# MANAGEMENT OF HIGH-RISK PREGNANCIES WITH RECOMMENDATIONS

Editor
Erdem Sahin

Health Sciences

LIVRE DE LYON
2022

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**Cover Design** • Mirajul Kayal
**Book Layout** • Mirajul Kayal
**First Published** • January 2022, Lyon

**ISBN:** 978-2-38236-252-5



**Publisher** • Livre de Lyon
**Address** • 37 rue marietton, 69009, Lyon France
**website** • http://www.livredelyon.com
**e-mail** • livredelyon@gmail.com

# PREFACE

I would like to thank all my colleagues who contributed to the preparation of this book. Our aim in preparing this book is to provide our assistants and experts with practical information by providing up-to-date and clear recomentadions during the diagnosis, management and treatment of high-risk pregnant women. Also, I would like to thank my wife, Mefkure Eraslan Sahin, to my father Yusuf Sahin and to my mother Lale Sahin who has always supported me during my editing and writing period. I'm glad you're here and I'm glad you're my family.

Associate Professor Erdem Sahin

# CONTENTS

# CHAPTER 1

# DELIVERY INDUCTION METHODS AND MANAGEMENT

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## 1. Introduction

Inducing delivery of a fetus is necessary when the continuation of pregnancy is associated with adverse outcomes for the mother or the fetus. Before inducing delivery, the indication should be reviewed, a pelvic examination should be conducted for cephalopelvic disproportion (CPD), the well-being of the fetus should be evaluated, and the estimated fetal weight and fetal position should be reviewed. If inducing delivery is elective, it should begin as early as possible after the morning visit by the obstetrician under elective conditions. The status of the cervix is evaluated first in pregnant women for whom delivery induction is decided and there are no contraindications. The suitability of the cervix for delivery induction is evaluated using the Bishop score[1]. A Bishop score <5 is defined as unfavorable (unfavorable cervix). In the presence of an unfavorable cervix, first, cervical ripening is required for inducing delivery.

**Table 1. Contraindications for Inducing Delivery [4].**

- Presence of previous classical cesarean section and other high-risk incisions (e.g., T incision)
- History of uterine rupture
- Presence of previous operations for a uterine anomaly or operation for wide uterine septum
- History of previous intramural myomectomy
- Active genital herpes
- Presence of human immunodeficiency virus infection
- Any unreliable fetal well-being (e.g., indication for urgent cesarean section)
- Invasive cervical cancer
- Malpresentations
- Total placenta previa and placenta invasion anomalies

Cervical maturation can be achieved either mechanically or medically. The choice should be based on the experience at each clinic and of each clinician. The mechanical or medical method has advantages and disadvantages, but the choice will be determined by which method with which the clinic has more experience[2,3]. In cases of cervical ripening, that is, with a Bishop score ≥6, labor should be induced with oxytocin.

## 2. Mechanical and Medical Methods

### *2.1. Misoprostol (Cytotec 200-mg tablet®)*

- Misoprostol is available in 200-mg tablets.
- Oral and vaginal administration can be preferred for cervical ripening.
- If there are no initial contraindications, Cytotec is applies at a dose of 50 mg (quarter tablet) vaginally. Although there are studies in the literature that recommend that the initial dose be 25 mg, it has been reported that this dose causes less hyperstimulation, while less vaginal delivery within 24 h and a greater need for augmentation with oxytocin have been reported [4,5].
- Fetal monitoring using the fetal nonstress test (NST) must be conducted for the first 30 min after Cytotec administration, after which fetal well-being should be monitored hourly.

**Table 2. Continuous Fetal Monitoring Indications.**

For patients at high risk for fetal distress, continuous follow up with NST during induction will prevent possible fetal morbidity and mortality.

Intrauterine growth restriction (IUGR)
Uncontrolled diabetes and type 1 diabetes
Intrahepatic cholestasis of pregnancy
Severe preeclampsia accompanied by magnesium and blood pressure control.
Anhydramnios, oligohydramnios, premature rupture of membranes

- Cervical ripening is contraindicated if the patient has two or more regular contractions within 10 min. During the first NST, regardless of the cervical condition at the time of presentation. Induction can be started according to the condition of the cervix where contractions decreases in the follow-ups.
- The administered dose is repeated every 4–6 h. If the patient's regular contractions have obtained, the clinician should wait 4-6 h before the dose is repeated. This is to prevent possible hyperstimulation.
- A maximum of three doses of Cytotec are applied. If there is no cervical ripening, the patient is allowed to rest and induction is resumed the next day. This protocol is used because prolonged induction has an increased risk of postpartum atony and increased adverse fetal outcomes. Because the effect of induction will continue for a certain period of time while the mother is resting, NST follow-up should be continued for at least 2 h, with more intermittent conditions.
- The most common side effect is hyperstimulation (uterine tachysystole)[6].
- Hyperstimulation is defined as 5 or more contractions within a 10-min NST.
- In patients who complicated hyperstimulation from vaginal application, the vagina should be washed with plenty of isotonic water and patient should be hydrated with isotonic solutions. Oxygen support should be provided by placing the mother in the left lateral position and continuous NST monitoring should be conducted [6].
- After cervical ripening is achieved, infusion with oxytocin must be started 4–6 h after the last Cytotec administration. The effect of Cytotec will wear off after 4–6 h and early administration of oxytocin will cause hyperstimulation and fetal distress.

### *2.2. Dinoproston (Propes® 10mg vaginal delivery system)*

- Each insert contains 10 mg Propes (prostaglandin E2) dispersed into the vaginal delivery system; hydrogel polymer and approximately 0.3 mg dinoprostone are released each hour for 24 h [4].
- Contraindications and indications are similar to that of misoprostol.
- Propes should be administrated for no more than 24 h and should be removed when the Bishop score ≥5, after which spontaneous or oxytocin should be iniated according to the patient's contractions and the follow-up should continue.
- If a membrane rupture occurs during the induction period, the Propes is removed, and oxytocin infusion is continued.
- The same rules apply when using misoprostol during induction with Propes.

### *2.3. Balloon catheter (Foley catheter)*

- The Foley catheter method can also be used to induce delivery.
- By creating a mechanical effect, the catheter will induce cervical ripening and secondary prostaglandin synthesis from desuda.
- This method has no systemic side effects.
- The risk of hyperstimulation is less compared to that with misoprostol.
- The catheter method is uncomfortable for the mother during and after the procedure.
- The Foley catheter is advanced from the cervical os and placed in the decidual space. Preferably, after inflating with 30–40 cc saline solution, it is applied to provide traction by weight (preferably, 1000cc isotonic solution available will be sufficient).
- It is most important to monitor fetal conditions using NST for the first 30 min after the procedure.
- NST tracking is similar to that described using misoprostol.
- The Foley catheter should remain no longer than 12 h, after which the patient should be able to rest. Medical cervical ripening may be the preferred protocol the next day.
- If the cervical ripening obtained after induction with the Foley catheter, oxytocin infusion can be started immediately after catheter removal.

### *2.4. Oxytocin (Synpitan forte® 5 IU/mL IM/IV ampoule)*

- Oxytocin should be preferred in cases with a Bishop score ≥6 spontaneously or after cervical ripening.

- Oxytocin should be started at a dose of 4 drops/min (2mU/9 min, and during this period, the NST device must be connected and the dose can be increased by 4 drops every 15 min up to a maximum of 32 drops (16mU/min) depending on fetal well-being and the state of uterine contractions.
- Antibiotic prophylaxis should be started in patients whose membrane rupture time exceeds 12 h.

### *2.5. Amniotomy*

- Amniotomy may be preferred in cases where the fetal head is well apposed to the cervix and cervical ripening is provided. It should be noted that it is associated with umbilical cord prolapse in cases where the fetal head is not well apposed. Early amniotomy should be avoided.

## 3. Delivery Progress

- It is necessary to define and manage labor as latent phase and active phase. The duration of the latent phase differs between spontaneous and induced deliveries, but progression in the active phase is similar for both groups. Therefore, active phase and second stage protraction disorders and arrest in induced pregnancies are diagnosed and managed in the same way as in women in spontaneous delivery.

### *3.1. Definition of failed induction*

- Failed induction defined as: failure to generate regular (eg, every 3 minutes) contractions and cervical change after at least 24 hours of oxytocin administration, with artificial membrane rupture as soon as feasible and safe[7].
- The time devoted to cervical ripening is not included when calculating the length of induction or diagnosing failed induction[8].
- Since rupture of the membrane is an important factor in the duration of induced labor, oxytocin should generally be administered for at least 12 hours after rupture of the membrane before considering the persistence of the latent phase as an indication for cesarean section.

### *3.2. Cephalopelvic disproportion*

- A disproportion in the size of the fetus relative to the maternal pelvis can result in failure to progress in the second stage and has been termed

cephalopelvic disproportion (CPD). CPD is a subjective clinical assessment based on physical examination and course of labor. It usually manifests as a prolonged second stage. It may also manifest as failure of the head to engage. Antepartum, the clinician is generally unable to predict maternal pelvis/fetal size discordance leading to arrest of labor requiring cesarean birth.

### *3.3. Protraction*

- The diagnosis of a protracted active phase in nulliparous or parous patients at ≥6 cm dilation who dilate <1 to 2 cm over two hours, acknowledging that rates of dilation are slightly faster in parous patients and in those at greater dilation.

### *3.4. Arrest*

- The diagnosis of active phase arrest and consider cesarean birth in nulliparous or parous patients with ruptured membranes, cervical dilation ≥6 cm, and one of the following
  - o No cervical change for ≥4 hours despite adequate contractions (assessed qualitatively or objectively defined as >200 Montevideo units [MVU] in patients with an intrauterine pressure catheter in place)
  - o No cervical change for ≥6 hours of oxytocin administration with inadequate contractions.

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CHAPTER 2

# MANAGEMENT OF PREECLAMPSIA, PREECLAMPSIA-RELATED COMPLICATIONS, AND LOW-DOSE ASPIRIN PROPHYLAXIS FOR PREECLAMPSIA PREVENTION

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## 1. Preeclampsia and severe preeclampsia diagnostic criteria

### *1.1. Diagnosis*

Hypertension is the main finding in typical preeclampsia during pregnancy. Typically, hypertension is diagnosed as systolic blood pressure (BP) ≥140 mmHg and diastolic BP ≥90 mmHg measured twice at least 4 h apart in a previously normotensive pregnant woman at the 20th gestational week and accompanied by one or more of the following criteria[1]:

- Proteinuria ≥ 0.3 g in a 24-h urine sample, or a protein/creatinine ratio of ≥ 0.3 in a spot urinalysis, or ≥ 2+ with a dipstick in cases where a quantitative urine measurement is not possible.
- Thrombocytopenia < 100000 platelets (plts)/μL.
- Serum creatinine value >1.1 mg/dL or a doubling of the creatinine value compared to the initial value in the absence of known renal disease.
- Depending on the hospital biochemistry cutoff values, at least a two-fold increase in liver transaminase (aspartate transaminase [AST] and alanine transaminase [ALT]) values in the upper limit of the hospital cutoff.
- Pulmonary edema.
- New onset or persistent headache.
- Presence of visual symptoms.

### *1.2. Descriptions*

The most important point when measuring BP is that the measurement is obtained at rest and by experienced personnel. It is important to measure the BP of a pregnant woman at the clinic after she has rested for at least 15 min. The diagnosis of hypertension is defined as a BP ≥140/90 mmHg. BP ≥160/110 mmHg will be classified as severe hypertension[1].

If the first BP measurement is from 140/90 to 160/110 mmHg, the value should be measured again after 4 h to be able to diagnose preeclampsia. During this period, a non-stress test (NST) should be requested for the women who are at >28 gestational weeks and the amniotic fluid and fetal well-being should be evaluated. During this period, the clinicians should request a complete blood count (CBC), biochemical parameters (blood urea nitrogen [BUN], creatinine, AST, ALT, and lactate dehydrogenase [LDH]) and spot urinalysis. If the spot urine analysis is not possible, proteinuria should be checked using a dipstick. The diagnosis will be clear from the results of these tests until the control BP value. The control BP value can be measured at shorter intervals along with the results in line with the clinician's foresight[2].

### *1.3. Severe preeclampsia criteria (signs of end-organ damage or alarms)[1]*

1. BP ≥160/110 mmHg: the most important result from the first measurement. In cases for which BP ≥160/110 mmHg, the control BP value should be measured again after a very short period of time, the fetal well-being should be urgently evaluated, and if the control BP ≥160/110 mmHg, acute antihypertensive treatment should begin, the patient should be hospitalized, and severe preeclampsia management should be provided. Any prodromal semptoms must be questioned.
2. Thrombocytopenia (plt< 100000 μL).
3. Serum creatinine value > 1.1 mg/dL or doubling of creatinine value compared to the initial value in the absence of known renal disease.
4. An increase of at least two times above the upper limit of liver AST and ALT values according to clinic values; epigastric, upper abdominal, or retrosternal pain caused by stretching of the Glisson capsule.
5. Pulmonary edema: defined as the presence of new onset dyspnea, orthopnea, and saturation ≤93 measured by pulse oximetry.
6. New onset or persistent headache: a severe headache is typical and does not respond with analgesic. The patient describes this pain as “the most severe pain in my life”. The cause of severe headache is cerebral edema, severe vasospasm in the cerebral vessels, and ischemic/hemorrhagic changes in brain tissues.
7. Visual symptoms: photopsia (flashes of light), scotoma (presence of black dots or gaps in the visual field), blurred vision, double vision, or development of temporary blindness caused by vasospasms in the retinal artery and the developing cerebral edema.

**Figure 1. Algorithm of preeclampsia and severe preeclampsia diagnosis [2].**

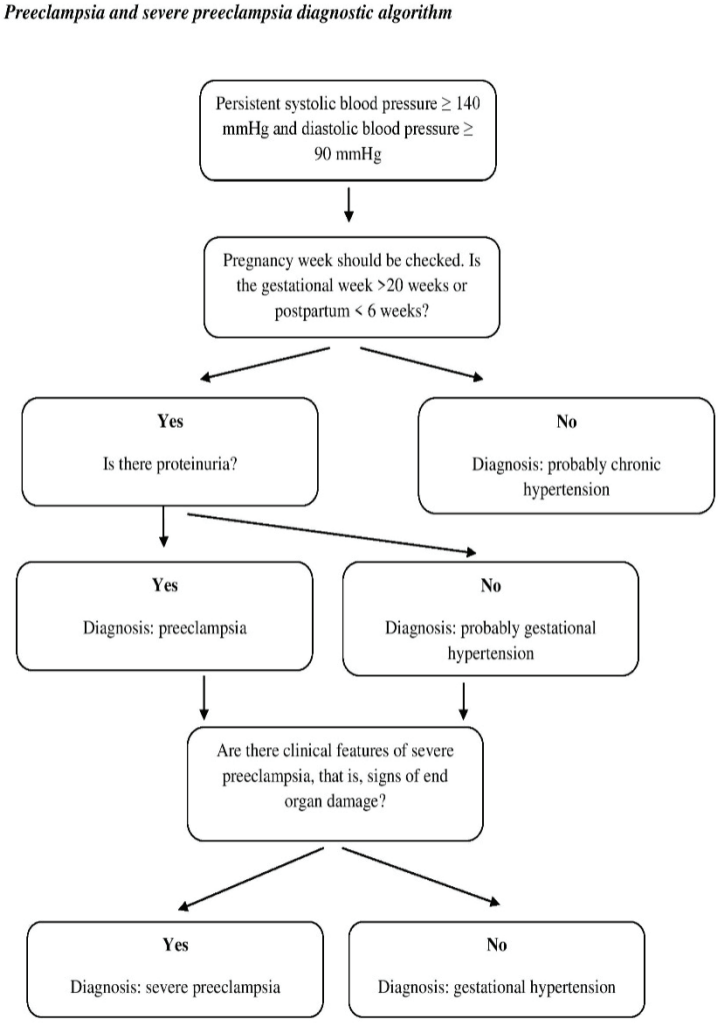
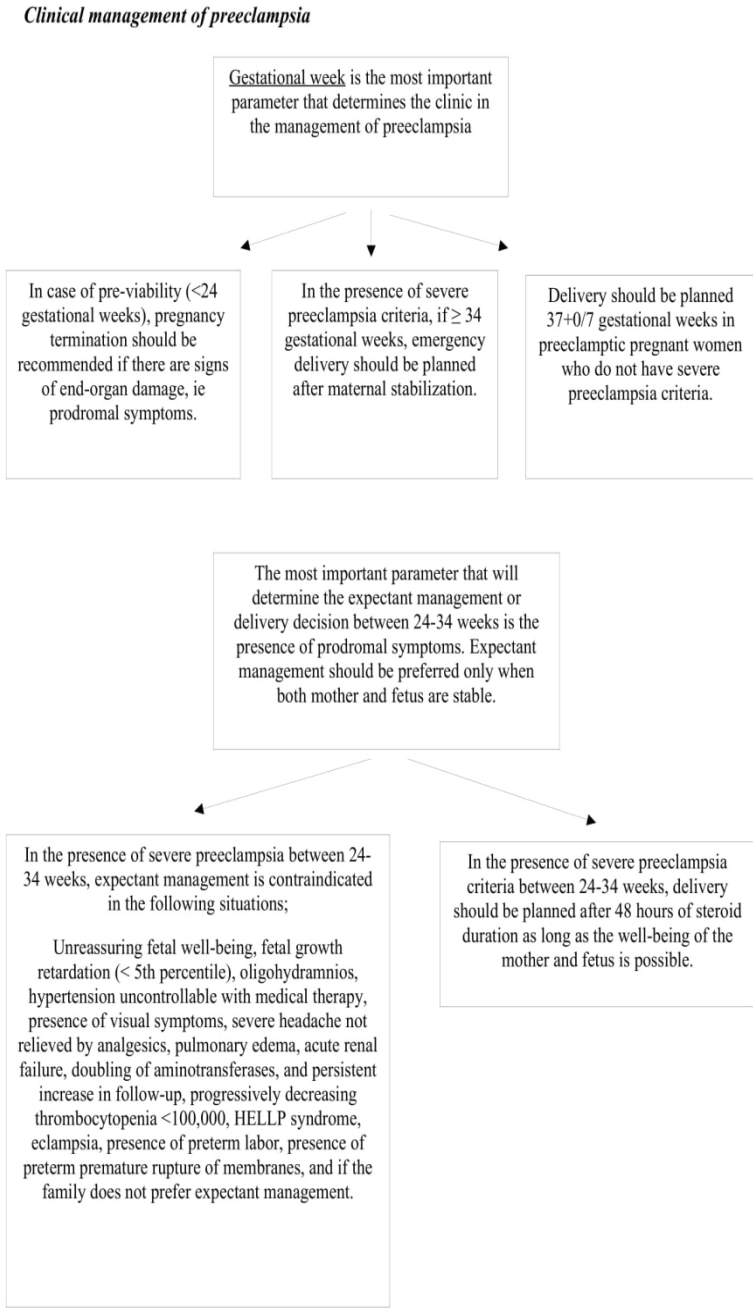


