SCIENTIFIC LETTER

DOI: 10.5336/jcog.2020-78741

GUIDELINE ON PRETERM LABOR AND DELIVERY by the Society of Specialists in Perinatology (Perinatoloji Uzmanları Derneği-PUDER), Turkey

Metin ALTAY[a], Merih BAYRAM[b], Aydan BİRİ[c], Esra ESİM BÜYÜKBAYRAK[d], Özgür DEREN[e], Fedi ERCAN[f], Derya EROĞLU[g], Aytül ÇORBACIOĞLU ESMER[h], Cihan İNAN[ı], Hakan KANIT[i], K. Emre KARAŞAHİN[j], M. Tamer MUNGAN[k], Özlem PATA[l], Berkan SAYAL[m], Hakan TİMUR[n], Miğraci TOSUN[o], Mert TURĞAL[ö], Nihal ŞAHİN UYSAL[p], Filiz F. YANIK[r]

[a]Private Clinic, Ankara, TURKEY
[b]Division of Perinatology, Gazi University Faculty of Medicine, Ankara, TURKEY
[c]Division of Perinatology, Koru Hospitals, Ankara, TURKEY
[d]Division of Perinatology, Marmara University Faculty of Medicine, İstanbul, TURKEY
[e]Division of Perinatology, Hacettepe University Faculty of Medicine, Ankara, TURKEY
[f]Division of Perinatology, Şanlıurfa Training and Research Hospital, Şanlıurfa, TURKEY
[g]Division of Perinatology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, TURKEY
[h]Division of Perinatology, Biruni University Faculty of Medicine, İstanbul, TURKEY
[ı]Division of Perinatology, Trakya University Faculty of Medicine, Edirne, TURKEY
[i]Private Clinic, İzmir, TURKEY
[j]Division of Perinatology, Gülhane Faculty of Medicine, Ankara, TURKEY
[k]Division of Perinatology, Koru Hospitals, Ankara, TURKEY
[l]Division of Perinatology, Acıbadem Mehmet Ali Aydınlar University Faculty of Medicine, İstanbul, TURKEY
[m]Division of Perinatology, Health Science University Antalya Training and Research Hospital, Antalya, TURKEY
[n]Division of Perinatology, Ordu University Training and Researh Hospital, Ordu, TURKEY
[o]Division of Perinatology, Ondokuz Mayıs University Faculty of Medicine, Samsun, TURKEY
[ö]Division of Perinatology, Koç University Faculty of Medicine, İstanbul, TURKEY
[p]Division of Perinatology, Başkent University Faculty of Medicine, Ankara, TURKEY
[r]Private Clinic, Ankara, TURKEY

This guideline is prepared as a consensus report of the Preterm Labor and Delivery Workshop of PUDER, in Bolu, on 22 February 2020.
The authors are listed according to the alphabetic order of surnames.

ABSTRACT Preterm delivery (PTD) occurs between $20^{0/7}$-$36^{6/7}$ weeks of pregnancy and is a major cause of perinatal mortality and morbidity. The prevalence is around 12% in Turkey, ranging between 10 to 15% in different centers. Indicated preterm deliveries due to maternal or fetal reasons constitute approximately 20-30% of the total. The rest occur as a result of spontaneous preterm labor (PTL) or preterm prelabor rupture of the membranes (PPROM), about half and half. Although etiology of spontaneous preterm birth has not been fully elucidated, several risk factors are defined. History of PTD and short cervix are two most important risk factors, particularly in singleton pregnancies. If the cervical length is measured to be <25 mm via transvaginal ultrasonography before the 32nd gestational week, it is defined as short cervix. In women with prior PTD, progesterone preparations are recommended between 16th-36th gestational weeks and cervical length is monitorized; additional preventive measures may be required if short cervix is diagnosed. In women without prior PTD, we universally offer transvaginal ultrasonographic cervical length measurement at the time of midtrimester fetal anomaly scan. When short cervix is determined in such cases, cervical cerclage, vaginal progesterone, cervical pessary, alone or in combination, may be recommended depending on the measurement and the gestational age. Asymptomatically dilated cervix, PTL, and PPROM are generally managed according to the gestational age on a case-by-case basis. Data are limited in twin and higher order multiple pregnancies to recommend standart prevention and management protocols.

Keywords: Premature birth; obstetric labor, premature; preterm premature rupture of the membranes

Correspondence: Filiz F. YANIK
Private Clinic, Ankara, TURKEY
E-mail: bilginyanik@yahoo.com

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 01 Sep 2020 ***Accepted:*** 27 Sep 2020 ***Available online:*** 12 Nov 2020

INTRODUCTION AND OVERVIEW

Preterm labor (PTL) is the presence of uterine contractions with sufficient intensity and frequency resulting in cervical effacement and dilation between $20^{0/7}$ and $36^{6/7}$ weeks of gestation. Preterm delivery (PTD) is the delivery between $20^{0/7}$-$36^{6/7}$ weeks.[1-3] Some authorities accept the lower limit as $22^{0/7}$ weeks or 500 g of newborn weight.[2]

About 10% of all the deliveries are preterm.[1,2] The prevalence is around 12% in Turkey, ranging between 10 to 15% in different centers.[2,4-7] PTD is one of the leading causes of perinatal mortality and morbidity, responsible for almost 75% of neonatal deaths in the absence of congenital anomalies.[8]

According to the gestational age at delivery, preterm births (PTBs) are classified as follows:

- $20^{0/7}$-$27^{6/7}$ weeks: Extremely preterm (5.3% of all PTBs),
- $28^{0/7}$-$31^{6/7}$ weeks: Very preterm (10.4% of all PTBs),
- $32^{0/7}$-$33^{6/7}$ weeks: Moderate preterm,
- $34^{0/7}$-$36^{6/7}$ weeks: Late preterm.[1,2]

Accurate knowledge of the gestational age is extremely important for diagnosis and management. Gestational age is determined according to the last menstrual period (LMP). If there is a difference of 5 days or more in ultrasonographic (USG) measurements in first 8 weeks of pregnancy, or 7 days or more in 9-15 weeks, LMP should be corrected based on the USG measurements.[9]

According to the cause of the birth, preterm deliveries are classified as spontaneous or indicated. Indicated preterm deliveries, constituting approximately 20-30% of the total, are the deliveries following induction of labor or cesarean deliveries for maternal or fetal indications such as preeclampsia and fetal growth restriction. The rest occur as a result of spontaneous PTL or preterm prelabor rupture of the membranes (PPROM), about half and half.[10]

Although etiology of spontaneous PTB has not been fully elucidated, four main mechanisms are mentioned in the pathogenesis (Table 1).[1] These mechanisms yield to PTL, PPROM, or shortening of the cervix, finally ending up with preterm deliveries.

