection	1 minute
2	Continuous Intravebous loading infusion for 3 hrs	1.5	7.5 ml (5 ml + 2.5 ml)	56.25 mg	300 mcg / min	60 drops / min	12 drops / min	3 hours
3	Subsequent Intravenous infusion	1.5 every 9 hrs	7.5 ml (5 ml + 2.5 ml) every 9 hours for 5 times	281.25 mg	100 mcg / min	20 drops / min	4 drops / min	9 hours (To be repeated at the end of every 9 hrs for times upto 45 hrs)

Adverse effects:

Side effects are rare. The most common side effects are gastrointestinal, like nausea and vomiting. Cardiovascular effects like hot flushes, hypotension, and tachycardia may also be seen. Headache, dizziness, hyperglycemia, injection site reactions, insomnia, pruritus, rash, pyrexia, uterine hemorrhage, and atony are other rare adverse effects. No specific adverse reaction is seen in the newborn. It is more efficacious than -agonists and much safer, with a 10-fold decrease in cardiovascular side effects and a 15-fold decreased need to discontinue treatment owing to unacceptable side effects.

Contraindications:

Gestational age <24 or >33 weeks, premature rupture of membranes >30 weeks of gestation, uterine hemorrhage requiring immediate delivery, eclampsia, severe pre-eclampsia, intrauterine growth retardation, abnormal fetal heart rate, intra-uterine fetal death, suspected intra-uterine infection, placenta praevia, abruptio placentae, any other condition of the mother and the

fetus in which continuation of the pregnancy is hazardous and hypersensitivity to Atosiban or excipients.

Renal impairment is not likely to warrant a dose adjustment. But, it should be used with caution in hepatic impairment. Its safety and efficacy in pregnant females < 18 years of age have not yet been established.

Drug interactions:

Atosiban is not involved in CYP450 mediated drug-drug interactions. No clinically relevant interaction has been found between Atosiban, betamethasone, and labetalol. However, a few cases have reported an increased risk of pulmonary edema with other tocolytic drugs.

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Magnesium Sulfate for Fetal Neuroprotection

Dr Pratik Tambe

NICE Guideline: Preterm Labour and Birth

The NICE guideline no 25 on Preterm Labour and Birth published November 2015 was last updated on 2nd August 2019.[1] The evidence was reviewed and new recommendations were made on the effectiveness of prophylactic vaginal progesterone and prophylactic cervical cerclage. Changes were also made without an evidence review viz.,

- Recommendations to show cervical length of 25 mm or less is indicative of high risk of preterm birth
- Updated recommendations for erythromycin and magnesium sulfate
- Updated time period when corticosteroids are offered to women with suspected preterm labour
- Updated advice on tests in case scenarios of PPROM

As per the NICE Guideline NG 25, the use of magnesium sulfate for fetal/neonatal neuroprotection in the setting of preterm birth is now strongly recommended as there is ample evidence of benefit:

1.10.1 For women between 23+0 and 23+6 weeks of pregnancy who are in established preterm labour or having a planned preterm birth within 24 hours, discuss with the woman (and her family members or carers as appropriate) the use of intravenous magnesium sulfatefor neuroprotection of the baby, in the context of her individual circumstances. [2019]

1.10.2 Offer intravenous magnesium sulfate for neuroprotection of the baby to women between 24+0 and 29+6 weeks of pregnancy who are:

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

1.10.3 Consider intravenous magnesium sulfatefor neuroprotection of the baby for women between 30+0 and 33+6 weeks of pregnancy who are:

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

1.10.4 Give a 4 g intravenous bolus of magnesium sulfate over 15 minutes, followed by an intravenous infusion of 1 g per hour until the birth or for 24 hours (whichever is sooner).

1.10.5 For women on magnesium sulfate, 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.

1.10.6 If a woman has or develops oliguria or other signs of renal failure:

- monitor more frequently for magnesium toxicity
- think about reducing the dose of magnesium sulfate.

Largest meta-analysis

A meta-analysis in 2016 based on PRISMA Guidelines studied 10 trials including 6 randomised controlled trials and 5 cohort studies involving 18,655 preterm infants. The primary outcomes included fatal death, cerebral palsy (CP), intraventricular hemorrhage, and periventricular leukomalacia.[2]

MgSO4 showed the ability to reduce the risk of moderate to severe CP which was statistically significant (odds ratio [OR] 0.61, 95% confidence interval [CI] 0.42-0.89, P=0.01). The comparison of mortality rate between the MgSO4 group and the placebo group but did not reachstatistical significance (OR 0.92, 95% CI 0.77-1.11, P = 0.39). They concluded that MgSO4 is both beneficial and safe to be used as a neuroprotective agent for premature infants before a valid alternative is discovered.

Neuroprotection in growth restricted fetuses

The Canadian Preterm Birth Network Investigators found that of 336 growth-restricted fetuses born before 29 weeks, 112 (33%) received magnesium sulfate. Intrapartum magnesium sulfate was associated with reduced odds of composite of death or significant neurodevelopmental impairment for infants classified according to both fetal standards (OR 0.42; 95% CI, 0.22-0.80) and neonatal standards (OR 0.44; 95% CI 0.20-0.98).[3]

Meta-analysis Mar 2020

In a more recent meta-analysis, a group of researchers identified six eligible trials (5,917 women). They found that MgSO4 intervention in women at imminent risk for preterm birth decreased the offspring's CP risk (RR 0.68, 95% CI 0.54-0.85; TSA RR 0.69, 95% CI 0.48-0.97).[4]

MASP Research Group RCT April 2020

14 Danish obstetric departments collaborated in a double blind randomised placebo controlled multicentric trial from Dec 2011 to Jan 2018 where 560 women at risk for preterm delivery received 5 gm MgSO4 loading dose followed by 1 gm/hr. The children born were followed up at a corrected age of 18 months.