**Figure 2. Algorithm of clinical management of preeclampsia [2].**



## 2. Clinical Management of Preeclampsia

### *2.1. For hospitalized patients in the presence of non-severe preeclampsia*

- Fetal well-being should be evaluated by daily NST and measuring the amniotic fluid.
- In the presence of fetal growth retardation, Doppler blood flow measurements should be conducted semi-weekly in addition to NST (twice a day in the morning and evening), and the daily amniotic volume measurement.
- Antenatal corticosteroids should be administered less than 34 gestational weeks.
- CBC and necessary biochemical parameters should be checked semi-weekly.
- Anti-hypertensive treatment should begin for hypertension regulation. BP follow-up-timing should be determined according to the patient, and follow-up should continue at between 4 and 6 h for stable patients.
- More importantly, the clinicians must recognize that these patients may progress to severe preeclampsia during follow-up.

### *2.2. For hospitalized patients in the presence of severe preeclampsia*

- The treatment for severe preeclampsia is delivery according to the criteria mentioned above.
- Acute antihypertensive treatment should be initiated.
- Magnesium sulfate should be started to prevent seizures.
- For pregnant women ≥34 gestational weeks, delivery should be planned after maternal stabilization.
- If expectant management is preferred between 24 and 34 weeks according to the criteria above, steroids should be used for fetal pulmonary maturation.
- During management, CBC and necessary biochemical parameters should be analyzed every 6 h in terms of progression to hemolysis, elevated liver enzymes, and low plt (HELLP) syndrome.
- BP monitoring should be conducted hourly. Volume loading should be avoided in terms of pulmonary edema.
- NST follow-up should be decided according to the patient's clinic and fetal well-being.
- In line with the patient's clinic and follow-up, care should be taken related to the necessity of maternal and fetal intensive care, and the relevant intensive care clinicians should be consulted in advance.

### *2.3. Mode of delivery and intrapartum monitoring*

- Mode of delivery is planned according to standard obstetric indications.
- In the presence of severe preeclampsia, seizure prophylaxis should be given before both vaginal delivery and cesarean section, and a maintenance dose of magnesium sulfate should be started for at least 24 h after the loading dose. In the presence of gestational hypertension and non-severe preeclampsia, magnesium sulfate is not recommended.
- Continuous fetal monitoring should be conducted during delivery.
- The agent for induction should be determined according to the patient's Bishop score, and if Bishop score <5, the cervix should be ripened.
- Cesarean section should be planned in cases in which delivery induction will be prolonged and fetal well-being cannot be ensured as follows:
  a. Severe preeclampsia cases <32 gestational weeks, nulliparous, and Bishop score <5.
  b. Intrauterine fetal growth retardation cases <34 gestational weeks.
  c. In the presence of a decrease in end-diastolic flow in the umbilical artery, reverse flow, and a reversed a wave in the umbilical vein upon Doppler examination at any gestational week.

## 3. Acute Antihypertensive Therapy [3]

- In the presence of severe preeclampsia, the most urgent action is to regulate severe hypertension (≥160/110 mmHg) to prevent serious complications for both the mother and fetus[4]. Labetalol, hydralazine, and nifedipine immediate-release capsules are the current therapeutic agents. The preferred agent in the treatment depends on the obstetrician. For example, an obstetrician in a district hospital may choose nifedipine immediate-release capsules as the first choice when labetalol and hydralazine are difficult to obtain. For reference center hospitals, the experience of the clinic in terms of current drugs and the frequency of use is the most important parameter, and intravenous treatment is apriority [3].
- The most important clinical parameter is the target BP value during treatment. Systolic BP should be between 130 and 150 mmHg and diastolic BP should be between 80 and 100 mmHg. A sudden decrease in BP and one beyond the target values will cause hypoxia and disrupt tissue perfusion.

**Table 1. Treatment options and algorithm[3].**

| | | |
|---|---|---|
| **Labetalol** | Labetalol ampoule is available as 100/2mm/L IV solution. There is 5mg labetalol in 1-mL solution, which makes dose calculations easier. | **Initial dose:** 20mg IV administered as a slow infusion over 2 min. Blood pressure is measured at 10-min intervals after labetalol administration.<br>**Control 1:** If the blood pressure has not reached the target value after the first dose, 40mg IV is administered as a slow infusion over 2 min.<br>**Control 2:** If the target value is not reached after 10 min, 80mg IV is administered as a slow infusion over 2 min.<br>**Control 3:** If the target value is not reached after 10 min, 80mg IV is administered as a slow infusion over 2 min.<br>**Control 4:** If the target value is not reached after 10 min, 80mg IV is administered as a slow infusion over 2 min.<br>The maximum dose is 300 mg. If blood pressure cannot be controlled, a different antihypertensive agent is used. |
| Hydralazine | | **Initial dose:** 5 mg IV as a slow infusion over 2 min.<br>After administration of hydralazine, blood pressure is measured at 20-min intervals.<br>**Control 1:**If the target value is not reached after 20 min, 5 or 10 mg IV is administered as a slow infusion over 2 min.<br>**Control 2:** If the target value is not reached after 20 min, 10mg IV is administered as a slow infusion over 2 min.<br>The maximum dose is 30 mg. If blood pressure cannot be controlled, a different antihypertensive agent is used. |
| Nifedipine immediate-release capsule | Each capsule contains 10 mg nifedipine. Capsules should be administered orally and should not be used sublingually because of the risk of sudden blood pressure reduction. | **Initial dose:** 10mg capsule orally.<br>After administration of nifedipine, blood pressure is measured at 20-min intervals.<br>**Control 1:** If the target value is not reached after 20 min, 10 or 20 mg nifedipine is administered orally again.<br>**Control 2:** If the target value is not reached after 20 min, 10 or 20 mg nifedipine is administered orally again.<br>If blood pressure cannot be controlled, a different antihypertensive agent is used. |

## 4. HELLP Syndrome

### *4.1. Diagnosis*[1]

- Hemolysis
  - o Observation of schistocytes (fragmented erythrocytes) in a peripheral smear.
  - o Serum bilirubin ≥1.2 mg/dL.
  - o Serum haptoglobin≤ 2.5 mg/dL.
  - o LDH ≥600 IU/L.
  - o Severe anemia (Hb< 8mg/dL) without bleeding.
- AST and ALT values increase by at least twice the upper hospital reference value.
- Thrombocytopenia
  - o Plt< 100000 µLand exclusion of other causes of thrombocytopenia

### *4.2. Management of HELLP syndrome*[1]

- After the diagnosis of HELLP syndrome, delivery must be immediately planned after maternal stabilization is achieved.
- Magnesium sulfate is started for seizure prophylaxis.
- If there is severe hypertension, acute antihypertensive therapy is started.
- Required maternal hemodynamics for delivery is provided and plt and erythrocyte replacement should be performed if indicated.
- According to the clinic in which the mother and fetus are admitted, if both are stable, steroids can be administered before 34 gestational weeks.
- If gestational weeks ≥34, emergency delivery is required after maternal stabilization.
- If gestational weeks <34 in the presence of unreliable fetal well-being, suspicion of placental abruption, pulmonary edema, eclampsia, maternal hepatic bleeding, stroke, acute kidney failure, or disseminated intravascular coagulopathy (DIC), emergency delivery is required after maternal stabilization without waiting steroid administration.
- In the absence of the above-mentioned contraindications and provided that the mother and fetus are stable, very close follow-up should be conducted and two doses of steroids should be administered for 48h. If a contraindication develops during follow-up, delivery is necessary without waiting for the steroid period.

### *4.3. Mode of delivery and intrapartum monitoring*

- Delivery type and management are similar to that in severe preeclampsia.
- Mode of delivery is planned according to standard obstetric indications.
- In the presence of HELLP syndrome, seizure prophylaxis should be administered before both vaginal delivery and cesarean section, and maintenance magnesium sulfate should be continued for at least 24 h after the initial loading dose.
- Continuous fetal monitoring should be performed during delivery.
- During the follow-up, CBC, biochemical parameters and a coagulation panel (prothrombin time and international normalized ratio [PT/INR], activated partial thromboplastin time [aPTT], PT, fibrinogen) should be checked at intervals of 4–6 h, and maternal stabilization should be ensured for necessary replacements when indicated.
- The agent for induction should be determined according to the patient's Bishop score, and if Bishop score <5, the cervix should be ripened.
- Cesarean section should be planned in cases in which induction will be prolonged and fetal well-being cannot be assured in the presence of the belief that delivery will be prolonged:
  - Severe preeclampsia <32 gestational weeks, nulliparous, and Bishop score <5.
  - Intrauterine fetal growth retardation <34 gestational weeks.
  - In the presence of EDF loss in the umbilical artery, reverse flow, and a reversed a wave in the umbilical vein upon Doppler examination at any gestational week.
- Placing a drain on the anterior surface of the uterus/douglas and rectus muscle after cesarean section is very important to reduce possible bleeding complications and should not be standard protocol.

### *4.4. Postpartum period*

- It is most important to recognized that the systemic effects of postpartum HELLP syndrome are increased liver transaminases, decreased plt count, and hemolysis that will continue to deteriorate for 48 h. During this period, CBC, biochemical parameters, and a coagulation panel (PTINR, aPTT, PT, fibrinogen) should be followed up at 6- to 12-h intervals according to clinic protocols, and necessary replacements should be provided in terms of hematological terms.

- This follow-up should be continued until all hematologic parameters return to normal.
- The desired increase in plt count and the desired decrease in LDH and transaminases will be observed close to the fourth day after delivery if there are no complications.
- Primary thrombotic microangiopathy should be considered if values do not improve on the fourth day.
- Severe cases should be followed under intensive-care conditions.
- Clinicians should keep in mind that 50% of these cases may be complicated by bleeding and 20% by DIC.

## 5. Seizure Prophylaxis[1]

- In the presence of severe preeclampsia, magnesium sulfate is the preferred first agent administered during both intrapartum and postpartum periods. The primary effect of magnesium sulfate is the central effect. It increases the seizure threshold with its effect on N-methyl D-aspartate (NMDA) receptors. It decreases acetylcholine conduction at the motor nerve junction with its secondary nonspecific calcium channel blocker effect [5].

**Table 2. Dose of magnesium sulphate.**

Seizure prophylaxis should be started with a loading dose before delivery. There is 1.5g magnesium sulfate in 1 ampoule. The loading dose is added as 6 g (4 ampoules) into 100cc isotonic water and started as a slow infusion for 15–20 min.

In maintenance treatment, magnesium sulfate should be adjusted at a rate of 2g/h and continued for 24 h.

Magnesium sulfate is contraindicated in the presence of myasthenia gravis and renal failure (creatinine>2.5mg/dL).

If the creatinine is ≥1.1 to ≤2.5 mg/dL, maintenance treatment should be administered at a rate of 1g/h, that is, at half-dp, after a standard loading dose of 4.5–6.0 g.

- It is very important to inform the patient and their relatives of any side effects when beginning magnesium sulfate. Because it will cause peripheral vasodilation in the mother, sweating, flushing, nausea, vomiting, headache, muscle weakness, visual disturbance, and palpitation from a rapid decrease in BP are common side effects. Magnesium sulfate freely crosses the placenta, and there will be loss of variability in the fetal heartbeat and a decrease in the baseline within normal limits.
- Clinical signs of magnesium toxicity should be checked hourly during magnesium sulfate infusion. Hourly measurement of magnesium levels in maternal blood is not recommended. Follow-up should be preferred clinically. A urinary catheter should be attached to the patient, a chart should be prepared, and the patella reflex, respiratory rate, and hourly urine output should be monitored hourly.

**Table 3. Magnesium sulphate toxicity findings[1].**

The target value of magnesium in maternal blood is 4.8–8.4 mg/dL. If clinical toxicity is suspected, magnesium sulfate should be discontinued immediately, and the serum magnesium level should be measured in the maternal blood. The measurement should be obtained at 2-h intervals until the magnesium level <8.4 mg/dL.

- Loss of deep tendon reflex – 8.5–12 mg/dL.
- Respiratory paralysis –12–16 mg/dL.
- Onset of cardiac side effect ≥ 18 mg/dL.
- Cardiac arrest >30mg/dL.

When should the magnesium sulfate level be measured?

- When there is a seizure while treating magnesium sulfate.
- In the presence of renal insufficiency (creatinine > 1.1 mg/dL), it should be checked every 4–6 h together with clinical findings.
- In the presence of clinical signs of toxicity.

**Table 4. Magnesium sulphate toxicity treatment.**

The antidote to magnesium sulfate is calcium gluconate.

In 1 ampoule, there are 10 mL 10% calcium gluconate (calcium picken 10%, 10mL ampoule)

In the presence of severe cardiac toxicity or cardiac arrest, 15–30 mL (1.5–3.0 ampoules) are administered intravenously over 2–5 min.

For patients with less severe, but life-threatening, cardiorespiratory failure, an initial dose of 10 mL 10% solution is used.

The desired clinical response should be obtained quickly; if not, infusion should be continued up to three consecutive ampoules.

Simultaneously, 1 ampoule of 20mg lasix ampoule (furisemide) should be administered to accelerate the urinary excretion of magnesium.

## 6. Eclampsia and management[1]

- Eclampsia is the convulsive manifestation of severe preeclampsia. The most important point is that most women experience preliminary signs and symptoms hours before a seizure. Headache, hypertension, and visual symptoms are observed in approximately 75% of the cases.
- The seizure is typically tonic–clonic in nature. Initially, there is a sudden loss of consciousness usually accompanied by a scream. The muscles of the arms, legs, chest, and back become stiff (tonic phase), after about 1min, the muscles then twitch for 2 min. The patient may bite her tongue and a bloody and foamy secretion may come out of her mouth. With the end of the twitching movements, the postictal period begins. The patient will first be in a deep sleep and then gradually wake up. Most patients will begin to respond within approximately 20 min after the seizure.
- If a seizure is witnessed, airway patency should be maintained, the patient should be turned to the left lateral position to prevent aspiration, and the patient should be protected from possible trauma during the seizure.
    - o Prevent maternal hypoxia and trauma (8–10L/min oxygen is provided by mask if possible).
    - o In the presence of severe BP, acute antihypertensive treatment is started.