TABLE 1: Pathogenetic mechanisms of spontaneous preterm delivery.[1]

Premature activation of maternal or fetal hypothalamo-pituitary-adrenal axis due to maternal/fetal stress (30%)
Infection/inflammation (40%)
Abruption/decidual bleeding (20%)
Mechanical stretching of the uterus (10%)

TABLE 2: Risk factors for preterm delivery.

History and maternal features
Advanced maternal age (≥35 years)
Adolescent pregnancies (<18 years of age)
Interpregnancy interval shorter than 6 months
History of late abortion (second trimester abortion: at $14^{0/7}$-$19^{6/7}$ weeks) or preterm delivery ($20^{0/7}$-$36^{6/7}$ weeks)
History of preterm delivery of a twin pregnancy under 34 weeks
The mother herself having been born prematurely
Maternal chronic renal or hepatic disease
Smoking
Uterine anomalies
Previous cervical operations
Endocervical polyp
Vaginal dysbiosis (changes in the vaginal microbiota)
Low socioeconomic level
Inadequate maternal nutrition
Prepregnancy maternal weight of <50 kg
Maternal stress
Current pregnancy characteristics
Maternal anemia (Hb<11 g/dL in the first or third trimester, <10.5 g/dL in the second trimester)
Antenatal bleeding (especially in the second or third trimester)
In-vitro fertilization
Multiple pregnancy
Placental insufficiency
Placenta previa
Early (first trimester) co-twin demise
Polyhydramnios
Oligohydramnios
Infections
Preterm labor
Short cervix (cervical length of <25 mm before 32 weeks)

RISK FACTORS FOR PRETERM DELIVERY

Several risk factors for PTD can be anticipated before or during the pregnancy based on the history and physical examination (Table 2).[11-13] "History of PTD" and "cervical length of <25 mm at 22 to 24 weeks" have been determined as the most important risk factors in singleton pregnancies.[12,14] In recent years, re-

search studies are also focused on vaginal microbiota and genetic predispositions.

PREDICTION OF PRETERM DELIVERY

The benefits of various risk-scoring systems for predicting PTD could not be demonstrated.[11] On the other hand, The Preterm Prediction Study, which is a large-scale multicenter study, has revealed that the risk of PTD before 32 weeks was 50% in women with a history of spontaneous PTD, when the transvaginal sonographic cervical length measurement was <25 mm between 22nd-24th gestational weeks and the cervicovaginal fetal fibronectin (fFN) test was positive; thus these risk factors were reported to be of utmost importance.[12]

If possible, cervical length measurement by transvaginal ultrasonography (TVUSG) is recommended for all pregnant women, especially for those in the risk group at the time of the second trimester fetal anatomic scan at 18-24 weeks (Figure 1, Table 2). A measurement of <25 mm is considered as a short cervix. If TVUSG cannot be performed, evaluating the cervix by transabdominal USG can also give a rough idea.

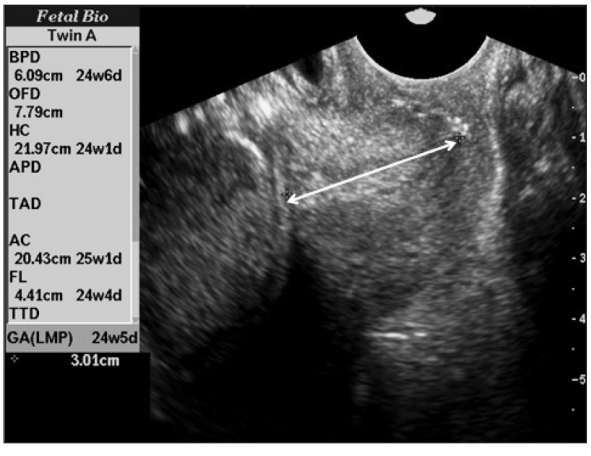

FIGURE 1: Cervical length measurement by transvaginal ultrasonography (TVUSG). Measurement technique:
-After the 14th gestational week,
-Empty bladder,
-TVUSG is performed avoiding excessive pressure on the cervix and the distance between the internal os and the external os should be measured,
-Particularly a long cervical canal may have a curved image. In such cases, the distance from the internal os to the external os can be measured directly again, ignoring the curvature,
-Three measurements should be obtained and the shortest should be accepted as the cervical length,
-Measurements above 50 mm may be related to the contraction of the lower uterine segment and may not show the real cervical length.

PREVENTION OF PRETERM DELIVERY

Several pathogenetic mechanisms are described for PTD and more than one mechanism may play a role in a case (Table 1). Therefore, the interventions to prevent PTD may not be successful in all the pregnant women at risk.[15-18] Despite the preventive efforts, PTB rates have not decreased throughout the world over the years.[16]

GENERAL PRECAUTIONS

- Prevention of multiple pregnancies.
- Prevention of adolescent pregnancies.
- Interpregnancy interval should be more than 12 months, preferably.
- Maintaining the ideal body weight with proper nutrition: Ideally, the pre-pregnancy body mass index (BMI) should be 18.5-24.9 kg/m^2 and weight gain in singleton pregnancies should be 11.5-16 kg-the leaner ones gaining more, and the heavier ones gaining less, within this range.[19]
- Screening for bacterial vaginosis is not recommended during pregnancy, but it is treated if diagnosed.
- For the detection of asymptomatic bacteriuria, urine culture is recommended at the first antenatal visit.
- The option of multifetal pregnancy reduction should be offered in multifetal pregnancies with triplets or more.

HISTORY-BASED PREVENTIVE MEASURES

History of Late Abortion (≥14 weeks) / Preterm Delivery

- If there is a history of late abortion or PTD in any of the previous pregnancies:

- Progesterone is recommended from the 16th gestational week on, until the 36th gestational week.[20,21] Studies with 17α-OH progesterone caproate (17-OHPC) have shown that 34% of the PTBs before 37 weeks could be prevented.[21] Which progesterone should be used and how to use it may be decided on

TABLE 3: Progesterone preparations and dosages.[20,21]

17α-OH progesterone caproate (17-OHPC): 250 mg, intramuscular (IM), weekly.
Progesterone 90 mg gel: vaginally, once a day.
Progesterone 100 or 200 mg capsule: as a vaginal suppository or per oral (PO), once a day.

a case-by-case basis (Table 3). Micronized progesterone may be preferred due to its proximity to natural progesterone, and less systemic side effects and higher bioavailability with vaginal route.