The rates of moderate to severe CP were lower in the MgSO4 group (2% vs 3.3% respectively OR 0.61 95%CI 0.23 - 165). The researchers concluded that antenatal MgSO4 before 32 weeks of gestation decreases the likelihood of moderate to severe CP.[5]

Optimum dose and duration

Brookfield KF et al in a recent article studied different dosing regimens with a view to finding the optimum dose of the drug and the duration for which it could be safely administered without maternal/fetal compromise.

Retrospective secondary analysis of the beneficial effects of antenatal magnesium sulfate trial database and prospective pharmacokinetic/pharmacodynamic modelling indicatedthat magnesium sulfate administration for duration longer than 18 h, given within 12 h of delivery and maintaining a maternal serum level of 4.1 mg/dL may maximise the neuroprotective benefits of the drug.[6]

Neonatal benefits

A PLOS Medicine meta-analysis of five trials with 5,493 women and 6,131 babies showed that there was a significant reduction in the risk of death or CP with magnesium sulphate treatment compared with no treatment (RR 0.86, 95% CI 0.75 to 0.99, 4,448 babies, 4 trials), with no significant heterogeneity (p = 0.28). The number needed to treat (NNT) to benefit was 41 women/babies to prevent 1 baby from either dying or having CP.

For cerebral palsy in survivors, magnesium sulphate treatment had a strong protective effect in both the overall analysis (RR 0.68, 95% CI 0.54 to 0.87, 4,601 babies, 5 trials, NNT to benefit 46) and the neuroprotective intent analysis (RR 0.68, 95% CI 0.53 to 0.87, 3,988 babies, 4 trials, NNT to benefit 42).

The treatment effect varied little by the reason the woman was at risk of preterm birth, the gestational age at which magnesium sulphate treatment was given, the total dose received, or whether maintenance therapy was used.

They concluded that antenatal magnesium sulphate given prior to preterm birth for fetal neuroprotection prevents CP and reduces the combined risk of fetal/infant death or CP. Benefit is seen regardless of the reason for preterm birth, with similar effects across a range of preterm gestational ages and different treatment regimens. Widespread adoption worldwide of this relatively inexpensive, easy-to-administer treatment would lead to important global health benefits for infants born preterm.[7]

Conclusions

There is now an overwhelming surfeit of evidence in favour of administration of magnesium sulphate for fetal neuroprotection. This should be adopted by obstetricians in proven cases of preterm labour and should form a part of standard teaching in training curricula.

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Enhances uterine quiescence: Controls uterine contractibility and cervical competence[1,2]

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE 2018

Vaginal Progesterone Capsule is more effective than Dydrogesterone, 17-OHP injection & Oral progesterone for Prevention of Preterm Birth in women with short cervix (CL≤ 25 mm)[3]

Vaginal Progesterone Capsule prevented Preterm Birth in 94.1% women with short cervix compared to Cerclage (73.3%) and others - Dydrogesterone/17-OHP/ OP (8.3%)[3]

For the use of registered medical practitioner or a hospital or a laboratory only.

1. Czyzyk A et al. Gynecol Endocrinol. 2017 Jun;33(6):421-424. 2. Shah D, Nagarajan N, Indian J Endocrinol Metab. 2013 Jan;17(1):44-9 3. Pustotina O et al. J Matern Fetal Neonatal Med. 2018 Jul;31(14):1830-1838.
17-OHP: 17-hydroxyprogesterone caproate injection, OP: oral progesterone, CL: Cervical Length

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ABPI:

Composition: Tosiban 6.75 mg/0.9 ml & Tosiban 37.5mg/5 ml. **Therapeutic Indications:** Tosiban is indicated to delay imminent pre-term birth in pregnant adult women with pre-term labour diagnosed between gestational age from 24-33 completed weeks. **Posology & Method of Administration:** Tosiban is administered intravenously in three successive stages: an initial bolus dose of 0.9 ml (6.75mg) immediately followed by a loading infusion 300 micrograms/min of Tosiban 37.5 mg/5 ml during three hours, followed by 100 micrograms/min of Tosiban 37.5mg/5 ml up to 45 hours. **Contraindications:** Hypersensitivity to atosiban. **Drug Interactions:** Atosiban is not involved in clinically relevant drug-drug interactions. **Special Warnings & Precautions:** Renal impairment does not require a dose adjustment. In impaired hepatic function, atosiban should be used with caution. **Adverse Drug Reactions (ADRs):** Nausea is the most commonly reported ADR in mother. For the newborn, the clinical trials and post-marketing surveillance did not reveal any specific ADR. **Special Precautions for Storage:** Store in a refrigerator (2°C -8°C). Store in the original package in order to protect from light.
(For detailed information please write to Zuventus Healthcare Limited, 5119, 5th floor, D-Wing, Oberoi Garden Estates, Chandivali, Andheri (E), Mumbai 400 072 or email to medico@zuventus.com).

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