  - Magnesium sulfate is the primary treatment and first choice to prevent recurrence of the seizure. After the 6-g loading dose, the 2-g/hour maintenance dose should be continued for at least 24 h. Diazem should be preferred in the presence of status epilepticus, which is resistant seizures, not eclampsia. It should be noted that the use of diazem has serious side effects, such as respiratory depression.
  - While the intervention continues, the necessary planning for delivery should be done quickly and detailed information should be given to the anesthesia and pediatrics departments.
- Fetal bradycardia will develop during the seizure and within approximately 5min after the seizure. With the resolution of seizure activity, fetal tachycardia and loss of viability will be observed. Persistent bradycardia in fetal heart rate > 5 min should definitely suggest placental abruption.
- The treatment of eclampsia is delivery in line with fetal and maternal well-being.
- The decision of the mode of delivery is similar to the criteria in severe preeclampsia, but cesarean delivery will be a suitable method for these patients.
- Postpartum patients should be followed under intensive-care conditions for a certain period of time.
- All patients should be evaluated in terms of complications, such as intracerebral hemorrhage, temporary blindness, hepatocellular damage, renal dysfunction, and coagulopathy.

## 7. Use of aspirin during pregnancy for the prevention of preeclampsia[6]

- Low-dose aspirin (81mg/d) prophylaxis is recommended in the presence of high-risk factors for the development of preeclampsia and should be started at 16 weeks'gestation (can be started between 12 and 28 weeks'gestation), if possible[6].
- Low-dose aspirin prophylaxis should be started if two or more of the moderate risk factors in Table 5 are present.
- Low-dose aspirin prophylaxis is not recommended in the presence of unexplained stillbirth, fetal growth retardation, and spontaneous preterm delivery not associated with preeclampsia.
- Low-dose aspirin prophylaxis should not be used for prophylaxis in the presence of early pregnancy loss.

**Table 5. Risk factors that suggest beginning aspirin prophylaxis[6].**

| Risk | Factor | Recommendation |
|---|---|---|
| High | • History of preeclampsia, particularly associated with adverse perinatal outcomes<br>• Multiple pregnancies<br>• Chronic hypertension<br>• Type 1 and type 2 diabetes<br>• Renal failure<br>• SLE and antiphospholipid antibody syndrome | Presence of one of the risk factors is an indication for starting low-dose aspirin. |
| Medium | • Nulliparity<br>• BMI>30kg/m$^2$<br>• A family history of preeclampsia<br>• Maternal age ≥35 years<br>• Low birth weight or history of SGA | If two or more of the risk factors are present, low-dose aspirin is an indication. |

Notes: SLE: systemic lupus erythematosus; BMI: body mass index.

- Randomized controlled studies and systematic reviews have shown that the use of low-dose aspirin is not associated with placental abruption or postpartum hemorrhage. The circulating life of plts is 7 d. The use of low-dose aspirin (60–150mg/d) irreversibly inhibits the cyclogenase-1 enzyme. This causes a decrease in thromboxane A2 (a potent vasoconstrictor and promoter of plt aggregation) without affecting prostacyclin production (a potent vasodilator and inhibitor of plt aggregation) in the vascular endothelium[7]. Although not associated with postpartum bleeding, decreased thromboxane A2 may cause bleeding. It is important to place a hemovac drain preferably on the anterior surface of the uterus in the cesarean section. In cases with bleeding, plt functions should be replaced, which may require plt replacement. One unit of plt replacement will increase the plt count by 10,000, and one unit pooled platelet replacement will increase the plt count by 50,000 units.
- Low-dose aspirin treatment does not have a risk of developing congenital anomaly on the fetus.
- Low-dose aspirin is contraindicated in the presence of aspirin allergy (in the presence of asthma and nasal polyps), history of gastrointestinal and genitourinary system bleeding, active peptic ulcer, and severe liver failure.

- Although there is no clear consensus on when aspirin should be discontinued, it may be an appropriate approach to discontinue aspirin at 36 weeks of gestation to ensure adequate pltfunction and to be safe in terms of bleeding, considering that the delivery of these high-risk pregnant women is usually at ~37 weeks of gestation.

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CHAPTER 3

# DIAGNOSIS AND MANAGEMENT OF GESTATIONAL AND CHRONIC HYPERTENSION DURING PREGNANCY

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## 1. Diagnosis and antenatal management of gestational hypertension

- Gestational hypertension (GHT) is defined as new-onset hypertension without proteinuria after 20 weeks'gestation. For the diagnosis of hypertension, as defined in the preeclampsia section, the resting blood pressure (BP) measured at 4-h intervals should be ≥140/90mmHg [1].

- Preeclampsia must be excluded for diagnosis.
- The most critical point in GHT follow-up is to understand that these patients may progress to preeclampsia. We find during follow-up, that 10–50% of pregnant women progress to preeclampsia.

### *1.1. GHT with mild and moderate hypertension*

- Antihypertension treatment should begin and target BP values should be reached (Table 2).
- At home, BP should be monitored as at least once per day, and the measurements should be recorded.
- Antenatal corticosteroids are not recommended in pregnant women whose non-severe BP is regulated by antihypertension medication.

### *1.2. GHT with severe hypertension*

- Severe GHT is defined as BP ≥160/110mm/Hg without proteinuria.
- It is urgent that fetal well-being be evaluated and acute antihypertension therapy be provided.
- The patient must be hospitalized.
- After acute antihypertension treatment, antihypertension medication should begin for BP regulation (Table 2).
- Antenatal corticosteroids should be administered if <34 weeks'gestation.
- After BP is regulated, the patient can be discharged according to the gestational week after the regulated BP values are monitored for at least 24 h.
- After discharge, patients should continue to monitor their BP at home, should receive information at discharge about BP regulation, and should be contacted for weekly outpatient follow-ups.
- With the aim of predicting the progression of preeclampsia, a BP follow-up chart should be evaluated at each control, and a complete blood count (CBC), aspartate aminotransferase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), and creatinine values should be analyzed.
- For pregnant women whose BP is regulated, a weekly fetal nonstress test (NST) and amniotic fluid measurement should be conducted beginning at 32 weeks' gestation.
- For pregnant women with a poor obstetric history, NST and amniotic fluid measurements should be followed beginning at 28 weeks' gestation.

### *1.3. Mode of delivery and intrapartum monitoring*

- Mode of delivery is planned according to standard obstetric indications[1].
- It is not recommended to begin magnesium sulfate.
- Intrapartum NST follow-up should be determined according to fetal well-being, preferably continuous monitoring during induction or NST follow-up at 1-h intervals.
- Delivery time[2]
  - o If BP is between 140/90 and 160/110mm/Hg despite treatment and there is no risk factor that may cause additional comorbidity and adverse perinatal outcomes, delivery between $38^{0/7}$ and $39^{0/7}$ gestational weeks is preferred.
  - o In the presence of risk factors in those BP is between 140/90 and 160/110mm/Hg despite treatment, and there is additional comorbidity that may cause adverse perinatal outcomes, delivery at $37^{0/7}$ weeks'gestation is preferred.
  - o Emergency delivery is preferred after maternal stabilization at >34 weeks'gestation in patients with BP ≥160/110mm/Hg that cannot be controlled with antihypertension agents.

### *1.4. Postpartum management*

- The majority of pregnancies complicated by GHT will become normotensive in the first postpartum week.
- Postpartum antihypertension treatment should be continued for a while, BP monitoring should be continued at home after discharge, and the measurements should be recorded on a chart.
- Deep-vein thrombosis risk factors should be evaluated at discharge, and low molecular–weight heparin should be prescribed for patients when indicated.
- If the BP values return to normal without the use of antihypertension agents at the $12^{th}$ postpartum week, the diagnosis would be transient hypertension of pregnancy; however, in 15% of these cases, hypertension will continue and will be diagnosed as chronic.

## 2. Diagnosis and antenatal management of chronic hypertension

- Chronic hypertension is defined as elevated BP detected before the 20weeks' gestation or preconception period[3]. Chronic hypertension is characterized by increased maternal and fetal adverse outcomes during pregnancy, and superimposed preeclampsia develops in approximately 10–40% of cases.

**Table 1. Recommended at First Clinical Visit[3].**

- Basal laboratory values should be requested. CBC, fasting glucose, BUN, creatinine, Na, K, AST, ALT, and LDH should be evaluated, and other pregnancy routines requested. The protein/creatinine ratio should be evaluated in spot urine, or the microprotein level should be evaluated in 24-h urine.
- The antihypertension agent should be revised according to pregnancy.
- Cardiology consultation and transthoracic ECHO examination should be planned.
- At home, at least one measurement should be recorded daily by monitoring blood pressure.
- Pregnant women should be informed about the recommended weight gain during pregnancy.

Notes: CBC, complete blood count; BUN, blood urea nitrogen, Na, sodium; K, potassium, AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase.

### *2.1. Recommendation and follow-up [3,4]*

- If there is no contraindication, 80mg/d aspirin prophylaxis should begin between 12 and 16 weeks'gestation to prevent the development of preeclampsia.
- After 20 weeks' gestation, the patient should be informed about the signs of preeclampsia in terms of possible superimposed preeclampsia.
- NST and amniotic fluid measurement follow-up should begin at 28 weeks' gestation and biweekly until 32 weeks' gestation, and weekly antenatal follow-up should be conducted after 32 weeks' gestation. In selected pregnant women with a poor obstetric history, this follow-up may be semiweekly after 32 weeks'gestation.
- If BP, which is regulated at the end of the second trimester or at the beginning of the third trimester, becomes severe and tends to increase during the follow-ups, preeclampsia should be considered and evaluated.

### *2.2. Mode of delivery and intrapartum monitoring*

- Mode of delivery is planned according to standard obstetric indications.
- In pregnant women who are not treated with antihypertension medication and whose BP is regulated, delivery is planned between $38^{0/7}$ and $39^{6/7}$ gestational weeks.
- In pregnant women who are treated with antihypertension medication and whose BP is regulated, delivery is planned between $37^{0/7}$ and $39^{0/7}$gestational weeks.
- In pregnant women whose BP is difficult to control with medical treatment, delivery is planned between $34^{0/7}$ and $36^{6/7}$ gestational weeks.
- There is no indication for magnesium sulfate during delivery and the postpartum period, and delivery induction is preferred as described in the first section of this book.
- After 24-h postpartum, normal BP is monitored, and the patient should be discharged with a recommendation of administration of low molecular–weight heparin within the indications.
- In pregnant women whose BP is not regulated after delivery, antihypertension medication should begin as presented in Table 2. A BP follow-up chart should be prepared, and the dose should be regulated according to BP values.

### *2.3. Antepartum and postpartum antihypertension treatment*

- One of the most important points is that although the American Journal of Obstetrics and Gynecology recommends antihypertension therapy for BP ≥160/110mmHg, considering the presence of endothelial dysfunction caused by chronic hypertension, neurologic involvement, and possible end-organ damage, antihypertension therapy should begin when BP ≥150/100 mmHg.
- The target BP value after treatment should be within the range of 130–150/80–100 mmHg. In the presence of signs of cardiac or renal end-organ damage, these values should be within the range of 120–140/80–90mmHg.
- Considering the National Institute for Health and Care Excellence guidelines, it is recommended to begin antihypertension treatment at BP ≥140/90 mmHg and to maintain BP within the range of ≤135/85mmHg.

**Table 2. Antihypertension drugs and doses[3].**

| | | |
|---|---|---|
| Labetalol | Available in100-mg tablets. | Treatment begins at a dose of 100mg 2*1.<br>If the target blood pressure (BP) is not reached after 3-day BP monitoring, the dose is increased to 200mg 2*1, and follow-up is continued.<br>Usually the effective dose is 200–800mg/d divided into two doses.<br>The maximum dose that can be used is 2400mg/d. |
| Nifedipine extended-release | Available as 30-mg and 60-mg capsules. | The starting dose of treatment is 30–60 mg/day.<br>If the target BP is not reached within the 7- to14-d target range, the dose is increased, and BP monitoring is continued. Usually, the effective dose is 30–90mg/d divided into two doses. The maximum dose that can be used is 120mg/d. |
| Methyldopa | Available as 250-mg tablets. | Treatment is started at a dose of 250mg 2*1 or 3*1 doses.<br>If the target BP is not reached after 3-d BP monitoring, the dose is revised.<br>Usually the effective dose is 250–1000mg/d divided into three doses.<br>The maximum dose that can be used is 3000mg/d. |

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CHAPTER 4

# DEFINITION AND MANAGEMENT OF INTRAUTERINE GROWTH RESTRICTION

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## 1. Definition of Intrauterine Growth Restriction

Classically, intrauterine growth restriction (IUGR) is defined as an estimated fetal weight (EFW) or fetal abdominal circumference (AC) measured by ultrasonography below the 10th percentile. An EFW or AC below the 3rd percentile is defined as severe IUGR. Cases starting under 32 weeks of gestation

should be defined as early-onset, and cases starting after 32 weeks of gestation should be defined as late-onset IUGR[1].

- Symmetrical and asymmetrical IUGR definition is defined based on fetal biometric measurements. During clinical visits, defining the pregnant woman as early-onset or late-onset, severe or not severe IUGR rather than presenting it as IUGR will further clarify the clinical importance.
- SGA (Small for Gestational Age) is defined as fetuses without any structural anomalies and pathologies, with normal Doppler blood flow and intrauterine growth retardation. It should be noted that SGA is associated with increased perinatal adverse outcomes.
- Before the diagnosis of IUGR, it must be confirmed with the previous period ultrasounds in addition to the last menstrual period.

**Table 1. Comfirmation of LMP and Ultrasonographic Paramaters**[2]

| **Gestational age** | **Measured parameter** | **The gestational week to be considered between the LMP and the ultrasound date** |
|---|---|---|
| ≤13 $^{6/7}$ weeks<br>• ≤8 $^{6/7}$ weeks<br>• 9 $^{0/7}$-13 $^{6/7}$ weeks | CRL | 5 days<br>7 days |
| 14 $^{0/7}$- 15 $^{6/7}$ weeks | BPD, HC, AC, FL | 7 days |
| 16 $^{0/7}$- 21 $^{6/7}$ weeks | BPD, HC, AC, FL | 10 days |
| 22 $^{0/7}$- 27 $^{6/7}$ weeks | BPD, HC, AC, FL | 14 days |
| ≥ 28 $^{0/7}$ weeks | BPD, HC, AC, FL | days |

LMP, last menstrual period; CRL, crown-rump length; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

- Clinical management after the diagnosis of IUGR should be based on the etiology of IUGR[1].
  - o Preeclampsia accompanies approximately 50-60% of cases. It is important that all patients are examined and evaluated with preeclampsia diagnostic criteria.
  - o If polyhydramnios accompanies IUGR, chromosomal and morphological anomalies should come to mind first. Perinatal screening tests, anomaly screening report and karyotype analysis results, if any, should be requested from the patient, otherwise these tests should be planned according to the week of gestation.

- The results of TORCH group infections should be requested, otherwise tests should be requested.
- Perinatology consultation should be requested in necessary cases and management should be carried out accordingly after the etiologic cause has been determined.

## 2. Clinical management of IUGR cases

IUGR management should be done in line with;

- Gestational age
- Amniotic fluid amount (AFA)
- Non-stress test and biophysical profile
- Doppler findings

**AFM management**

In the presence of anhydramnios at 34 weeks or more, delivery should be planned regardless of Doppler findings.

In the presence of oligohydramnios at 37 weeks or more, delivery should be planned regardless of Doppler findings.

**Doppler findings management**

If there is an increase in end-diastolic flow (EDF) resistance in the umbilical artery, delivery should be planned at $\geq 37^{0/7}$ weeks.

If there is loss of EDF in the umbilical artery, emergency deliveries should be planned at $34^{0/7}$ weeks.

If there is reverse flow in EDF in the umbilical artery, emergency deliveries should be planned at $32^{0/7}$ weeks.

If there is persistent reverse a wave in the ductus venosus, emergency deliveries should be planned at $32^{0/7}$ weeks.

Administering steroids for fetal lung development and gaining steroid duration should be done for these fetuses if NST and fetal well-being is possible. Continuous fetal monitoring is required.