- In these cases, cervical length is also monitored every two weeks starting from the 16th gestational week on. If short cervix is detected, additional interventions are required [see Preventive Measures in the Presence of Short Cervix (Based on Ultrasonography)].

■ If there is a history of late abortion or PTD in two or more of the previous pregnancies, particularly with painless cervical dilation and before the 28th gestational week (typical history of cervical insufficiency):

- Prophylactic cervical cerclage is recommended at 12-14 weeks, after fetal anomaly and aneuploidy screening tests are performed; the intervention can also be performed at later weeks depending on the obstetric history.

- McDonald and Shirodkar cerclage are not proven to be superior to each other (Figure 2).[22]

- Routine antibiotic prophylaxis is controversial in cerclage operations (but it is recommended in physical examination-indicated cases with cervical dilation); cephalosporin group is preferred when necessary.[22]

- The benefit of preoperative-postoperative progesterone use in prophylactic cervical cerclage cases has not been demonstrated.[22] The treatment can be continued after the cerclage in cases who are already on progesterone due to bleeding or any other reason.

- Sutures are held until 36th-37th gestational weeks, if labor does not start or delivery is indicated for any reason.

- If McDonald or Shirodkar cerclage fails, transabdominal cervico-isthmic cerclage via laparoscopy or laparotomy is recommended before or during the next pregnancy. Those women with transabdominal cerclage should definitely give birth by cesarean section.

History of Cervical Operation

- In women with previous cervical operations such as radical trachelectomy, conization or deep loop electrosurgical excision procedure (LEEP), cerclage is recommended at 12-14 weeks of pregnancy.

- When the remaining cervical tissue is insufficient (cervical length <15 mm) transabdominal cervico-isthmic cerclage can be performed before pregnancy.

PREVENTIVE MEASURES IN THE PRESENCE OF SHORT CERVIX (BASED ON ULTRASONOGRAPHY)

Asymptomatic Pregnant Women (Without Painful Uterine Contractions, No Cervical Dilation)

■ No history of late abortion or PTD in previous pregnancies:

- If the cervical length is measured to be <25 mm via TVUSG at the 18th-24th week fetal anomaly scan, or at any random scan before the 32nd gestational week, vaginal progesterone is recommended and continued until the 36th week. Cervical length of 25 mm corresponds to the 3rd percentile at 16-22 weeks and 10th percentile at 22-32 weeks.[24]

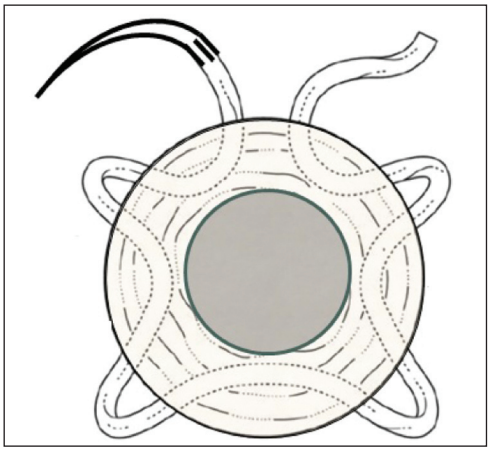

FIGURE 2: McDonald cervical cerclage.
Cerclage is performed as history or sonography or physical examination-indicated, usually from 12nd-14th to 24th-26th gestational weeks. Until which week it is to be performed should be determined according to the neonatal outcomes and viability of each center; cerclage is not recommended beyond 28 weeks. Polyester or mersilene tape suture can be used for the procedure.[22,23]

- If the cervical length is <10 mm before 24-26 weeks, cervical cerclage may be offered in addition to vaginal progesterone.[25]

- If the cervical length is <15 mm and the gestational age is ≥24-26 weeks, cervical pessary may be tried in addition to vaginal progesterone (Figure 3).[26,27] Pessary is not recommended beyond 32 weeks.

■ History of late abortion or PTD in previous pregnancies and already using progesterone:

- Starting at the 16th gestational week, cervical length is measured via TVUSG every two weeks and the management is planned accordingly.

- If the cervical length is measured to be <25 mm before 24-26 weeks, cervical cerclage is recommended in addition to progesterone. After the cerclage procedure, the use of vaginal progesterone preparations is preferred rather than other routes.

- If cervix is shortened (<25 mm) after 24-26 weeks up to 32 weeks, cerclage is not recommended, however pessary may be used (Figure 3). Progesterone treatment should be continued preferably via vaginal route.

- Although the classical recommendation is cervical cerclage for short cervix detected before 24-26 weeks in women already using 17-OHPC, continuing the treatment with vaginal progesterone preparations instead of 17-OHPC is suggested to be as effective as cerclage.[20,28]

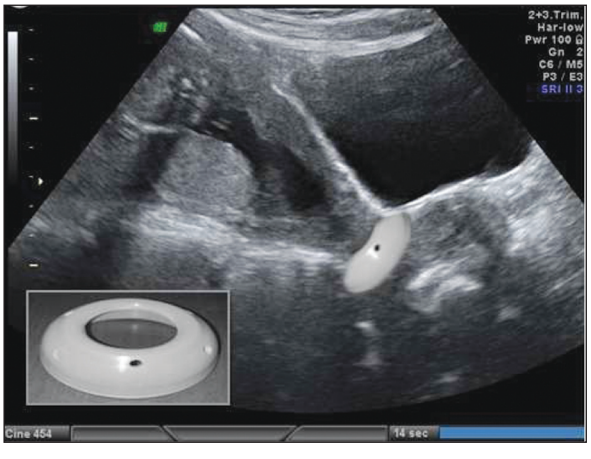

FIGURE 3: Cervical pessary.
Mechanism of action:[26,27]
-Uterocervical angle is decreased,
-The pressure exerted by the membranes on the internal os is reflected to the anterior wall of the lower uterine segment,
-The risk of ascending infections is decreased due to narrowing of the internal cervical os.
It frequently increases the vaginal discharge.

Symptomatic Pregnant Women (With Painful Uterine Contractions, No Cervical Dilation On Pelvic Examination)

This condition is named as threatened preterm labor (TPTL). The management is explained in detail in the section of "Diagnosis and Management of Preterm Labor".

PREVENTIVE MEASURES IN THE PRESENCE OF DILATED CERVIX (BASED ON PELVIC EXAMINATION)

When cervical dilation is detected in pregnant women without any uterine contractions, physical examination-indicated cerclage (emergency cerclage) is recommended.

- Lethal fetal anomalies, chorioamnionitis, ruptured membranes, active bleeding, placental abruption, PTL, and cervical dilation of ≥4 cm, are contraindications.

- The probability of intra-amniotic infection is higher especially when cervical dilation is 2 cm or more. In order to rule out any subclinical intra-amniotic infection, amniocentesis can be performed before the cerclage operation by considering the risk-benefit ratio.[22] As the risk of amniocentesis is undoubtedly higher in those pregnancies, such as membrane rupture or infection, another option may be to carry out the cerclage operation under broad-spectrum antibiotic prophylaxis, without performing a preoperative amniocentesis. The ampirical antibiotic regimens may be adopted from the antibiotic treatment regimens used in PPROM (see Diagnosis and Management of Preterm Prelabor Rupture of the Membranes).

- McDonald cerclage may be preferred as it is easier to perform (Figure 2).

- Although routine antibiotic prophylaxis is controversial in cerclage operations, it may be useful in physical examination-indicated cases.[29] Cephalosporins can be used for prophylaxis.

- The benefit of preoperative-postoperative progesterone use could not be demonstrated.[22]

- In physical examination-indicated cerclage cases, the procedure itself might further increase the

prostaglandin synthesis, indomethacin as a single dose of 100 mg rectal suppository may be used preoperatively, and continued after the operation for 48 hours as 4x25 mg/day, orally.[29]

- Cerclage is not recommended beyond 28 weeks due to satisfactory neonatal outcomes. It is controversial at 24 to 28 weeks of gestation. General attitude is not to perform cerclage beyond 24 weeks, which is the widely accepted lower limit of viability.

- Sutures are held until 36th-37th gestational weeks, if labor does not start or delivery is indicated for any reason.

PREVENTIVE MEASURES IN TWIN PREGNANCIES

- Progesterone, cervical cerclage or pessary is not recommended just for the single indication of multiple pregnancy.

- The benefit of using 17-OHPC in cases with a history of PTD, is controversial.[30,31]

- Prophylactic cerclage may be offered in the presence of a typical history of cervical insufficiency.[32]

- Vaginal progesterone can be recommended in twin pregnancies with a short cervix (<25 mm) under 32 weeks.[33] Based on the recent studies, pessary may be offered as an option.[34,35] Cerclage is not recommended.

- If there is cervical dilation, emergency cerclage based on the pelvic examination is recommended.[32]

DIAGNOSIS AND MANAGEMENT OF PRETERM LABOR

PRETERM LABOR

PTL is defined as the presence of painful regular uterine contractions observed at least 4 times within 20 minutes or 8 times within an hour, as well as an increase in cervical effacement and dilation, between $20^{0/7}$ and $36^{6/7}$ weeks of gestation. The diagnosis is directly confirmed if cervical dilation is >1 cm and effacement is ≥80% in the presence of regular uterine contractions. Tocolytic therapy intending to stop the contractions in PTL, is not generally recommended for pregnancies <24 weeks or ≥34 weeks.

THERATENED PRETERM LABOR

Painful regular uterine contractions are observed without any cervical dilation. In such cases, cervical length measurement via TVUSG may predict the PTD. When the cervix is shorter, the probability of PTD is higher:

- If the cervical length is <20 mm, it is accepted as PTL.

- If the cervical length is >30 mm, follow-up is recommended. Meanwhile, hydration with intravenous lactated Ringer's solution may be helpful. The pregnant woman may be discharged home if the symptoms regress and cervical changes are not observed.

- If the cervical length is 20-30 mm and the woman is symptomatic, fFN test should be performed. When the result is positive, the case is accepted as PTL and managed accordingly; if negative, follow-up with intravenous hydration is recommended. In our country fFN test is not widely used, therefore, based on the studies in the literature, it will be appropriate to accept those cases with a cervical length of <25 mm as PTL and manage accordingly.

MANAGEMENT OF PRETERM LABOR

Delivery is indicated in some cases of PTL, and should not be prevented. Emergency cesarean delivery may also be required on a case-by-case basis (Table 4).

Certain laboratory examinations should be performed in pregnant women with PTL:

-Whole blood count,

-C-reactive protein (CRP),

TABLE 4: Indications for delivery in preterm labor.

Intrauterine fetal demise
Lethal fetal anomalies
Fetal distress
Preterm prelabor rupture of the membranes (tocolysis might be initiated on a case-by-case basis while transferring to a tertiary center or applying antenatal steroid regimen)
Clinical chorioamnionitis (fever, uterine tenderness, pain, foul smelling discharge)
Placental abruption
Maternal bleeding causing hemodynamic instability
Severe preeclampsia/eclampsia

-Urinalysis,

-Urine culture, cervicovaginal and anal cultures and tests to screen for urogenital infections (including gonorrhea, *Chlamydia* and *Mycoplasma* infections, if applicable).

Hospitalization and restriction of the activities are recommended (however absolute bed rest is not approved).

Tocolytic treatment: Is recommended to delay the delivery for 48-72 hours, between $24^{0/7}$ and $33^{6/7}$ weeks of pregnancy. It saves time for antenatal steroids to act or for the referral of the pregnant woman to a tertiary center for delivery. Rarely, it may be used in pregnancies at the 23rd week or ≥34 weeks on a case-by-case basis. The purpose of tocolysis is not to carry the pregnancy till term, therefore long-term use is not recommended. Tocolytic agents are generally similarly effective in delaying birth; one has not been shown to be superior to the other.[3] Ease of use and side-effect profiles determine the preferences (Table 5).

TABLE 5: Tocolytic agents.