## 3. Clinical follow-up and explanations regarding management

### *3.1. For SGA babies with normal Doppler findings and AFA, but EWF and AC values below the 10th percentile;*

- NST and AFA measurement at 3-day intervals
- Weekly biophysical profile and Doppler measurement
- Fetal development follow-up at 2-week intervals
- Steroids should be administered for fetal lung maturation
- In cases where the mother and fetus are stable, delivery should be planned at 39 $^{0/7}$ weeks.

### *1.2. If there is increased resistance in EDF in the umbilical artery (cerebroplacental ratio >1.1, umbilical artery PI > 95th percentile, MCI PI < 5th percentile);*

- NST and AFA measurement at 3-day intervals
- Weekly biophysical profile and Doppler measurement
- Fetal development follow-up at 2-week intervals
- Steroids should be administered for fetal lung maturation
- The follow-up of these pregnant women can be done under the conditions of the outpatient clinic for conscious patients. Hospitalization and follow-up of pregnant women who cannot come to their current follow-up or will delay their follow-up may be a choice for clinical management.
- In cases where the mother and fetus are stable, delivery should be planned at 37 $^{0/7}$ weeks.

### *1.3. In the presence of loss of EDF in the umbilical artery;*

- Patients should be hospitalized
- NST follow-up should be 2 or 3 times a day based on fetal well-being and daily AFA measurement
- Biophysical profile and Doppler measurement at 3-day intervals
- Steroids should be administered for fetal lung maturation
- In cases where the mother and fetus are stable, delivery should be planned urgently at 34 $^{0/7}$ weeks.

### *1.4. In the presence of reverse flow in EDF in the umbilical artery;*

- Patients should be hospitalized urgently and fetal well-being should be evaluated

- In the presence of reverse flow, ductus venosus Doppler should also be evaluated
- Presence of reverse flow is associated with possible chronic fetal hypoxia
- In cases where the mother and fetus are stable, delivery should be planned urgently at 32 $^{0/7}$ weeks
- In pregnancies below 32 weeks, where the mother and fetus are stable, it should be aimed to gain steroid duration by applying steroids as much as possible, with continuous fetal monitoring and fetal well-being.

### *1.5. In the presence of persistent reverse a wave in ductus venosus Doppler*

- It is associated with severe chronic fetal hypoxia
- Patients should be hospitalized urgently and fetal well-being should be evaluated
- In cases where the mother and fetus are stable, delivery should be planned urgently at 30 $^{0/7}$ weeks
- Follow-up under 30 weeks should be individualized in terms of gaining steroid duration and management should be planned according to fetal well-being. In line with my general clinical experience, the first NST connected to this pregnant woman will be reported diagnostically for fetal distress. If steroid period can be gained, emergency delivery should be planned as soon as the period is completed.

## 4. Mode of delivery in IUGR pregnancies [3]

- Induction of labor and vaginal delivery should be preferred in pregnant women with normal Doppler findings and increased resistance in EDF. Fetal distress is possible during induction, and continuous fetal monitoring should be performed and more attention should be paid to fetal distress, especially in the period after the first induction.
- If there is loss of EDF in umbilical artery Doppler, reverse flow and reverse a wave in ductus venosus, cesarean delivery should be preferred.
- In cases with severe preeclampsia, magnesium sulfate should be started for seizure prophylaxis.
- If the birth will take place under 32 weeks, magnesium sulfate should be started in terms of neuroprotective effect and magnesium sulfate period should be gained if possible [4].
- An experienced pediatrician should definitely be called to the delivery room and operating room, and they should be informed before birth that these

fetuses may be associated with chronic asphyxia, neonatal resuscitation protocol and intubation may be required.

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CHAPTER 5

# PREVENTION OF PRETERM DELIVERY, ANTENATAL CORTICOSTEROID ADMINISTRATION, CERVICAL CYCLAGE AND CORTICOSTEROID ADMINISTRATION IN PREGNANTS AT RISK OF LATE PRETERM DELIVERY

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## 1. Diagnosis and Management of Preterm Labor

Accurate and early diagnosis of preterm labor (PTL) will allow convenient managements that can make better neonatal outcomes. Antenatal administration of corticosteroid, infection prophylaxis for group B streptococcal (GBS), magnesium sulfate for neuroprotection, and transfer (if necessary) to an institution with proper neonatal care should be the main goals of treatment [1].

**Table 1. Diagnosis of Preterm Labor** [1]

| |
|---|
| The diagnosis of PTL requires orderly uterine contractions that lead to cervical alteration such as effacement or dilation |
| Uterine contractions (≥4 in 20 minutes or ≥8 in 60 minutes) and at least one of the following |
| Cervical dilation ≥3 cm or |
| Cervical length <20 mm on transvaginal ultrasound or |
| Cervical length 20 to <30 mm on transvaginal ultrasound and positive fetal fibronectin test |

**Table 2. Initial Management of Preterm Labor**

| |
|---|
| • Antenatal steroid is administered for fetal lung maturation. A single dose of reminder steroid administration is required for patients under 28 weeks and at least 14 days ago.<br>• Tocolysis is started for 48 hours to ensure the maximum fetal effect of the steroid.<br>• Antibiotics are started for GBS prophylaxis.<br>• If a possible delivery is foreseen between 24th and 32th gestational weeks, magnesium sulfate is started for neuroprotective effect.<br>• Progesterone supplementation has no role in the treatment of acute PTL. |

- For the diagnosis of PTL in twin pregnancies, the diagnostic criteria in terms of uterine contraction and cervical dilation are similar to those single pregnancies.

- Transvaginal cervical length criteria differ in twin pregnancies, and the high-risk limit of cervix length is accepted as 25 mm. If possible, fetal fibronectin test is recommended for cervical length between 25-35 mm.

## 2. Inhibition of Acute Preterm Labor (Tocolysis)[1]

In the presence of acute PTL, the main goals of tocolysis treatment should be:

- Delay birth for at least 48 hours (when safe) to achieve maximum fetal/neonatal effects of antenatal corticosteroids (primary or rescue).
- Provide time, if necessary, for the mother to be safely transported to a facility with a suitable level of neonatal care in the event of a premature delivery.
- Prolonging the pregnancy (when safe) if there are underlying, self-limiting conditions that may induce delivery such as pyelonephritis or abdominal surgery.
- The Maternal-Fetal Medicine Association and the American College of Obstetricians and Gynaecologists recommend that tocolysis should not be administered before 24$^{th}$ gestational weeks, but should be used at 23$^{th}$ gestational weeks depending on individual conditions. The 34$^{th}$ weeks of gestation should be considered as the upper limit because perinatal mortality and morbidity are low, the potential fetal and maternal risks and costs associated with the prevention of PTL and short-term labor delay have not been confirmed.
- The first-line tocolytic therapy for 24$^{th}$-32$^{th}$ gestational weeks is indomethacin. Nifedipine is recommended as an alternative tocolytic agent, if indomethacin therapy is contraindicated such as gastrointestinal ulcerative disease, bleeding disorder or platelet dysfunction, liver or renal disorder, or asthma (in women with aspirin hypersensitivity).
- For pregnant women at 32$^{th}$-34$^{th}$ gestational weeks, nifedipine should be used for first-line therapy given the potential for adverse fetal effects from the use of indomethacin at these weeks of gestation.
- Combined use of tocolytic drugs should be refrained due to the increased side effects and insufficient evidence. In particular, the simultaneous use of Nifedipine and magnesium sulfate may be associated with serious adverse outcomes.
- It is recommended to discontinue tocolytics 48 hours after the first dose of steroids.
- If a second event of acute preterm labor occurs, our indications for retreatment are the same as for the primary episode (i.e. administration of corticosteroids, primary or rescue) and/or delayed delivery for maternal transfer. There are no data on the role of repeated courses of tocolytics in the treatment of recurrent preterm birth.

**Table 3. The Most Commonly Used Tocolytic Drugs, Their Mechanism of Action, Usage Patterns and Maternal and Fetal Side Effects**

| | **Mechanism of action** | **Usage patterns** | **Maternal and fetal side effects** |
|---|---|---|---|
| Indomethacin (Endol 25mg capsule) | Nonspecific Cyclooxygenase (COX) inhibitor | A 50 to 100 mg loading dose (can be given orally or rectally), followed by 25 mg orally every four to six hours. Indomethacin should not be continued for longer than 48 hours. In case of longer use, sonographic evaluation should be performed at least once a week for oligohydramnios and narrowing of the fetal ductus arteriosus.<br>Indomethacin is contraindicated in women with platelet dysfunction, bleeding diathesis, liver or renal disorder, gastrointestinal ulcerative disease, and asthma (in pregnant women with aspirin hypersensitivity). | Maternal- nausea, esophageal reflux, gastritis and vomiting Narrowing of the fetal ductus arteriosus and oligohydramnios Neonatal -bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, periventricular leukomalacia and intraventricular hemorrhage |
| Calcium channel blocker, Nifedipine (Nidilat 10mg capsule) | Calcium channel blockers directly block the flow of calcium ions across the cell membrane. | 20 to 30 mg orally Nifedipine is suggested as an initial loading dose, and then is continued 10 to 20 mg orally every 3 to 8 hours during 48 hours. The maximum dose of Nifedipine is 180 mg/day.<br>Plasma concentrations peak within 30 to 60 minutes. The half-life of Nifedipine is approximately two to three hours, and a single orally administered dose has a duration of action of up to six hours. Nifedipine is usually metabolized in the liver and then eliminated by the kidneys.<br>Contraindication: Drug hypersensitivity, hypotension, or preload-related cardiac lesions, women with heart failure with low ejection fraction.Concomitant use of Magnesium sulfates and Nifedipine may act synergistically to suppress muscle contraction, which may cause respiratory depression. | Maternal palpitations Flushing Headache Dizziness Nausea, Reflex tachycardia Total vascular resistance may decrease.<br>There are no data on fetal adverse events related to commonly used oral doses for labor inhibition. |

- Beta-agonists (i.e. terbutaline), magnesium sulfate, oxytocin receptor antagonist (i.e. atosiban) and nitric oxide containing agents (i.e. nitroglycerin) are other tocolytic agents. Due to the high side effects, low maternal tolerance to drugs and limited tocolytic effects, their use is done in line with the experiences and preferences of each clinic.
- Are antibiotic therapy, progesterone therapy and bed rest, hydration effective in acute treatment? Subclinical genital tract infection obviously contributes to the pathogenesis of preterm labor. However, antibiotic therapy has no evidence-based role in preventing preterm labor. In the presence of acute PTL, patients do not benefit from progesterone supplementation. There is no convincing evidence that bed rest, hydration, or sedation are effective for the prevention or treatment of PTL.

### *2.1. Antenatal corticosteroid administration* [2]

- It is known that respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis and neonatal mortality are reduced by approximately 50% with antenatal corticosteroid administration.
- Considering these benefits, antenatal corticosteroid should be administered to pregnant women who are between 23$^{th}$ and 34$^{th}$ weeks of gestation and have a high probability of preterm birth within seven days.
- The treatment dose is for an antenatal course of corticosteroids; two doses of 12mg intramuscular betamethasone 24 hours apart or 4 doses of 6 mg dexamethasone 12 hours apart.
- It is suggested that benefits for newborn begin to occur within hours of antenatal corticosteroid application. Maximum influence occurs when delivery occurs two to seven days after application of the first dose of antenatal corticosteroid.
- After antenatal steroid administration, loss of variability in NST may be observed and temporary decrease in fetal heart rate within normal limits. These changes should be expected between 2-7 days when the effect of the steroid is maximum. Antenatal corticosteroid indication and treatment dose are similar for multiple pregnancies.
- If a possible delivery is foreseen between 24$^{th}$ and 32$^{th}$ gestational weeks, magnesium sulfate is started for neuroprotective effect[3].
- For diabetic pregnant women, secondary hyperglycemia should be followed up after antenatal corticosteroid administration. The effect of steroids on blood sugar usually starts 12 hours after the first administration and continues for the next 5 days. Diabetic ketoacidosis should be avoided and

closer blood glucose monitoring should be provided for pregnant women with impaired blood sugar regulation.

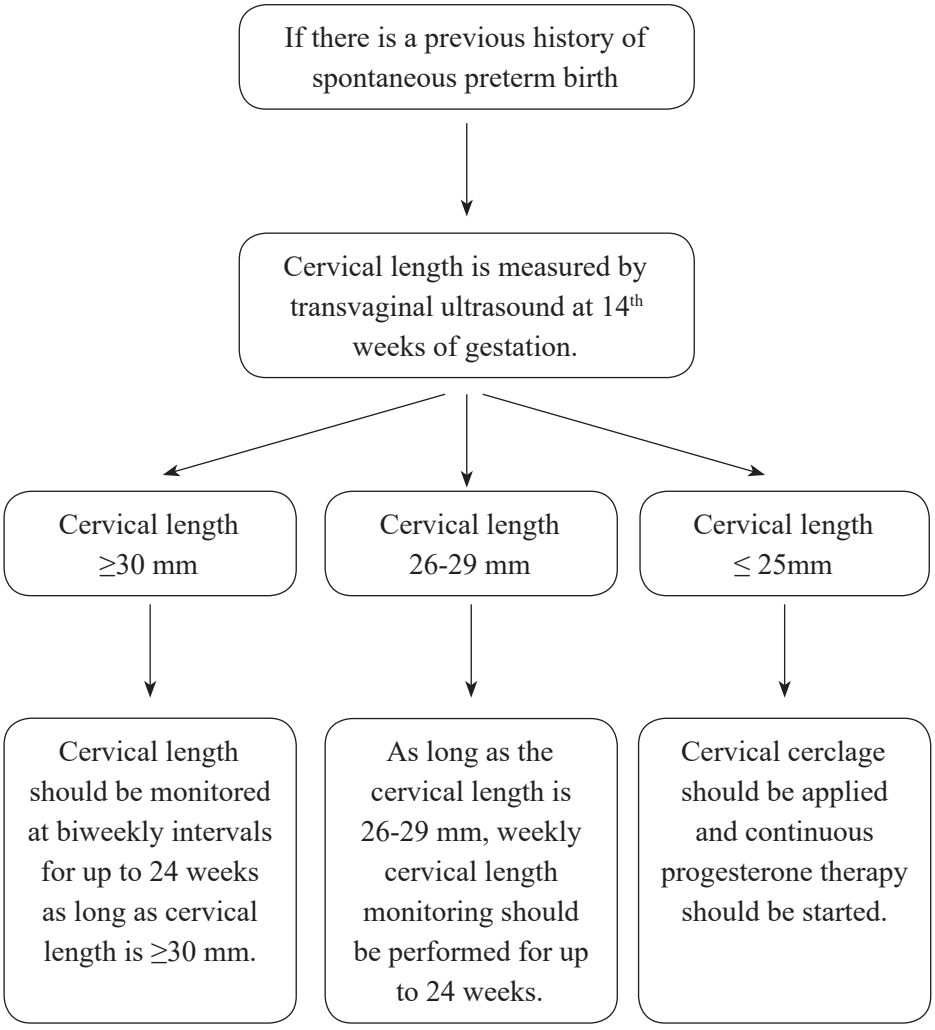
### *2.2. Reminder dose (support or rescue dose)[2]*

- Because there is not enough consistent and long-term data about the count of cures that are safe for the fetus, and the proper time interval among treatments, and the optimum dose for repeated cures, or the overall outcome of a single cure, we cannot make any strong recommendation.
- A cure of rescue (support) therapy is recommended only if the patient is clinically estimated to be at high risk of birth within seven days and more than two weeks have passed since the first antenatal corticosteroid administration.
- In addition, it is recommended to use 12 mg betamethasone as a single dose instead of two doses, and to limit the treatment to this additional dose before 34 weeks of gestation.
- For antenatal corticosteroid administration over 34 weeks, considering the long-term side effects of steroids, each clinic should individualize their decisions in line with their preferred guidelines (ACOG, WHO, NICE and Ministry of Health).

## 3. Cervical insufficiency, cervical cerclage and progesterone use in pregnancy[1]

- The two most important parameters in the treatment are the patient's previous history of spontaneous preterm birth and the length of the cervix measured transvaginally.
- Cervical length should be measured routinely by transvaginal ultrasound around the $20^{th}$ ($18^{th}$ -$24^{th}$) gestational weeks for pregnant women with a singleton pregnancy who do not have a history of spontaneous preterm birth.
- Routine antenatal follow-up is recommended for pregnant women with a cervical length >25mm. In cases where the cervix is <25 mm, vaginal progesterone should be started and continued until the $36^{th}$ week of pregnancy**.**

**Algorithm 1. Cervical length Fallow-up of high Risk Pregnancies**[4]




### *3.1. Cervical insufficiency diagnostic evaluation*

- Diagnosis based on obstetric history — Classically defined as the presence of ≥2 consecutive second trimester (ie, <28 weeks) pregnancy loss with mild or no history of symptoms.
- Ultrasound-based diagnosis — Defined as cervical insufficiency when cervical length ≤25 mm before 24 weeks as presented in the algorithm above. Since cerclage is rarely performed after this period, TVUS scanning is terminated at 24 weeks of gestation.

- Diagnosis based on physical examination — Cervical insufficiency is diagnosed based on physical examination in women between 14 and 27 weeks of gestation who have a dilated and effaced cervix on physical examination, no contractions, or weak irregular contractions that appear insufficient to explain cervical dilation. For the diagnosis of cervical insufficiency in these patients, labor, infection, placental abruption and placenta previa should be excluded by physical examination and ultrasound examination.

***3.2. Cervical cerclage***

- For patients diagnosed with cervical insufficiency as described above, cerclage is indicated at 12 to 14 weeks of gestation instead of ultrasound monitoring of cervical length. These patients should also be started on progesterone and continued until the 36th week of pregnancy.
- Cervical cerclage is recommended for pregnant women diagnosed with cervical insufficiency according to ultrasound. See algorithm.
- Cervical cerclage is recommended for pregnant women diagnosed with cervical insufficiency based on physical examination. Since the incidence of intraamniotic infection in these patients is approximately 20-50%, amniocentesis is recommended for the diagnosis of subclinical infection before cerclage placement when the cervix is dilated ≥2 cm on manual or speculum examination.
- Routine cerclage for women with twin or multiple pregnancies is controversial and should be individualized.
- History-based cervical cerclage should be repeated in subsequent pregnancies for successful pregnant women who had cervical cerclage in their previous pregnancies.

## 4. Administration of progesterone[5]

- The first alternative is hydroxyprogesterone caproate (Proluton depot 500mg/2ml 1 ampoule). Natural progesterone administered vaginally is a reasonable alternative.
- 100 mg micronized progesterone vaginal tablet can be preferred at a dose of 100-200mg every night vaginally from the moment of diagnosis until the 36th week of pregnancy. In multiple pregnancies, it is recommended not to routinely supplement with progesterone**.**

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# CHAPTER 6

# DIAGNOSIS AND MANAGEMENT OF PRE-GESTATIONAL AND GESTATIONAL DIABETES MELLITUS

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## 1. Gestational Diabetes Mellitus

### *1.1. Diagnosis*

Gestational diabetes mellitus (GDM) is a type of carbohydrate intolerance that occurs especially during the midtrimester of pregnancy. Patients who do not require insulin treatment and whose serum glucose levels are regulated by diet and exercise are classified as GDMA1 and those who require insulin to regulate serum glucose levels are classified as GDMA2.

**Table 1. Gestational Diabetes Mellitus (GDM) Screening and Diagnosis.**

Pregnant women with high risk factors for GDM should be screened during their first prenatal visit and again between 24 and 28 weeks of gestation, even if the first screening is negative.

The American Journal of Obstetrics and Gynecology recommends that all pregnant women be screened between 24 and 28 weeks of gestation[1].

What are high risk factors?[1]

- A body mass index ≥ 25 kg/m2 and at least one of the other factors below.
- Physical inactivity, maternal age ≥40 years, history of DM in first-degree relatives, delivery history ≥ 4000 g, GDM in previous pregnancy, pre-gestational hypertension, presence of polycystic ovary syndrome, high-density lipoprotein <35mg/dL and triglycerides>250mg/dL, HbA1c≥5.7 percentile, and a history of cardiovascular disease.

**Table 2. Gestational Diabetes Mellitus (GDM) Screening Methods.**

According to the obstetrician's preference, screening can be conducted using a 50-g two-step method or 75-g one-step method.

Two-step screening: the 50 g glucose method is preferred in the first step, and the cut-off value for serum glucose within the first hour after loading is 140mg/dL. In some clinics, the accepted value is 130 or 135mg/dL. If the test is positive, the 100-g glucose method is conducted. After loading with 100 g glucose, two of the following upper limit values are enough for diagnosing GDM: (1) fasting-95mg/dL, (2) first hour- 180mg/dL, (3) second hour- 155mg/dL, or (4) third hour- 140mg/dL[2].

Single step screening: After loading with 75 g glucose, one of the following upper limit values are enough for diagnosing GDM: (1) fasting – 92mg/dL, (2) first hour- 180mg/dL, or (3) second hour- 153mg/dL[3].

### *1.2. Maternal glucose regulation and fallow-up*

- After the diagnosis, treatment with diet, exercise, or insulin, serum glucose levels should be monitored and kept at target levels. The recommended follow-up is four times/d, with one fasting and three postprandial measurements. To provide better glycemic control, postprandial first-hour measurements are preferred.
- Target levels to reduce complications and macrosomia with good glycemic control are as follows[1]:

Fasting ≤ 95mg/dL

Postprandial first hour ≤ 140 mg/dL

Postprandial second hour ≤120 mg/dL

- The primary treatment option is diet and exercise. Pregnant women should be referred to the endocrinology or internal medicine department, and diet charts should be prepared at the recommendation of a dietitian. If the target levels cannot be reached with diet and exercise, treatment with insulin is the primary and standard protocol. The starting dose of insulin is 0.7–1.0 units/kg. The use of short-, medium-, or long-acting insulin should be determined by the endocrinology or internal medicine department to ensure regulation of blood glucose levels.
- The use of oral antidiabetics in pregnant women with GDM has not yet been approved by the U.S. Federal Drug Administration; however, studies have indicated that these are increasingly recommended to be used as a first choice of treatment.

### *1.3. Antenatal management and delivery*

- Fetal well-being assessment (nonstress test and amniotic fluid measurement) should begin at 32 weeks of gestation and continue as routine antenatal follow-up in GDMA1 patients whose serum glucose is regulated by diet and exercise.
- Fetal well-being assessment should begin at 28 weeks of gestation in GDMA2 patients whose serum glucose is not regulated and who use insulin. According to serum glucose regulation, follow-up should be conducted weekly, semiweekly or by hospitalization.

**Table 3. Delivery Time of Patients[1].**

GDMA1 patients with good glycemic control should not be delivered before 39 weeks of gestation.

For GDMA2 patients with good glycemic control, $39^{0/7}$ is the recommended delivery week.

GDMA2 patients with poor glycemic control should be delivered between $37^{0/7}$ and $38^{6/7}$.

If glycemic control cannot be regulated despite hospitalization, delivery between $34^{0/7}$ and $36^{6/7}$ is necessary.

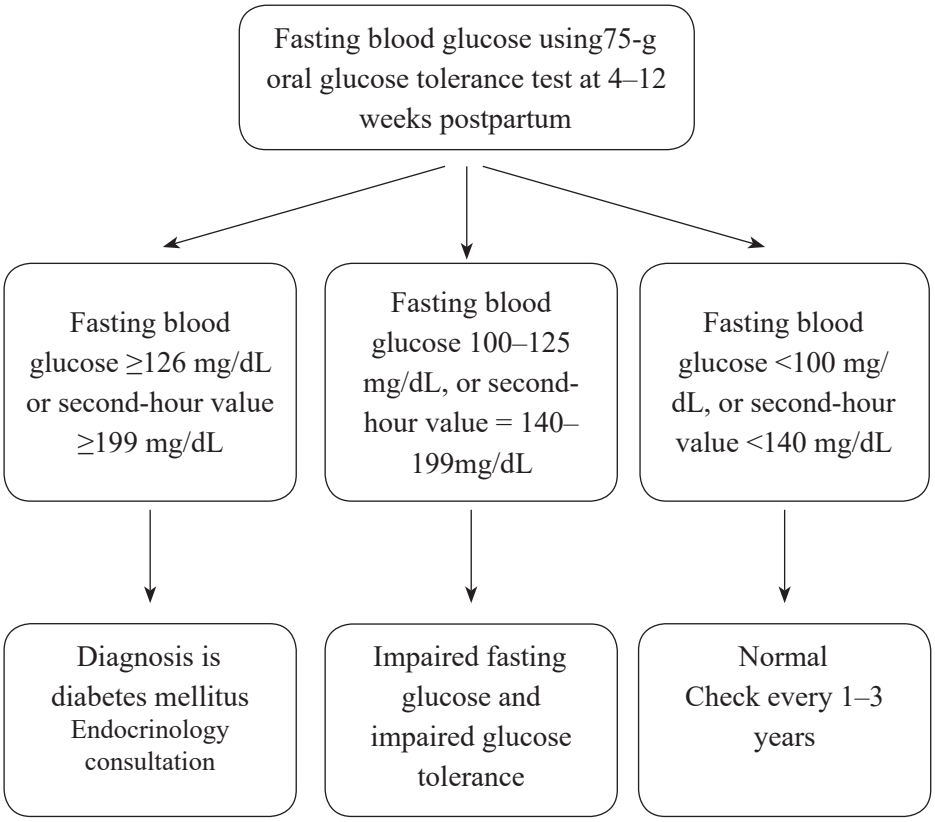
### *1.4. Intrapartum management of GDM*

- Increased maternal glucose levels during intrapartum follow-up are associated with neonatal hypoglycemia; therefore, maternal glucose monitoring should be conducted at 2-h intervals for GDMA1 patients, and at ≤1-hintervals for GDMA2 patients whose glucose is not regulated or who are treated with insulin.
- Target serum glucose values are as follows:
  Intrapartum maternal glucose levels of 140–180 mg/dL are associated with neonatal hypoglycemia. In intrapartum monitoring, the target value should be kept between 70 and 110 mg/dL.

### *1.5. Postpartum management of GDM*

All pregnant women should be screened for fasting blood glucose levels using the75-g oral glucose tolerance test between 4 and 12 weeks postpartum[1].

**Algorithm 1. Postpartum Management of Patients with GDM.**




## 2. Pre-gestational Diabetes Mellitus

### *2.1. Diagnosis and Pre-pregnancy Counselling*

Under this title, we aimed to evaluate type 1 pre-gestational diabetes and type 2 diabetes mellitus. Although type 1 pre-gestational diabetes occurs as a result of pancreatic beta cell damage due to autoimmune reasons and is more frequently associated with vascular, renal and neuropathic complications, type 2 diabetes mellitus is the most common form and is associated with peripheral insulin resistance, relative insulin deficiency, and obesity.

- The main approach is to provide a healthy blood glucose regulation in the pre-pregnancy period in order to prevent fetal marformations, spontaneous abortion, fetal death and neonatal morbidity, and this makes the pre-pregnancy period very important.
- The patients should be informed about these potential complications at the pre-pregnancy visit. Hypertension, nephropathy, retinopathy and

cardiovascular diseases should be reviewed before pregnancy. HbA1C must be kept at an optimal value before pregnancy (<6,5 percent). Folic acid supplementation should be started for women planning pregnancy[4].

- In the first trimester (first clinical visit), HbA1C, 24-hour urine microprotein and electrocardiogram should be planned in addition to routine prenatal tests. Ophthalmology, neurology, nephrology, cardiology and endocrinology consultations should be requested for the patient.
- Successful preconception care programs have used the following preconception glucose targets. Before meal capillary blood glucose concentration is maintained between 80 to 110 mg/dL. Two-hour postprandial glucose concentration must be <155 mg/dL.
- Although the optimal week is the 16th week of pregnancy, low-dose aspirin should be started between 12-28 weeks of gestation.
  Fetal echocardiography should be planned between 18-22 weeks of gestation due to the frequency of anomaly screening and fetal cardiac anomaly.

### *2.2. Antenatal follow-up*

- Antenatal fetal follow-up is usually accomplished at 32 weeks of gestation, but in the presence of uncontrolled diabetes, preeclampsia, and poor obstetric history, it is important to start at 28 weeks of gestation[4].
- Antepartum follow-up should be done with NST, modified biophysical profile and biophysical profile and should be done once a week or twice a week depending on the clinical picture of the disease. After 36 weeks of gestation, antenatal follow-up should be increased to twice a week[4].
- The upper thresholds recommended by the American College of Obstetricians and Gynecologists (ACOG) for target blood glucose values in capillary blood are based on consensus expert opinion[4].

**Table 4. Target Blood Glucose Values During Antenatal Follow-up**[4]

| |
|---|
| Fasting, preprandial, and nocturnal glucose 70 to 95 mg/dL (3.9 to 5.3 mmol/L) and |
| One-hour postprandial glucose 110 to 140 mg/dL (6.1 to 7.8 mmol/L) or |
| Two-hour postprandial glucose 100 to 120 mg/dL (5.6 to 6.7 mmol/L) |
| Mean capillary glucose concentration 100 mg/dL (5.6 mmol/L) |

- Although pregnancies complicated by diabetes are generally characterized by accelerated growth, it should be kept in mind that fetal growth restriction may occur due to vasculopathy, and follow-up in the third trimester should therefore be more frequent and specific.
- Antenatal corticosteroid administration is very important in the presence of a possible preterm delivery and it is known to significantly improve neonatal outcomes. Obstetrician must be careful for maternal hyperglycemia and ketoacidosis. It should be kept in mind that the hyperglycemic effect will continue for up to five days, especially starting at 12 hours. Close blood glucose levels should be followed, especially after the 12th hour; hourly or two-hour follow-ups should be preferred until regulation is achieved.

### *2.3. Delivery and Intraparum Management*

- Specifically, it should be noted that high fetal insulin levels lead to immature lung function.
- The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine suggested that[4];

**Table 5. Delivery time of Patients[4]**

| |
|---|
| If the presence of well-controlled glucose levels and no vascular disease deliver at 39+0 to 39+6 weeks. |
| If the presence of poorly controlled glucose levels or vascular disease (even earlier if severity of complications warrants earlier delivery) deliver at 36+0 to 38+6 weeks. |
| Expectant management beyond 40+0 weeks is not recommended. |
| Preterm delivery is performed for the usual obstetric indications or for worsening maternal renal insufficiency or active proliferative retinopathy. |

- Delivery of patients with pre-gestational diabetes should occur at institutions with health care providers experienced in caring for such individuals.
- Diabetes alone is not an indication for cesarean delivery in the absence of the usual obstetric indications. Presence of macrosomia is an important cesarean indication. In fetuses around 4000g, the possibility of shoulder dystocia should be discussed with the family and the cesarean option should be individualized.

- During labor, the mother and fetus should be constantly monitored for possible non-reassuring NST and fetal distress.
- Providing euglycemia during labor is essential.
- Induction of labor or cesarean delivery should be planned early in the morning whenever possible, thus facilitating the management of glucose and insulin in the patient.
- During induction of labor, maternal glycemia can be controlled with an intravenous infusion of short-acting (commonly regular) insulin, an "insulin drip," titrated to maintain hourly readings of blood glucose levels less than 110 mg/dL.
- Good glycemic control during labor will reduce the likelihood of neonatal hypoglycemia. For this reason, hourly blood glucose monitoring should be performed during labor.
- In the absence of proven goals, a reasonable target range for intrapartum glucose levels is >70 and <126 mg/dL as this range has not been associated with clinically important neonatal hypoglycemia in insulin-requiring women.
- This target range encompasses recommendations of both the American College of Obstetricians and Gynecologists (ACOG; 70 to 110 mg/dL Intrapartum glucose levels above 140 to 180 mg/dL have been shown to be associated with neonatal hypoglycemia.
- In pregnant women complicated with type 1 diabetes, insulin will always be required in follow-up, therefore, if hypoglycemia develops, intravenous dextrose should be given and the insulin infusion rate should be reduced.
- Continuous basal infusion should generally be reduced by approximately 50% to prevent hypoglycemic episodes in women using an insulin pump.
- After delivery of the placenta, the insulin resistant state that characterizes pregnancy rapidly dissipates and insulin requirements drop precipitously.

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# CHAPTER 7

# MANAGEMENT OF MACROSOMIA AND SHOULDER DISTOCIA

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## 1. Introduction

Macrosomia is considered a fetal weight greater than 4000 to 4500 grams. Macrosomia is characterized by an increased risk of major complications such as maternal and/or fetal trauma and neonatal hypoglycemia. Long-term-obesity and insulin resistance are other known complications.

- There are 3 grades of macrosomia[1]:
  Grade 1: 4000-4500 g
  Grade 2: 4500- 5000 g
  Grade 3: 5000g and above
- Maternal morbidity and mortality are coralated with degree of macrosomia. The incidence of LGA and macrosomia is higher in pregnant and obese patients with a diagnosis of GDMA2.