Tocolytic agent groups	Maternal side-effects	Fetal/neonatal side-effects	Other features	Frequently used agents and dosages
Non-selective cyclo-oxygenase (COX) inhibitors (indomethacin, sulindac, nimesulide)	Nausea, gastritis, platelet dysfunction, cerebrovascular events	When used in pregnancies ≥32 weeks and for more than 48 hours, transient closure of ductus arteriosus and tricuspid regurgidation (sometimes permanent), oligohydramnios, patent ductus arteriosus and bronchopulmonary dysplasia in the neonate	These agents are not recommended in maternal pulmonary infections (such as COVID-19), as they might aggrevate the hypoxic pulmonary hypertension by disrupting the protective mechanism against hypoxia	**Indomethacin:** Loading dose of 50-100 mg PO/rectal, thereafter 25 mg PO every 4-6 hours. Maximum dose: 200 mg/day, use over 48 hours is not recommended. It may be the first tocolytic agent of choice in pregnancies <32 weeks, use in pregnancies ≥32 weeks is not recommended
Calcium channel blockers	Facial flushing, headache, palpitations, hypotension due to peripheral vasodilation	Usually none	They are preferred because of their low side-effect profile	**Nifedipine:** A total loading dose of 30-40 mg within one hour, as 10 mg PO every 15-20 minutes, thereafter 10-20 mg PO every 3-8 hours. Maximum dose: 180 mg/day. It is usually the first choice in pregnancies ≥32 weeks.
Beta agonists (ritodrine, terbutaline, salbutamol, hexoprenaline)	Tachycardia, chills, shortness of breath, pulmonary edema, hypokalemia, hyperglycemia	Fetal tachycardia, neonatal hypoglycemia		**Terbutaline:** 0.25 mg subcutaneous (SC), repeat the dose every 20-30 minutes if necessary, maximum 4 doses
Oxytocin receptor antagonists	Hypersensitivity, injection-site reaction	Some studies have reported that there might be an increase in fetal/neonatal mortality rates[36]		**Atosiban:** 6.75 mg intravenous (IV) bolus, followed by IV infusion of 300 µg/min for the first 3 hours and thereafter 100 µg/min IV infusion for up to 45 hours
Magnesium sulphate	Sweating, nausea, vomiting, facial flushing, toxicity (loss of reflexes, respiratory arrest, cardiac arrest) with increased serum levels. Treatment of toxicity: 1 g of calcium gluconate IV within 5-10 minutes	A decrease in fetal heart rate variability at cardiotocography, thus a decrease in fetal biophysical profile test score, can be observed	It should not be used in patients with myasthenia gravis. It should be used with caution in patients with renal dysfunction. The maintenance dose is reduced when serum creatinine level is >1 mg/dL, and cancelled when it is >2,5 mg/dL	**Magnesium sulphate:** Loading dose: 4-6 g, slow IV bolus within 15-20 minutes. Maintenance dose: 2 g/hour IV infusion. Tocolytic effect is more prominent at doses higher than recommended for eclampsia prophylaxis. It is thought to act by antagonizing calcium
Nitric oxide donors	Headache, hypotension, facial flushing, palpitations	Decrease in the biophysical profile test score due to maternal hypotension		**Glyceryl trinitrate:** 10 mg transdermal form is applied on the abdominal skin and if necessary a second one is applied after 1 hour; both should be removed after 24 hours. Alternatively, it may be applied via IV infusion at a dose of 20 µg/min

Antenatal steroids: Accelerate fetal lung maturation. Betamethasone or dexamethasone can be used (Table 6).[37] Betamethasone is generally preferred as it is more effective than dexamethasone. It is conventionally recommended between $24^{0/7}$-$33^{6/7}$ weeks of pregnancy. It may sometimes be applied at the 23rd week or in the late preterm period ($34^{0/7}$-$36^{6/7}$ weeks), depending on the case. The maximum effect is observed 48 hours after the initial dose and may last up to 2 weeks. Diabetes in pregnancy is not a contraindication for antenatal steroids; however the blood sugar regulation may be disrupted for up to 5-7 days, thus necessary measures should be taken accordingly. There is no difference in the antenatal steroid regimen in multiple pregnancies.

Group B Streptococcus Prophylaxis:

- Except for group B streptococcus (GBS) prophylaxis, there is no place for routine antibiotic use in PTL cases when no infection is detected.

-Vaginal and rectal samples are taken for GBS culture.

-GBS prophylaxis is recommended for women with the diagnosis of PTL, after the samples for culture are taken (Table 7).[38] If the culture result is negative, the prophylaxis is stopped. The prophylaxis is also stopped if PTL ceases. If the culture result is positive and the labor continues, GBS prophylaxis is continued until the delivery.

Neuroprophylaxis with magnesium sulphate (MgSO4): It is recommended between the gestational weeks of $24^{0/7}$ and $31^{6/7}$ to reduce the risk of cerebral palsy. Neuroprotective effect is more pronounced particularly under 28 weeks. $MgSO_4$ is applied if delivery is expected within 24 hours. The regimen is similar to that used in eclampsia prophylaxis (loading dose: 4-6 g slow IV bolus within 15-20 min, maintenance dose: 1-2 g/h IV infusion).[39] If delivery does not occur, $MgSO_4$ is stopped after 48 hours of treatment.

TABLE 6: Antenatal steroid regimens.[37]

-Betamethasone: 12 mg intramuscular (IM), once a day, for 2 days
-Dexamethasone: 6 mg IM, twice a day, for 2 days

If more than 2 weeks have passed after a course of antenatal steroids (two days of treatment), a rescue course is recommended for pregnancies <34 weeks when preterm delivery is imminent.

TABLE 7: Antibiotic regimens for group B streptococcus prophylaxis.[38]

Ampicillin 2 g IV, thereafter continued as 6x1 g or 4x2 g IV/day.
In case of penicilin allergy without any risk for anaphylaxis:
Cefazolin 2 g IV, followed by 3x1 g IV/ day.
In case of penicilin allergy and risk for anaphylaxis:
Clindamycin 3x900 mg IV/day or vancomycin 2x1 g IV/day.

DIAGNOSIS AND MANAGEMENT OF PRETERM PRELABOR RUPTURE OF THE MEMBRANES

DEFINITION AND OVERVIEW

The rupture of chorionic and amniotic membranes before labor begins, is called as prelabor or premature rupture of the membranes (PROM). When the pregnancy is <37 weeks, it is called as preterm PROM (PPROM).

The risk factors for PPROM are similar to those for PTL and delivery (Table 2). However intra-amniotic infection is more prominent in the etiology, particularly in the earlier weeks of pregnancy.[40] The risk of postpartum infection is also high in PPROM cases and is around 15-20%.[41] Due to intrauterine infection and inflammation, the risk of neurological damage in the newborn is higher. In the presence of severe and long-lasting oligohydramnios, especially in pregnancies under 24 weeks, pulmonary hypoplasia, Potter's syndrome (atypical facies, low set ears) and limb deformities may develop.[42]

Latency is the time from membrane rupture to birth. Latency is generally longer in the earlier gestational weeks and shorter in the later weeks.

DIAGNOSIS OF PRETERM PRELABOR RUPTURE OF THE MEMBRANES

- **History:** Sudden rush of a watery fluid out of the vagina, more than the amount of normal vaginal discharge.

- **Manual pelvic examination with a sterile glove:** Cervical effacement and dilation are assessed and in the meanwhile the watery discharge may be detected.

- **Sterile speculum examination:** The observation of amniotic fluid pooling in the vagina or pouring out of the external cervical os with valsalva

maneuver, may directly lead to the diagnosis of PPROM.