## 2. Diagnosis

- Physical examination and 2-dimensional ultrasonography are used for the diagnosis of macrosomia. Fetal abdominal circumference (AC) is the most important factor for determining macrosomia. Fetal AC above the 90th percentile or 2-3 weeks before the confirmed gestational week is an important indicator for macrosomia. The growth of fetal AC starting at 21-22 weeks is guiding in predicting macrosomia.
- The reliability of USG in macrosomia decreases as the grade of macrosomia increases.
- The HC/AC ratio has no proven value in recognizing macrosomia, but the risk of shoulder dystocia is increased in those with HC/AC > 50 mm, regardless of EFW. If AC > 35 cm, macrosomia can be predicted.
- Fetal weight can be estimated by simple palpation and measurement with fundal distance in the womb. This estimate is influenced by fetal presentation, AFI, maternal obesity, and examiner experience. Fundal height is more effective in excluding than recognizing macrosomia.

**Table.1 Maternal and Featal Complications of Macrsomia**[1]

- Cerebroplacental distribution
- Obstructed labour
- Caesarean section
- APGAR <4
- Birth traumas
- Shoulder dystocia and clavicle fracture
- Postpartum bleeding
- Genital injuries
- Chorioamnionitis
- Hypoxia or asphyxia
- Brachial plexus paralysis

## 3. Management of Delivery [1]

- If the EFW is over 4500 g, cesarean delivery is indicated. However, birth trauma has increased significantly in vaginal deliveries over 4000 g. When the limit for cesarean delivery is increased to 4000 g, the frequency of cesarean section has been reported to double.

- Induction of labor in term pregnant women with suspected macrosomia increases the rate of delivery by cesarean section without reducing shoulder dystocia or neonatal morbidity[1].
- If macrosomia is predicted above 37 weeks of gestation, expectant management or labor induction may be preferred. According to the expectant management decision, in patients for whom labor induction is preferred; no difference was observed in terms of emergency cesarean section, shoulder dystocia, brachial plexus paralysis. Fetal hyperbilirubinemia and need for phototherapy increase in patients who have induction of labor before 38 weeks of gestation.
- ACOG does not recommend delivery before the 39 gestational week unless there is any indication[1].
- Cesarean delivery is recommended over 4500 g in patients with GDM and over 5000 g in patients without diabetes. And cesarean delivery reduces the possibility of brachial plexus paralysis and birth traumas.
- In vaginal delivery of macrosomic fetuses, phase 2 and phase 3 are prolonged.
- Prolonged phase 2 is an indication for cesarean section in a patient who is planned for vaginal delivery with an estimated birth weight of more than 4500 g.
- The use of vacuum in vaginal deliveries increases the risk of shoulder dystocia 3-4 times. However, the effect of forceps delivery on this risk is uncertain.
- Macrosomia is not an obstacle for vaginal delivery after cesarean section. However, induction of labor is more likely to fail and uterine rupture is more likely than non-macrosomics.

**4. Shoulder dystocia[2]**

It is a life-threatening obstetric emergency and is unpredictable.

- Shoulder dystocia is the attachment of the fetal anterior shoulder to the sympiphyseal pubis. In some cases, the posterior shoulder may become attached to the maternal promontory. Shoulder dystocia is diagnosed when the shoulders cannot be delivered despite the correct head position and classical delivery maneuvers.
- Turtle sign in the maternal perineum is suggestive of shoulder dystocia but not diagnostic.
- According to the risk factors, cesarean delivery is recommended if there is prolonged phase-2 in pregnant women who are determined to be at high risk.

**Table.2 Risk Factors of Shoulder Dystocia**

- High birth weight
- Obesity
- Diabetes Mellitus
- Male gender
- Advance maternal age
- History of shoulder dystocia
- Postterm birth
- Prolonged labor

- Although higher birth weight is a major risk factor, shoulder dystocia is seen in 15%.
- Maternal pelvic evaluation or fetal biometric measurements were insufficient for prediction to predict shoulder dystocia.
- Especially in fetal biometric measurements of diabetic pregnant women: HC/AC ratio, FL/AC ratio, BPD, humerospinous distance, distance between cheeks are the measurements used for orientation
- In addition, if abdominal diameter >90 percentile and EFW> 4000 gr shoulder dystocia risk increases.

**Table.3 Maternal and Neonatal Complications of Shoulder Dystocia** [2]

- Postpartum bleeding
- Deep perineal lacerations
- Separation of the maternal symphysis
- Lateral femoral cutenous neuropathy
- Anal sphincter damage
- Cervico-vaginal lacerations
- Uterine rupture
- Urethra damage
- Bladder lacerations
- Clavicle fracture, humerus fracture
- Brachial plexus paralysis
- Erb palsy, Klumpke's palsy
- Hypoxic-ischemic encephalopathy
- Fetal death
- Asphyxia

- Routine cesarean section is not recommended in patients with a history of shoulder dystocia. Risk factors can be explained to the patient and a decision can be obtaine with the family.

### *4.1. Management of Shoulder Dystocia*[2]

- Mc Roberts maneuver is the first method when shoulder dystocia occurs.
- In this maneuver, two people flex the maternal legs towards the abdomen. In this way, the symphysis pubis allows fetal cephalic rotation and flattening of the lumbar lordosis, so that the stuck shoulder can be released. Another person assisting the birth puts suprapubic pressure. Because of this pressure, the pressure on the attached shoulder is directed laterally.
- Fundal pressure should be avoided while performing these actions. May cause uterine rupture or deepening of dystocia. If these maneuvers do not effective and if the shoulder is not released, the fetal posterior arm may be tried.
- If unsuccessful, the Rubin maneuver is attempted. The hand is placed behind the vagina and posterior fetal shoulder, and the fetal face is turned anteriorly.
- In addition, with the Wood Screw maneuver, rotation is performed by pressing the clavicular area from the anterior of the posterior shoulder to change the direction of the fetus, until the anterior shoulder comes out from the back of the maternal sympiphysis.
- With the Gaskin all-fours maneuver, while the mother continues to give birth on her hands and knees, the shoulder is removed by pulling up or against the maternal sacrum.
- If all these maneuvers do not work, all of them are repeated.

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CHAPTER 8

# MANAGEMENT OF PRETERM PREMATURE RUPTURE OF UTERINE MEMBRANES AND CHORIOAMNIONITIS

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## 1. Introduction

Preterm premature rupture of membranes (PPROM) is the rupture of uterine membranes without uterine contractions at <37 gestational weeks and occurs in~3% of pregnancies. Gestational week and risk factors are the major factors in managing PPROM. Active management is conducted in patients with PPROM at our clinic at >34 gestational weeks, and this chapter specifically includes the clinical management of pregnant women at <34 gestational weeks.

## 2. Diagnosis of PPROM [1]

- Most PPROM is diagnosed using patient history and a physical examination. Physical examinations should be conducted under sterile conditions, minimizing the possibility of infection.
- During the examination using a sterile speculum, cord prolapse, extremity prolapse, cervical dilatation, vaginal pH, and cervical infection should be evaluated.
- Vaginal pH is evaluated using nitrazine paper. Normal vaginal pH is between 3.8 and 4.5, and amniotic fluid pH is between 7.1 and 7.3.
- A placental alpha microglobulin-1 (PAMG-1; AmniSure) test is used in the diagnosis. It is not affected by semen and trace amounts of bleeding. The used strip is kept in the vagina for 1 min and then left in solution for 1min. The result is determined between 5 and 10 min. One line indicates a negative result for amniotic fluid and two lines indicate a positive result.
- Fetal fibronectin can be measured for diagnostic purposes. It is sensitive but not specific. Negative tests indicate intact membranes, but positive results are not necessarily a diagnostic indicator for PPROM.
- In ultrasonography, an amniotic fluid index evaluation guides the diagnosis, but is not diagnostic.

## 3. Antepartum and Intrapartum Management of PPROM [1]

- In patients with PPROM, first, gestational week, fetal presentation, and fetal well-being should be determined at the time of diagnosis. Subsequently, intrauterine infection, cord prolapse, and ablatio placentae should be excluded. A fetal nonstress test should be followed up, and uterine contractions should be monitored.
- PPROM management is determined by gestational week for maternal and fetal well-being.
- In the presence of PPROM at <34 gestational weeks, after the maternal and fetal well-being is ensured, expectant management is recommended.

**Table 1. Recommendations After Hospitalization**

- Provide antibiotic prophylaxis.
- Provide antenatal corticosteroids.
- Use tocolysis if necessary.
- Monitor semi-weekly CRP and WBC.
- Follow up for maternal fever.
- Monitor for maternal and fetal tachycardia.
- Evaluate daily NST or BFP and amniotic fluid index.
- Question any abdominal and fundal tenderness.

Notes: CRP, C reactive protein; WBC, white blood cell; NST, nonstress test; BFP, big fat positive pregnancy test.

- A 7-day regimen is provided for antibiotic prophylaxis. Ampicillin 4x2 g IV (effective against group B *Streptococcus*[GBS], most Gram-negative bacilli) for the first 2 day, followed by oral amoxicillin 3x500 or 2x875mg orally for 5 day, plus oral azithromycin (effective against uroplasm and some anaerobes) 1x1g orally for 7 day[2]. The use of amoxicillin and clavulanic acid is not preferred because they increase the risk of neonatal necrotizing enterocolitis[3].
- Corticosteroid administration reduces the risk of neonatal mortality, respiratory disease syndrome (RDS), intraventricular hemorrhage, and necrotizing enterocolitis. Corticosteroid administration is recommended in preterm PPROMs between $24^{0/7}$ and $33^{6/7}$ gestational weeks. There is no indication for corticosteroid use in pre-viability; however, in PPROM diagnosed at $23^{0/7}$ gestational weeks, it can be used if the family requests it and delivery is not expected within one week[4].
- In patients whose delivery is planned before $32^{0/7}$ gestational weeks because of maternal and fetal indications, magnesium sulfate infusion should begin for neuroprotection. It has been shown to reduce the risk of cerebral palsy in surviving infants.
- Tocolysis is not recommended in late preterm PPROM. It can be used for 48 h to ensure maximum effectiveness of corticosteroids at <34 gestational weeks. Longer use of tocolysis has not been shown to have maternal or fetal benefits but has been associated with a higher risk of chorioamnionitis. Tocolysis is not recommended at <24 gestational weeks.

- Active management is conducted on PPROM patients in our clinic at>$34^{0/7}$gestational weeks and delivery is recommended.
- The mode of delivery is planned according to standard obstetric indications.
- The agent for induction should be determined according to the patient's Bishop score, and if <5, the cervix should be ripened.
- The fetus should be continuously monitored during delivery.
- Before determining that induction is unsuccessful, induction must be continued for 12–18 h.

## 4. Diagnosis, Treatment, and Management of Chorioamnionitis[3]

- Clinical chorioamnionitis or intraamniotic infection is a disease characterized by acute inflammation of the placental membranes and chorion resulting from a polymicrobial bacterial infection and typically in women who have had membrane rupture.
- It is a common complication of pregnancy associated with potentially serious adverse maternal, fetal, and neonatal effects, as well as increased long-term risks for cerebral palsy and other neurodevelopmental disabilities. Treatment comprises both antibiotic therapy and removal of infected pregnancy material.

**Table 2. Clinical Findings of Chorioamnionitis[1].**

- Fever (100%).
- Maternal leukocytosis (as a white blood cell count >12000/$aa^{3}$ or >15000/$aa^{33}$).
- Maternal tachycardia >100/min.
- Fetal tachycardia >160/min.
- Uterine tenderness.
- Bacteremia.
- Purulent or foul-smelling amniotic fluid.

The diagnostic gold standard is an amniotic fluid culture; however, its use is limited because it takes several days before the results can be determined. Gram stain, glucose concentration, white blood count (WBC) concentration, and leukocyte esterase activity can be checked in the amniotic fluid. Histopathological evidence of infection or inflammation of the placenta, fetal membranes, or umbilical cord vessels (funisitis), or both, is valuable in confirming the diagnosis.

A possible diagnosis of intra-amniotic infection (suspected TripleI) may be made for women using the criteria listed in Table 3 below.

**Table 3. TripleI Criteria**[1]

Fever ≥39.0°C once or between 38.0 and 38.9°C on two or more measurements 30 min apart PLUS one or more of the following:

- baseline fetal heart rate >160 beats/min for >10 min, excluding accelerations, decelerations, and periods of significant variability;
- maternal white blood cell (WBC) count >15000/mm in the absence of threecorticosteroids and ideally showing left shift (bandemia); or
- purulent-appearing fluid from the cervix viewed by speculum examination.

- Delivery is indicated in women with a suspected or confirmed Triple I diagnosis.
- Mode of delivery is determined by fetal and maternal well-being. Intra-amniotic infection is not an indication for cesarean section. The negative consequences of prolonging the delivery time of the patient who received antibiotic treatment have not been observed. In addition, in cesarean delivery, it increases the risk of pelvic capsitis, endometritis, wound infection, and venous thrombosis.
- Antibiotic therapy should begin as soon as a diagnosis is made.
- During the intrapartum period, 4X2 g IV ampicillin and 5 mg/kg 1x1 IV gentamicin should begin.
- Because of the risk of endometritis caused by anaerobes in patients who have had a caesarean section, 500 mg metronidazole orally or 900 mg 3x1 IV clindamycin should be added to the treatment.
- Antibiotic treatment is continued until the women are fever free and asymptomatic during the postpartum period.
- The opinion of the committee from the American College of Obstetricians and Gynecologists (ACOG) on intra-amniotic infection suggests that additional doses of antibiotics are not necessary after vaginal delivery and that at least one additional dose is indicated after a cesarean delivery[1].

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# CHAPTER 9

# UMBLICAL CORD PROLAPSUS AND MANAGEMENT

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## 1. Introducion

Umbilical Cord Prolapse (UCP) is a rare and unpredictable obstetric emergency that complicates pregnancy. Although it is rarely encountered, it may cause an increase in fetal-maternal morbidity and mortality if it occurs. Depending on the rapid diagnosis, appropriate treatment, decrease in grand-multiparity and increase in caesarean section rates, the incidence of prolapse is gradually decreasing. UCP is divided into 3 different classes[1]

- **Overt cord prolapse:** The cord is below the cervical opening and the presenting fetal section; and may be accompanied by ruptured membranes or intact membranes. The extension of cord prolapse can be graded as inside or outside of the vagina. It is the most common and risky type of cord prolapse.
- **Cord presentation:** The cord does not protrude from the cervical opening, it is above the cervix, not in front of but below the fetal presentation, and may also be accompanied with ruptured membranes or intact membranes. It is the second most risky cord prolapse.
- **Compound cord presentation:** The cord is above the cervix and next to the fetal presenting part. It may be accompanied by torn or intact membranes.

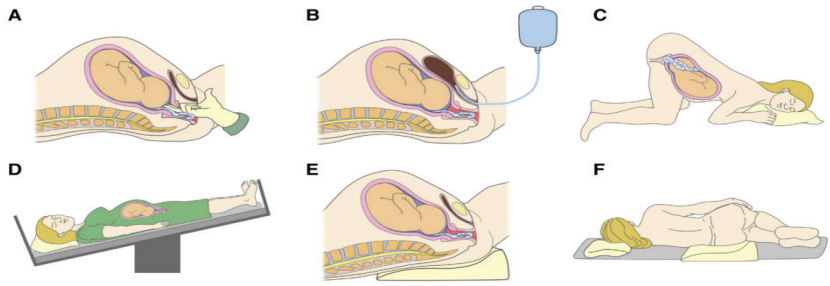
- Umbilical cord prolapse needs to be well defined and managed so as to evaluate fetal-maternal morbidity and mortality in deliveries complicated by UCP. Following fetal heartbeats and noticing fetal heartbeat changes due to prolapse in the early period constitute the most important point in diagnosing UCP.
- Unless vaginal delivery is imminent, treatment for cord prolapse is emergency delivery through caesarean section.
- Urgency is depended upon bradycardia and recurrent fetal heart stasis. Cases with bradycardia are the most urgent one. Cases with immediate treatment generally present a good prognosis.
- It is known that as time passed by of bradycardia to birth increases, the pH of the cord arterial blood decreases significantly and the Apgar score is adversely affected. Cord compression and cord vasospasm causing to fetal hypoxia, continue to be an important cause of perinatal mortality because of its adverse consequences for the fetus.
- The presence of other adverse fetal factors, the occurrence of cord prolapse whether in or outside the hospital, the extent of cord prolapse, and the different manoeuvres used to relieve cord compression are liable to affect all perinatal outcomes.