- **Vaginal pH:** In PPROM the normal vaginal pH (4.5-6) shifts to the basic values since the amniotic fluid pH is between 7.1-7.3. Blood, semen, alkaline antiseptics, bacterial vaginosis may cause false positivity. In the presence of prolonged PPROM and severe oligohydramnios, vaginal pH can be acidic, causing false negativity.

- **Transabdominal ultrasonography:** Vertical single pocket measurement is the most practical method for evaluating the amount of amniotic fluid. The depth of the deepest amniotic fluid pocket which doesn't contain fetal limbs or cord, is measured vertically. A measurement of less than 2 cm is accepted as oligohydramnios. When no amniotic fluid pocket is observed, it is anhydramnios. Oligohydramnios/anhydramnios supports the diagnosis of PPROM.

- **Placental alpha microglobulin-1:** This test detects the placental alpha microglobulin-1 protein in the vaginal discharge, which is normally present in the amniotic fluid. Minimal amounts may even be detected with a sensitivity of up to 99% (sensitivity: 94.4-98.9%, spesificity: 87.5-100%).[43] Insulin like growth factor binding protein-1 test, based on the same principle, also has a high diagnostic yield for PPROM, with high sensitivity and specificity; however it is not widely available in Turkey.

- **Amniocentesis and dye test:** Blue coloration of the vaginal discharge after the injection of indigo carmine dye into the amniotic cavity is directly diagnostic. On the other hand, it is not used in routine practice as it is an invasive test.

MANAGEMENT OF PRETERM PRELABOR RUPTURE OF THE MEMBRANES

■ Indications for delivery:

- They are similar to those in PTL (Table 4).

- When PTL accompanies the PPROM, delivery is indicated. Hence, on a case-by-case basis, tocolysis may be used during the period of antenatal steroid treatment or transfer to a tertiary center for delivery.

- <23 weeks: Termination of the pregnancy may be offered to the parents in the presence of severe oligohydramnios/anhydramnios. In case of a dichorionic diamniotic twin pregnancy with PPROM, selective feticide may be an option to give a chance of survival to the other fetus with intact membranes.

-≥34 weeks: Delivery is indicated depending on the neonatal care facilities. If the facilities are unsatisfactory, the pregnant woman must be referred to a tertiary center having a neonatal intensive care unit. Delivery is surely indicated when the pregnancy is ≥37 weeks.

■ Hospitalization and follow-up:

- It is appropriate to hospitalize the cases with PPROM and to restrict the activities. However absolute bed rest is not recommended.

- Whole blood count, CRP, urinalysis, urine culture, cervicovaginal and anal cultures and tests to screen for urogenital infections, are recommended for initial evaluation at hospitalization. Thereafter, white blood cell count (WBC) and CRP might be tested everyday, every other day or every week, depending on the case. The risk of infection is higher in those with cervical dilation, uterine contractions and severe oligohydramnios/anhydramnios, thus requiring closer follow-up. However, the fact that WBC and CRP are non-specific inflammatory markers, must be kept in mind.

-Within the range of $23^{0/7}$ and $33^{6/7}$ weeks, if delivery is not indicated and the case will be managed expectantly, close follow up for the symptoms and signs of clinical chorioamnionitis (fever, uterine tenderness, pain, foul smelling discharge) is required.

-Fetal growth is evaluated via sonographic fetal biometric measurements every two weeks.

-Fetal well-being is evaluated by non-stress test (NST) and fetal biophysical profile. NST is more valuable beyond 28 weeks. These tests may be performed twice weekly in more stable cases. However, particularly in patients with severe oligohydramnios/anhydramnios daily evaluation is necessary. NST may reveal variable fetal heart rate decelerations caused by umbilical cord compression due to decreased amniotic fluid levels. Decreased fetal movements and fetal distress signs in NST might be indicators of chorioamnionitis.

■ **Antibiotic treatment:** Broad-spectrum antibiotic treatment decreases the risk of chorioamnionitis and improves the perinatal outcomes in cases with PPROM. Based on the studies in the literature, several antibiotic regimens may be recommended:[1,44-46]

-Erithromycin 4x250 mg/day, PO, for 10 days.

-Cefazolin 4x1 g/day, IV+clarithromycin 2x500 mg/day, PO, both for 7 days or until the delivery.

-Ampicillin 4x2 g/day, IV, for 48 hours, followed by amoxicillin 3x500 mg/day, PO, for 5 days + azithromycin 1 g, PO, as a single dose.

-Cefazolin 3x1 g/day, IV, for 48 hours, followed by cefalexin 4x500 mg/day, PO, for 5 days+ azithromycin 1g, PO, as a single dose.

-Ceftriaxone 1x1 g/day, IV, until the delivery+ clarithromycin 2x500 mg/day, PO, until the delivery + metronidazole 3x500 mg/day, IV, for a maximum of 4 weeks.

The preferred regimens generally include penicillin derivatives or cephalosporins combined with macrolide antibiotics. However, amoxicillin+ clavulanic acid is not recommended as it was reported to cause neonatal necrotizing enterocolitis.[44]

■ **Antenatal steroids:** In the presence of PPROM, antenatal steroid therapy does not increase the risk of maternal or fetal infection, so is not contraindicated. Conditions of use and dosages are similar to those in PTL (Table 5).

■ **Group B Streptococcus Prophylaxis:** Vaginal and rectal samples are taken for GBS culture. After taking the samples, GBS prophylaxis must be initiated in cases supposed to deliver within a short time (Table 7).[38] As PPROM cases require antibiotic treatment anyway, GBS prophylaxis might be integrated with that treatment. If the culture result is negative, the prophylaxis is stopped. The prophylaxis is also stopped if PTL ceases and the case will be expectantly managed. If the culture result is positive and delivery is to occur, GBS prophylaxis is continued until the delivery.

■ **Neuroprophylaxis with $MgSO_4$:** Conditions of use and dosage are similar to those in PTL.

■ **Tocolytic treatment** (Table 5): May be used between $23^{0/7}$ and $33^{6/7}$ weeks of pregnancy, in order to delay the delivery for antenatal steroids to act or for the transfer to a tertiary center. This treatment will increase the latency period, meanwhile it might also increase the risk of chorioamnionitis.

MODE OF PRETERM DELIVERIES

The following parameters should be considered to determine the mode of delivery:

1) Gestational age,

2) Estimated fetal weight (EFW),

2) Presence of labor,

3) Cervical effacement and dilation,

4) Fetal presentation,

5) Singleton/multiple pregnancy,

6) Presence of acute/chronic fetal distress,

7) Presence of chorioamnionitis.