## 2. Manoeuvres to Manage Cord Prolapse[1,2]

- Most cases of cord prolapse require a caesarean delivery unless a vaginal birth is imminent.
- Because preparation phase for caesarean delivery takes some time, relieving or preventing cord compression throughout this process is crucial to reduce the risk of hypoxic brain injury and cerebral palsy and death.

- In case the umbilical cord is outside the vagina, a warm and moist dressing should be used to protect the cord from trauma and reduce vasospasm due to the cold external environment. Short-acting tocolysis should be given immediately in the presence of uterine contractions to reduce the pressure on the umbilical cord and prevent further protrusion of the cord, and also, mothers should be informed to avoid straining to reduce intrauterine pressure.
- A series of manoeuvres have been suggested to relieve cord compression, such as knee-chest position, transdelenburg position, and raising the maternal pelvis, which are among the positions that elevate the maternal pelvis, since the elevation of the fetal part of the presentation, the inflation of the maternal urinary bladder, the pulling with the force of gravity, and the pushing from below are more advantageous than the pushing from below[1].

**Figure 1. Different Maneuvers for Relieving Cord Compression**

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### *2.1. Transvaginal manual elevation of the presenting section (Figure 2,A)*

- In case of diagnosis of umbilical cord prolapse during vaginal examination, manual elevation of the incoming part can be done immediately to reduce cord compression.
- It is the most direct and fastest method compared to other manoeuvres; however, such a transvaginal approach is unpleasant for the patient and inconvenient for the doctor, especially during the transfer of the patient.
- Besides, it is technically difficult to push up the fetal presentation part when the level is high or the fetus is in a transverse position. Another possible downside is that it may create more room for the umbilical cord to prolapse further.

- There is also a potential risk of cord entrapment in the vagina by the examining fingers, especially if a cord loop is already outside the vagina.
- Although transvaginal manual elevation may be one of the first manoeuvres to relieve cord compression immediately after the diagnosis of cord prolapse, other more appropriate manoeuvres can be used if possible.

### *2.2. Filling the maternal urinary bladder (Figure 2,B)*

- Filling the mother's urinary bladder is another method of pushing to raise the presenting part of the fetus.
- It is recommended to add 500 to 750 mL of fluid to the bladder. It is one of the methods that successfully prevent perinatal mortality in cases of cord prolapse. With the volume of 500 mL infused, we raise the fetal presenting part by 2 levels, which is particularly effective in raising the fetal head when a delay in deliveryis expected or when the patient needs to be transported to a longer distance.
- It has an advantage over manual elevation because after bladder filling is complete, there is no need for continued assistance of qualified team.
- However, it is less effective when the head of the fetus is at a higher level, as the direction of elevation by the distended bladder is below the level of the presenting portion of the fetus.
- Other disadvantages include the need for equipment and time to fill the bladder. In practice, it may take some time to insert the catheter using aseptic technique from the removal of the equipment.
- This delay may affect perinatal mortality compared with the immediate effect of manual elevation, and there may also be a greater delay during caesarean delivery when the bladder needs to be emptied.

### *2.3. Knee-Chest Position (Figure 2,C)*

- Knee-Chest Positionhas been reported as one of the most effective methods and the elevation effect is not affected by the fetal level.
- It can be performed quickly by the patient independently without the need for any equipment. The position can be maintained independently by the patient without the assistance of personnel who may play a part in other critical roles in the emergency.
- Therefore, the genupectoral position should be the preferred manoeuvre as it is the most effective. The disadvantage is that for a pregnant woman, the position can be tiring and difficult to maintain; therefore, less preferred where long-distance transfer is envisaged.

- Furthermore, it can be difficult and risky to maintain the genupectoral position in patients who cannot cooperate in an emergency. If the umbilical cord is already protruding from the vagina, extra precaution is required to avoid trauma to the cord or inducing further vasospasm when turning the mother from the supine position to the Knee-Chest Position.

### *2.4. Trendelenburg position (Figure 2,D)*

- In the Trendelenburg position, the mother is placed in the upside-down position with the maternal pelvis tilted over the mother's head to pull the fetus up and away from the cervix by the force of gravity.
- The position can be achieved quickly if the patient is already in an adjustable bed. Further tilting of the bed may be more effective in separating the fetal section, but is limited by maternal discomfort.
- A slope of 15 degrees is a practical angle of inclination; however, an adjustable bed may not always be available.

### *2.5. Elevating the patient's hip (Figure 2,E&F)*

- The mother's hip can be raised by placing a thick pillow or support under her hip. These methods have a modest uplifting effect; however, the angle of inclination can be further increased if necessary at the expense of greater maternal discomfort. In addition, raising the mother's hip can also reduce the risk of further cord prolapse outside the vagina, making it more preferable to manually lifting it.

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# CHAPTER 10

# ANTENATAL MANAGEMENT AND DELIVERY IN TWIN PREGNANCY

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## 1. Introduction

Twin pregnancies have increased as a result of the widespread use of assisted reproductive techniques. Early ultrasound evaluation provides an accurate calculation of the gestational age, which is important in all pregnancies. Early ultrasound examination is critical in twin pregnancies, as complications are higher than in singleton pregnancies. Accurate calculation of the gestational age will minimize the developmental delay that occurs in many pregnancies. If there is inconsistency between the dimensions used in the estimation of gestational age, the dimensions of the larger fetus should be taken into account.

- Ultrasound is most important tool for determining amnionicity and chorionicity and the best time to identify them is after the 7th week.

- Amniocyte is used to indicate the number of inner lateral membranes. Chorionicity is used to describe the number of outer lateral membranes. The sonographic features used to evaluate chorionicity vary with gestational age. Its accuracy is highest in the first trimester and decreases with increasing gestational age.
- Detection of amnionicity and chorionicity is critical in the follow-up of specific serious pregnancy complications such as twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS) that may develop in monochorionic monaamniotic twin pregnancies.

## 2. Determination of Chorionicity[1]

- Firstly placenta must be evaluated to determine chorionicity. Monitoring of two separate placentas is a very reliable indicator of dichorionic twins in early pregnancy, because separate placentas often combine the following weeks.
- The second important method for determining chorionicity is to examine the membranes for which the presence of the intertwin membrane is required.
- The best time to evaluate the dice is 10-14. gestational weeks and becomes insignificant after the 20th gestational week. A concatenated membrane marked "twin peak" or "lambda (λ)" indicates dichorionic twins. If the obsttrician is unable to establish the diagnosis of intertwin membrane, the patient will have a monochorionic/monoamniotic twin pregnancy.
- The term twin peak or lambda sign is associated with the detection of the twin membrane originating from a fused placenta and spreading between the layers of the intertwin membrane.
- The third important method for determining chorionicity is the membrane thickness measurement.
- Although there is much discussion among the authors about the thick layer decision, the cut-off value can be accepted between 1.5 and 2 mm in the early pregnancy period. The thick membrane is one of the well-known properties of dichorionicity.
- Dichorionic twins have four leaves (two leaves for the amnion and two for the chorion), while monochorionic twins have two leaves. Detection of a twin membrane with a T sign indicates a monochorionic/diamniotic placenta, which is mainly due to the originality of the finding on the

thin twin membrane, the bilayer and at an angle of 90 degrees from the placenta.

- Marking 'possible' twins during routine antenatal follow-up is important for subsequent follow-up and management of potential complications. If the sex of each fetus is different, it will be easy for the clinician to mark them; however, this is not always possible. For same-sex twins, marking can be made using locations (right or left fetus or superior fetus), by specifying placenta implantation sites or placental cord insertion sites.

## 3. Antenatal Management of Twin Pregnancies[1,2]

- The routine antenatal care of patients with twin pregnancies has some differences from the routine prenatal care of singleton pregnancies.
- Congenital anomalies, preterm delivery, preeclampsia and diabetes mellitus are the most important risk factors in twin pregnancies.
- Measuring the nuchal thickness in 11-13 gestational weeks is the most useful screening method for Down syndrome.
- It would be appropriate to perform fetal anatomical scanning between 18-22. gestational weeks. The incidence of congenital anomalies in monocytic twins is three to five times higher than in dizygotic twins or singleton pregnancies. Monochorionic twins are certainly at high risk for congenital heart problems. In addition to anatomical scanning between 18-22 gestational weeks, echocardiographic examination is required in monocytic twins.
- In the presence of a congenital anomaly in a fetus, both the clinician and the family may seem to accept responsibility. In this case, all treatment options should be discussed with the family (pregnancy termination, pregnancy management and selective fetocide). On the other hand, sometimes the family may prefer the continuation of the pregnancy, in which case the clinician should explain how the abnormal fetus may affect each other due to chorionicity (eg, premature birth, organ damage).
- Serial USG examination can help the clinician diagnose IUGR. In the presence of IUGR, all patients should be examined twice a week with biophysical profile and umbilical cord doppler. Biophysical profile and doppler ultrasonography is not required for multiple pregnancies without any problems in pregnancy.

- It is recommended to start the fetal well being tests at 28th gestational week in the presence of monochorionic monoamniotic twins, at 30th gestational week in monochorionic diamniotic twins, and at 32nd gestational week in dichorionic diamniotic twins and to follow up twice a week.
- Chorionicity and amnionicity are the most important determining factors for delivery time. Spontaneous delivery in twin pregnancies occurs at 36 weeks on average, and therefore complications from prematurity pose a significant risk. Perinatal mortality increases again after 38 weeks of gestation. Based on this, the timing of delivery in uncomplicated twin pregnancies is recommended as follows [1,2];
  - o In dichorionic diamniotic twins without complications, at 38 weeks,
  - o Between 34 and 37 6/7 weeks in monochorionic-diamniotic pregnancies without complications,
  - o 32-34 weeks in monoamniotic pregnancies without complications.

**Table 1. Follow-up Pathway by Ultrasonography in Uncomplicated Dichorionic Twin Pregnancy**

| | |
|---|---|
| 11-14. gestational week | Gestational age, Labeling<br>Chorionicity<br>Screening for trisomy 21 |
| 20-22. gestational week | Detailed anatomy<br>Fetal biometry<br>Amniotic fluid volume<br>Cervical length measurement |
| 24-26. gestational week | Evaluation of fetal growth<br>Amniotic fluid volume<br>Fetal Doppler |
| 28-30. gestational week | |
| 32-34. gestational week | |
| 36-37. gestational week | |
| Delivery | |

**Table 2. Follow-up Pathway by Ultrasonography in Uncomplicated Monochorionic Twin pregnancy**

| | |
|---|---|
| 11-14. gestational week | Gestational age, Labeling<br>Chorionicity<br>Screening for trisomy 21 |
| 16. gestational week | Fetal growth<br>Deepest vertical amniotic pocket<br>Umbilical artery-pulsatile index |
| 18. gestational week | |
| 20. gestational week | Detailed anatomy<br>Fetal biometry<br>Deepest vertical amniotic pocket<br>Umbilical artery-pulsatile index<br>Middle cerebral artery-systolic peak flow velocity<br>Cervical length measurement |
| 22. gestational week | Fetal growth<br>Deepest vertical amniotic pocket<br>Umbilical artery-pulsatile index<br>Middle cerebral artery-systolic peak flow velocity |
| 24. gestational week | |
| 26. gestational week | |
| 28. gestational week | |
| 30. gestational week | |
| 32. gestational week | |
| 34. gestational week | |
| 36. gestational week | |

- The ideal mode of delivery varies according to the type of twin pregnancy, the presentation of the fetuses, the gestational week and the experience of the obstetrician.
- Twin pregnancy alone is not an indication for cesarean section.
- Only in monoamniotic pregnancies, cesarean delivery is necessary during the delivery of the first fetus in order to avoid cord complications that may develop in the other fetus.
- Normal vaginal delivery is indicated in the presence of head to head presentation.
- Despite the great efforts of obstetrician, twin pregnancies can be complicated by stillbirth or neonatal death. For this reason, many organizations (ACOG and the Society for Maternal-Fetal Medicine (SMFM)) recommend delivery at 34-37+6 gestational weeks of monochorionic diamniotic pregnancies[1].

- Because of the risks and high probability of complications, these pregnancies require complex management protocols and should be managed under the care of a perinatology specialist.
- Internal fetal manipulation or emergency cesarean section may be required during delivery. Women with multiple pregnancies are at risk for atony, postpartum hemorrhage, and emergency hysterectomy.
- Application of neuraxial analgesia facilitates operative vaginal delivery, external or internal cephalic version and total breech extraction in multiple pregnancies.

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# CHAPTER 11

# DIAGNOSIS AND MANAGEMENT OF INTRAHEPATIC CHOLESTAS OF PREGNANCY

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## 1. Clinical findings and diagnosis

- Intraheptic cholestasis of pregnancy (IHCP) is typically characterized by mild or intolerable itching on the palms and soles of the hands, especially at night. Clinical manifestations usually begin in the late second or third trimester.

- Diagnosis is confirmed by measuring the bile acid levels in maternal serum in addition to clinical findings. A serum bile acid level > 10mmol/L is the key laboratory finding for IHCP, and elevation is detected in 90% of affected pregnant women. Serum aminotransferase, alkaline phosphatase, and total and direct bilirubin are increased in this liver disorder, but not specific for a diagnosis. For IHCP diagnosis, other diseases that increase bile acid levels must be excluded. Pathologies of the maternal liver and gallbladder should be excluded by performing an ultrasound examination.

**Table1. Diagnostic Criteria of Intraheptic Cholestasis[1].**

Presence of typical itching symptoms
and
bile acid >10 mmol/L
and/or
increased liver transaminase levels.

- If there is a typical itch pattern for IHCP in the presence of normal bile acid and elevated liver transaminase, IHCP diagnosisshould be accepted after other causes have been excluded[1].

## 2. Adverse fetal outcomes of IHCP [2-4]

- Maternal bile acid can cross the placenta directly, and higher bile acid levels are characterized by more adverse fetal outcomes.
- The most important parameter determining IHCP in the clinic is the bile acid level in maternal serum.
- What does increased bile acid do to the fetus? The disorder is characterized by sudden intrauterine death, meconium-contaminated amniotic fluid, spontaneous or iatrogenic prematurity, neonatal respiratory distress syndrome, transient tachypnea of the newborn, and increased neonatal admission to the intensive care unit based on the increased bile acid level.
- Postpartum bleeding is the most critical maternal complication.
- Fetal death occurs when the bile acid level >100 mmol/L and suddenly without any findings from a fetal non-stress test (NST). There is increasing evidence that the presence of high bile acid levels causes cardiac arrest by acting on cardiac calcium receptors.

**Table 2. Disorder Severity According to Bile Acids [1,4].**

| |
|---|
| Maternal serum bile acid > 10mmol/L - <40 mmol/L defined as mild IHCP |
| Maternal serum bile acid > 40 mmol/ defined as modarate IHCP |
| Maternal serum bile acid > 100 mmol/L defined as severe IHCP |

## 3. Two main treatment goals of IHCP[5]

- First, reduce maternal clinical symptoms. Second, reduce perinatal morbidity and mortality.

**Table 3. Treatment of IHCP**

| |
|---|
| Ursodeoxycholic acid (UDCA) is the first agent of choice for treatment. |
| The initial dose is 10–15 mg/kg/d. The dosage must be divided into two doses. UDCA preparations are available in 250-mgcapsules. |
| Itching symptoms regress within 1–2 weeks, and biochemical markers regress within 3–4 weeks. |
| If the clinical findings do not improve after the initial UDCA dose, the dose should be increased. The maximum dose is 20mg/kg/d. |
| Antihistamines should be added to the treatment divided into two doses for itching. |
| No other treatmentagents (e.g., rifampicin, s-adenosyl methionine,orcholesterol) have been found to be superior to UDCA. |

## 4. Antepartum management of IHCP[5]

- The most important parameter determining management of IHCP is the maternal serum bile acid level.
- In pregnant women who improved with UDCA treatment and whose bile acid level was < 40 mmol/L:
  - o Beginning from the 28th gestational week until the 34th gestational week, weekly NST, amniotic fluid measurement, and a biophysical profile should be conducted.

- After the 34th week of pregnancy, semi-weekly NST, amniotic fluid measurement, and biophysical profile should be conducted.