■ **Vertex presentation**: Vaginal delivery is preferred if there isn't any obstetric indication for cesarean delivery. In singleton pregnancies with vertex presentation, irrespective of the gestational age, there is no difference between cesarean and vaginal delivery in terms of perinatal morbidity and mortality.[47]

■ **Breech presentation**: Cesarean section is recommended when EFW is <1500 g.[48]

■ **Fetal growth restriction (FGR):** Irrespective of the fetal presentation, cesarean delivery is preferred in preterm pregnancies with FGR, particularly when the gestational age is less than 34 weeks.[49]

■ **Twin pregnancy:**[50,51]

-When the first twin is in non-cephalic presentation, cesarean section is recommended.

-Even if the first twin is in cephalic presentation, cesarean section is recommended when the EFW of the second twin is <1500 g.

-Cesarean section is recommended for the delivery of monoamniotic twin pregnancies.

■ **Higher order multiple pregnancies (triplets and more):** Cesarean section is recommended.

■ **Presence of chorioamnionitis**: Since the risk of intraabdominal spread of the infection is higher in

case of cesarean section, vaginal delivery is preferred if it does not pose a serious risk to the fetus.

Delayed umbilical cord clamping (at least 30 seconds after the delivery of the baby, within 3 minutes maximum) improves the neonatal outcomes in preterm deliveries, particularly under 32 weeks; thus, is advised. It is not recommended in case of maternal bleeding, hemodynamic instability, fetal growth restriction and requirement of emergency neonatal resuscitation. Studies in multiple pregnancies are insufficient.[52,53]

Acknowledgment

We would like to thank Şule Girmen, MD, for editing the manuscript.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, Spong CY. Preterm birth. In: Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, Spong CY, eds. Williams Obstetrics. 25th ed. New York, USA: McGraw-Hill Education; 2018. p.803-34.
2. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 (Suppl 1):S2. [Crossref] [PubMed] [PMC]
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Practice bulletin no. 171: management of preterm labor. Obstet Gynecol. 2016;128(4): e155-64. [Crossref] [PubMed]
4. Hacettepe Üniversitesi Nüfus Etütleri Enstitüsü. Çocuk Sağlığı. 2018 Türkiye Nüfus ve Sağlık Araştırması. TÜBİTAK, T.C. Cumhurbaşkanlığı Strateji ve Bütçe Başkanlığı. Ankara, Türkiye: 2019. p.129-30.
5. Atasay B, Okulu E, Akın İM, Çandır O, Arsan S, Türmen T, et al. [The early clinical outcomes of late preterm newborns]. Turkish J Pediatr Dis Derg. 2010;4(1):30-5.
6. Ege E, Akın B, Altuntuğ K, Arıöz Düzgün A, Koçoğlu D. [Prevelance of spontaneus preterm birth and related factors]. Türk Jinekoloji ve Obstetrik Derneği (TJOD) Derg. 2009;6(3):197-205.
7. Yanık FF, Gulumser C, Sahin Uysal N. The problem of preterm delivery in twin pregnancies. Nice, France: 13th World Congress in Fetal Medicine; 2014.
8. Lyons CA, Garite TJ. Corticosteroids and fetal pulmonary maturity. Clin Obstet Gynecol. 2002;45(1):35-41. [Crossref] [PubMed]
9. Committee on Obstetric Practice, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine. Committee opinion no 700: methods for estimating the due date. Obstet Gynecol. 2017;129(5):e150-4 [Crossref] [PubMed]
10. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;5;371(9606):75-84. [Crossref] [PubMed]
11. Suhag A. Preterm birth prevention in asymptomatic women. In: Berghella V, ed. Obstetric Evidence Based Guidelines. 3rd ed. Boca Raton, USA: CRC Press, Taylor and Francis Group; 2017. p.193-212. [Crossref]
12. Goldenberg RL, Iams JD, Mercer BM, Meis PJ, Moawad AH, Copper RL, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. Am J Public Health. 1998;88(2):233-8. [Crossref] [PubMed] [PMC]
13. Perri T, Chen R, Yoeli R, Merlob P, Orvieto R, Shalev Y, et al. Are singleton assisted reproductive technology pregnancies at risk of prematurity? J Assist Reprod Genet. 2001;18(5):245-9. [Crossref] [PubMed] [PMC]
14. To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol. 2006;194(5):1360-5. [Crossref] [PubMed]
15. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet. 2008;371(9607):164-75. [Crossref] [PubMed]
16. Committee on Practice Bulletins-Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. Obstet Gynecol. 2012;120(4):964-73. [PubMed]
17. Romero R, Espinoza J, Erez O, Hassan S. The role of cervical cerclage in obstetric practice: can the patient who could benefit from this procedure be identified? Am J Obstet Gynecol. 2006;194(1):1-9. [Crossref] [PubMed] [PMC]
18. Khanprakob T, Laopaiboon M, Lumbiganon P, Sangkomkamhang US. Cyclo-oxygenase (COX) inhibitors for preventing preterm labour. Cochrane Database Syst Rev. 2012;17;10:CD007748. [Crossref] [PubMed]
19. Moore Simas TA, Waring ME, Sullivan GMT, Liao X, Rosal MC, Hardy JR, et al. Institute of medicine 2009 gestational weight gain guideline knowledge: survey of obstetrics/gynecology and family medicine residents of the United States. Birth. 2013;40(4):237-46. [Crossref] [PubMed] [PMC]

20. Romero R, Yeo L, Chaemsaithong P, Chaiworapongsa T, Hassan SS. Progesterone to prevent spontaneous preterm birth. Semin Fetal Neonatal Med. 2014;19(1):15-26. [Crossref] [PubMed] [PMC]
21. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;12;348(24):2379-85. [PubMed]
22. American College of Obstetricians and Gynecologists. ACOG practice bulletin no 142: cerclage for the management of cervical insufficiency. Obstet Gynecol. 2014;123(2 Pt 1):372-9. [Crossref] [PubMed]
23. Berghella V, Szychowski JM, Owen J, Hankins G, Iams JD, Sheffield JS, et al. Suture type and ultrasound-indicated cerclage efficacy. J Matern Fetal Neonatal Med. 2012;25(11): 2287-90. [Crossref] [PubMed] [PMC]
24. Simhan HN, Berghella V, Iams JD. Prevention and management of preterm parturition. In: Resnik R, Lockwood CJ, Moore TR, Greene MF, Copel JA, Silver RM, eds. Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice. 8th ed. Amsterdam, Holland: Elsevier; 2018. p.679-711.
25. Berghella V, Ciardulli A, Rust OA, To M, Otsuki K, Althuisius S, et al. Cerclage for sonographic short cervix in singleton gestations without prior spontaneous preterm birth: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol. 2017;50(5):569-77. [Crossref] [PubMed]
26. Saccone G, Ciardulli A, Xodo S, Dugoff L, Ludmir J, Pagani G, et al. Cervical pessary for preventing preterm birth in singleton pregnancies with short cervical length: a systematic review and meta-analysis. J Ultrasound Med. 2017;36(8):1535-43. [Crossref] [PubMed]
27. Saccone G, Maruotti GM, Giudicepietro A, Martinelli P. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial. JAMA. 2017;318(23): 2317-24. [Crossref] [PubMed] [PMC]
28. Conde-Agudelo A, Romero R, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, et al. Vaginal progesterone is as effective as cervical cerclage to prevent preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix: updated indirect comparison meta-analysis. Am J Obstet Gynecol. 2018;219(1):10-25. [Crossref] [PubMed] [PMC]
29. Miller ES, Grobman WA, Fonseca L, Robinson BK. Indomethacin and antibiotics in examination-indicated cerclage: a randomized controlled trial. Obstet Gynecol. 2014;123(6): 1311-6. [Crossref] [PubMed]
30. Awwad J, Usta IM, Ghazeeri G, Yacoub N, Succar J, Hayek S, et al. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. BJOG. 2015;122(1):71-9. [Crossref] [PubMed]
31. Dodd JM, Grivell RM, OBrien CM, Dowswell T, Deussen AR. Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy. Cochrane Database Syst Rev. 2019; 2019(11):CD012024. [Crossref] [PubMed]
32. Li C, Shen J, Hua K. Cerclage for women with twin pregnancies: a systematic review and metaanalysis. Am J Obstet Gynecol. 2019; 220(6):543-57.e1. [Crossref] [PubMed]
33. Romero R, Conde-Agudelo A, El-Refaie W, Rode L , Brizot ML, Cetingoz E, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. Ultrasound Obstet Gynecol. 2017;49(3):303-14. [Crossref] [PubMed] [PMC]
34. Goya M, de la Calle M, Pratcorona L, Merced C, Rodó C, Mu-oz B, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). Am J Obstet Gynecol. 2016;214(2): 145-52. [PubMed]
35. Liem SMS, van de Mheen L, Bekedam DJ, van Pampus MG, Opmeer BC, Lim AC, Mol BWJ. Cervical length measurement for the prediction of preterm birth in symptomatic women with a twin pregnancy: a systematic review and meta-analysis. Obstet Gynecol Int. 2013;2013:125897. [Crossref] [PubMed] [PMC]
36. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obstet Gynecol. 2000;182(5):1173-83. [Crossref] [PubMed]
37. Committee on Obstetric Practice. Committee opinion no. 713: antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2017;130(2): e102-e9. [Crossref] [PubMed]
38. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, Spong CY. Infectious diseases. In: Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, Spong CY, eds. Williams Obstetrics. 25th ed. New York, USA: McGraw-Hill Education; 2018. p.1209-34.
39. American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Committee opinion no. 573: magnesium sulfate use in obstetrics. Obstet Gynecol. 2013;122(3):727-8. [PubMed]
40. Varol F, Er N, Sut N, Sayın CN. Local study on antenatal features of preterm births at 26-32 versus 33-36 weeks of pregnancy. Gynecology Obstetrics & Reproductive Medicine (GORM). 2018;24:1-6. [Crossref]
41. Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin no. 188: prelabor rupture of membranes. Obstet Gynecol. 2018;131(1):e1-e14. [PubMed]
42. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol. 2009;201(3):230-40. [Crossref] [PubMed]
43. Igbinosa I, Moore 3rd FA, Johnson C, Block JE. Comparison of rapid immunoassays for rupture of fetal membranes. BMC Pregnancy Childbirth. 2017;26;17(1):128. [Crossref] [PubMed] [PMC]
44. Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomized trial. ORACLE Collaborative Group. Lancet. 2001;357(9261):979-88. [Crossref] [PubMed]
45. Lee JH, Romero R, Kim SM, Chaemsaithong P, Park CW, Park JS, et al. A new anti-microbial combination prolongs the latency period, reduces acute histologic chorioamnionitis as well as funisitis, and improves neonatal outcomes in preterm PROM. J Matern Fetal Neonatal Med. 2016;29(5):707-20. [Crossref] [PubMed] [PMC]
46. Chang KHJ, Kim HJ, Yu HJ, Lee J, Kim JS, Choi SJ, et al. Comparison of antibiotic regimens in preterm premature rupture of membranes: neonatal morbidity and 2-year follow-up of neurologic outcome. J Matern Fetal Neonatal Med. 2017;30(18):2212-8. [Crossref] [PubMed]
47. Bauer J, Hentschel R, Zahradnik H, Karck U, Linderkamp O. Vaginal delivery and neonatal outcome in extremely-low-birth-weight infants below 26 weeks of gestational age. Am J Perinatol. 2003;20(4):181-8. [Crossref] [PubMed]
48. Demirci O, Tuðrul AS, Turgut A, Ceylan S, Eren S. Pregnancy outcomes by mode of delivery among breech births. Arch Gynecol Obstet. 2012;285(2):297-303. [Crossref] [PubMed]

49. Perrotin F, Simon EG, Potin J, Laffon M. [Delivery of the IUGR fetus]. J Gynecol Obstet Biol Reprod (Paris). 2013;42(8):975-84. [Crossref] [PubMed]

50. Barrett JFR, Hannah ME, Hutton EK, Willan AR, Allen AC, Armson BA, et al. A randomized trial of planned cesarean or vaginal delivery for twin pregnancy. N Engl J Med. 2013;3;369(14):1295-305. [Crossref] [PubMed] [PMC]

51. Barzilay E, Mazaki-Tovi S, Amikam U, de Castro H, Haas J, Mazkereth R, et al. Mode of delivery of twin gestation with very low birthweight: is vaginal delivery safe? Am J Obstet Gynecol. 2015;213(2):219.e1-8. [Crossref] [PubMed]

52. Committee on Obstetric Practice. Committee opinion no. 684: delayed umbilical cord clamping after birth. Obstet Gynecol. 2017;129(1):e5-e10. [Crossref] [PubMed]

53. Mercer JS, Erickson-Owens DA, Vohr BR, Tucker RJ, Parker AB, Oh W, et al. Effects of placental transfusion on neonatal and 18 month outcomes in preterm infants: a randomized controlled trial. J Pediatr. 2016;168:50-5.e1. [Crossref] [PubMed] [PMC]