- In pregnant women with bile acid level > 40 mmol/L with UDCA treatment:
  - Hospitalization should be provided.
  - Beginning at the 28th week of pregnancy, semiweekly NST, amniotic fluid measurement, and a biophysical profile should be conducted.
  - Two doses of a steroid should be administered at <34 weeks of gestation for fetal lung maturation.
- How often should the maternal bile acid level be measured? Although there is no clear recommendation or consensus, I recommend weekly or semiweekly follow-up, especially in the presence of moderate or severe IHCP, to evaluate the response to treatment, determine the clinical follow-up, and determine the time of delivery.

## 5. Mode of delivery and intrapartum monitoring[5]

- Mode of delivery is planned according to standard obstetric indications.
- Delivery between $37^{0/7}$ and$38^{6/7}$ weeks of gestation maybe preferred for pregnant women whose bile acid is < 40 mmol/L in the follow-ups.
- Delivery between $36^{0/7}$ and $37^{0/7}$ weeks of gestation maybe preferred for pregnant women whose bile acid is between 40 and 99 mmol/L in the follow-ups.
- When bile acid >100 mmol/L in the follow-ups,
  - If unbearable and persistent maternal pruritus despite treatment, or
  - If liver transaminases and bile acid continue to increase despite treatment, or
  - If the patient has a history of intrauterine fetal death from IHC, delivery must be planned between $34^{0/7}$and$36^{0/7}$ weeks of gestation after antenatal corticosteroid administration.
- Continuous fetal monitoring should be conducted during spontaneous labor and labor induction. In the presence of severe IHCP, a decision for cesarean delivery should be preferred in the presence of nonreactive NST after 40 min without deceleration.
- In the presence of meconium-contaminated amniotic fluid during labor, a decision for cesarean delivery should be preferred.
- The family should be informed in detail about possible fetal and maternal complications. The risk of postpartum hemorrhage should not be ignored, and the mother's coagulation parameter values should be reevaluated.

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CHAPTER 12

# DEFINATION AND MANAGEMENT OF RH ISOIMUNIZATION DURING PREGNANCY

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## 1. Introduction

With a simple definition, Rh isoimmunization occurs as a result of the passage of 0.1 ml or less fetal erythrocytes in Rh (+) fetus into the circulation of the Rh (-) mother.

**Table 1. Diseases and Procedures that Require 300mg anti-D Immunoglobulin Administration**

Feto-maternal transmission in sufficient quantities to cause alloimmunization occurs most frequently during delivery. The other most important disease and procedured are listed and, 300mg anti-D immunoglobulin should be administered[1];

- Abortus imminens, spontaneous abortion, elective abortion
- Ectopic pregnancy
- Hydatiform mole
- Chorionvillus sampling, cordocentesis and amniocentesis
- Presence of intrauterine ex fetus
- Abdominal trauma
- External cephalic version
- Vaginal delivery or cesarean section

The most important thing to say at the beginning is that in every case of doubt in terms of indication, the decision should be to administer 300 mg of anti-D immunoglobulin.

## 2. First clinical visit and follow-up[1]

- In cases where the mother is Rh (-) and father is Rh (+), maternal blood group and indirect Coombs test should be requested at the first visit in pregnant women who have had blood transfusions before and in multiparous pregnants who delivered before.
- Indirect Coombs test should be requested again in cases with any fetomaternal hemorrhage during pregnancy, at 28 weeks of gestation and at delivery.
- Titrate must be requested for the indirect Coombs test.
- The critical titer value in affected cases, namely indirect Coombs test (+), varies between 1/8 and 1/32 in most centers for severe erythrobblastosis fetalis and hypops.
- In case of indirect coombs (-) at 28th gestational week, prophylactic 300mg anti-D immunoglobulin should be administered.
- Indirect coombs should be repeated at delivery and anti-D immunoglobulin should be repeated in cases where the baby is Rh (+).

The administration should be preferred after delivery in cases who applied to the clinic after the 34th gestational week and did not receive anti-D immunoglobulin before.

**Table 2. Critical Titer Value**

| |
|---|
| The critical titer value is 1/8. In cases where anti-D immunoglobulin was administered in the first trimester, 300 mg of anti-D immunoglobulin should be administered at values below 1/8 (1/2 or 1/4) at 28 weeks of gestation or after delivery. |

- If the indirect Coombs test is 1/2-1/4 at 24-28 weeks and there is no history of anti-D immunoglobulin, the pregnant women should be followed up for indirect coombs at 2-week intervals, if the titer persists or increases, it should be considered as immunized Rh and anti-D immunoglobulin administration should be skipped.
- All pregnant women with immunostained Rh should be referred to a tertiary center with a perinatology clinic.
- For pregnant women who received anti-D immunoglobulin at 28 weeks, the titer value at birth is 1/2-1/4 and if the baby is Rh (+), anti-D immunoglobulin should be repeated.
- In cases where anti-D immunoglobulin administration is missed due to a mishap, anti-D immunoglobulin administration for up to 4 weeks will be beneficial.

**Table 3. In the Presence of Excessive Bleeding**

| |
|---|
| Although the current study bulletins suggest that a single dose of 300 mg anti-D immunoglobulin is sufficient in pregnant women who develop ablatio placenta, placental invasion anomalies, abruption of the placenta and uterine atony, in such cases, it is necessary to increase the dose according to the clinician's preference, to increase the dose in order to prevent possible maternal immunization.<br><br>Although dose calculation can be determined more clearly by methods such as flow cytometry, it is not yet routinely used in clinical practice and hematology clinics. |

## 3. Middle cerebral artery (MCA) doppler monitoring[1]

- Because of the risk of developing erythroblastosis fetalis and hydrops fetalis in affected fetuses, follow-up is prefered with MCA Doppler measurements.
- MCA blood flow is followed by MoM values according to the gestational week, and a peak systolic flow rate of 1.5 MoM is associated with a sensitivity close to 100% for moderate to severe anemia.
- In pregnant women with an MCA Doppler value below 1.5 MoM, follow-up should preferably be at weekly intervals and antenatal tests should be started at 28 weeks of gestation.
- If the MCA Doppler value is above 1.5 MoM, cordocentesis should be performed, fetal Hb should be measured, and if fetal hemoglobin is more than two standard deviations below the mean value for gestational age, intrauterine transfusion should be preferred. Fetal blood sampling should be repeated one or two weeks later if fetal Hb is not below 2 standard deviations in cordocentesis.
- MCA MoM values and Hb values by week of gestation can be accessed from the available link[2].
- (https://www.uptodate.com/contents/rhd-alloimmunization-in-pregnancy management?search=mca%20doppler&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#subscribeMessage).
- If there is a history of severe hemolytic disease in previous pregnancies, the fetus died in the intrauterine or neonatal period with hydrops, history of intrauterine transfusion before 24 weeks of gestation, and if there is a titer of 1/256 and above in this pregnancy, and if there is evidence of hydrops, serial combined maternal plasmapheresis and intravenous immunoglobulin treatment should be preferred. Pregnant women should be consulted with hematology and it should be ensured that the practices are performed in the hematology clinic.
- As a determinant of clinical management, the evaluation of fetal blood group and Rh by cell-free DNA method at the first clinical visit in previously immunized pregnant women can be a non-invasive and very important approach. In cases where the fetus is Rh (-) and there is no additional fetal erythrocyte contact in the follow-up, the risk of developing hemolic disease for the Rh (-) fetus will be very low.

## 4. Delivery time and mode of delivery

- The standard approach is to continue the pregnancy until the possible week of gestation of the affected fetus.

- For pregnant women who do not develop hydrops fetalis and whose MCA doppler follow-up is normal, delivery should be preferred between 37 0/7-38 6/7 weeks of gestation.
- The risks of continuous cord blood sampling and transfusion should not be forgotten in fetuses requiring severe and multiple transfusions.
- The appropriate approach is to make the last transfusion between 30-32 weeks of gestation, and to plan a cesarean delivery between 32-34 weeks after the antenatal corticosteroid period is completed. Before delivery, pediatrician should be informed, appropriate conditions should be prepared for the fetus, and the pediatric department should be prepared for a possible exchange.

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CHAPTER 13

# MANAGEMENT OF PLACENTA PREVIA AND PLACENTA INVASION ANOMALIES

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## 1. Definition of Placenta Previa

Placenta previa is defined as partial or complete closure of the internal cervical os after abnormal placement of the placenta. It is the most common cause of third trimester bleeding and is associated with life-threatening bleeding due to its accompanying abnormal invasive placental (AIP)[1]. Around the 20th week of midwifery or during fetal anomaly screening, the position of the placenta should be evaluated, and in case of placenta previa, it is necessary to refer the patient to reference centers for further follow-up.

- The determinant of whether placenta praevia detected in the mid-trimester will transform into AIP or displace upwards is the history of previous cesarean section.

- Presence of placenta previa and AIP at 32 weeks of gestation should be repeated by a perinatologist in experienced centers.
- In the presence of total or partial placenta previa, delivery should be preferred with cesarean section at 37 weeks of gestation. Vaginal delivery may be preferred in pregnant women who end up close to the cervical os 1-2 cm away, and counseling should be given to the family in terms of possible severe bleeding complications at birth. Cesarean section at 37 weeks of pregnancy is an alternative approach for pregnant women who do not prefer vaginal delivery.
- In the presence of total placenta previa or AIP, there is no evidence of the benefit of follow-up with hospitalization or as an outpatient. This management is at the clinician's decision, and I believe that it is an appropriate approach to hospitalize all pregnant women who cannot reach the hospital in a short time in case of a possible bleeding, and to follow them until delivery.

## 2. Management of Placenta Previa

- In the patient who presents with third trimester bleeding, it is absolutely necessary to evaluate the fetal well-being and placental location of the placenta and to evaluate the stability of the maternal condition with vaginal examination and pre-touch ultrasonography.
- After detecting the presence of placenta previa, the severity of bleeding should be evaluated by speculum examination.
- In cases where bleeding is severe and fetal well-being is unstable, emergency cesarean section should be decided.
- In cases where the bleeding is heavy, fetal monitoring with NST is performed and the patient is taken to the bed. The amount of bleeding. During the follow-up, the patient should be hydrated and erythrocyte transfusion should be preferred if indicated under stable conditions according to the Hb value.
- For fetal lung development below 34 weeks of gestation, 2 doses of steroid should be administered at 24 hour intervals[1]. In the presence of fetal maternal stability between 34+0-36+5 weeks, a single dose of steroid should be administered.
- Calcium channel blockers should be avoided as tocolytic agents. For a bleeding patient, the vasodilation and negative inotropic effect of calcium channel blockers may cause hypovolemic shock by blocking the

compensation mechanisms that will develop due to bleeding. MgSO4 can be a suitable tocolytic with both tocolysis and neuroprotection effects. Before 32 weeks of gestation, indomethacin is an important alternative[1].

- If delivery is anticipated within 24 hours at before 32 weeks of gestation, MgSO4 should be started for fetal neuroprotection.
- A midline incision below the umbilicus in the lithotomy position should be preferred for any case with suspected AIP. With this incision, the amount of vaginal bleeding can be followed more clearly and it should not be forgotten that the necessary surgical interventions can be performed more easily.

## 3. Abnormal Invasive Placenta Spectrum

It is defined as the invasion of the placenta into the uterine myomatrum layer, and it is defined as placenta acreata when the placenta invades to the deep endometrium, placenta increate when it invades the myometrium, and placenta parkreta when the myometrium invades the uterine serosa and surrounding tissues[1].

- The two most important risk factors are a history of previous cesarean section and the presence of total placenta previa. The higher the number of cesarean sections increases the invasion risk, but all pregnant women should be routinely screened for AIP and placenta previa if there is a single cesarean history.
- Total placenta previa is the most important risk factor in my own clinical opinion.
- Today, AIP can be diagnosed by maternal demographic and ultrasonographic features from the first trimester[2].
- Estimating risky pregnancies from the first trimester and directing pregnant women to reference centers is the most important approach[3].
- Deliveries in hospitals without experience and blood transfusion centers are associated with maternal mortality.

## 4. Management of AIP Spectrum[1,4]

- It is necessary to classify the presence of AIP as low risk or high risk after the evaluation by the perinatologist at 32 weeks of gestation in patients with total placenta previa.
- In cases with low risk for AIP, Pfannenstiel and Kerr incisions can be preferred for cesarean section after the necessary preparations are obtain after 37 weeks of gestation.

- For high-risk cases, a midline incision below the umbilicus and a vertical incision without compromising the placental integrity of the uterus should be preferred in the lithotomy position. Disruption of placental integrity is the most important parameter affecting the amount of bleeding.
- In the presence of AIP, delivery should be carried out in referral centers at 37 weeks of gestation.
- Due to early term delivery and possible fetal respiratory complications, a single dose of antenatal corticosteroid should be administered at 34+0-36+5 weeks.
- Although the primary preference is a bakri balloon tamponade and systemic devascularization, the decision of cesarean hysterectomy should not be delayed in the presence of placenta parkreta and massive bleeding.
- Leaving the placenta in situ is an important alternative method in patients and fertility preservation desires, and a informed consent form must be obtained by informing the patient in detail in terms of infectious morbidity and mortality.
- Before the cesarean section, 4 units of erythrocyte suspension and 4 units of fresh frozen plasma should be kept ready, the anesthesiologist and blood center should be informed about the case, and intensive care conditions should be prepared.
- In terms of possible injuries, urology and surgeon consultant specialists should be informed in advance about the surgery place, time and the case[5].
- Although there are clinical studies showing the effectiveness of embolization of the main vascular vessels before the operation, it should not be forgotten that there are more important complications than the benefit of vascular injury and thrombus risk. Study bulletins do not routinely recommend these practices.
- In cases where the placenta is locally invaded, local excision of the invading placental area should be preferred.
- Written consent forms must be obtained by informing the patient, spouse and family in detail about all steps of the operation and the methods to be preferred.

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# CHAPTER 14

# MANAGEMENT OF POSTPARTUM HEMORRHAGE AND MASSIVE TRANSFUSION PRINCIPLES

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## 1. Introduction

Postpartum hemorrhage (PPH) is the most important obstetric emergency. If postpartum bleeding occurs in the first 24 hours, it is called primary or early bleeding, and bleeding between 24 hours and 12 weeks is called secondary bleeding or late bleeding.

**Table 1. Postpartum Bleeding Etiology**

| Primer PPH | Seconder PPH |
|---|---|
| Uterine atony | Subinvolution of the placental region |
| Lacerations | Infection |
| Rest placenta | Hereditary coagulation defect |
| Placental invasion anomaly | Rest placenta |
| | |
| Coagulation disorders | |
| Uterine inversion | |

## 2. PPH Symptoms and Signs[1]

- In the presence of 500-1000ml bleeding (10-15 percent blood loss)
  - o Systolic blood pressure (mmHg) normal and > 90
  - o Palpitations, lightheadedness, no or mild increase in heart rate
- In the presence of 1000 to 1500ml bleeding (15-25 percent blood loss)
  - o Systolic blood pressure (mmHg) 80 to 90
  - o Weakness, tachycardia (100 to 120 beats/min), tachypnea (respiratory rate of 20 to 24)
- In the presence of 1500 to 2000ml bleeding (25-35 percent blood loss)
  - o Systolic blood pressure (mmHg) 70 to 80
  - o Restlessness, confusion, pallor, oliguria, tachycardia (120 to 140 beats/min), cool skin
- In the presence of 2000 to 3000ml bleeding (35-45 percent blood loss)
  - o Systolic blood pressure (mmHg) 70 to 80
  - o Lathargy, air hunger, anuria, collapse, tachycardia (>140 beats/min)
- In 2017, ACOG defined PPH as the amount of bleeding >1000 mL or signs/symptoms of hypovolemia in the first 24 hours, regardless of the mode of delivery. The incidence of postpartum hemorrhage was determined to be 1-3% using estimated blood loss [2,3].
- With the separation of the placenta after delivery, the mechanism of hemostasis begins to occur. Uterine bleeding is controlled by contraction of the myometrium, hemostatic factors (tissue factor, plasminogen activator inhibitor, systemic coagulation factors (platelet, circulating coagulation factors) that cause coagulation. In most PPH, one or both pathways are deficient.
- The most important and most common cause of PPH is uterine atony. Uterine atony is associated with multiple pregnancy, polyhydramnios, macrosomia,

prolonged use of oxytocin, high parity, chorioamnionitis, general anesthesia, and multiple or large uterine fibroids.

- Genital tract trauma, retained placental tissue and abnormalities of coagulations are other important risk factors.
- This classification should be kept in mind as the 4T rule (Tonus, Trauma, Tissue, Thrombin).

## 3. Important and Most Common Cause of PPH

### *3.1. Local or Disseminated Uterine Atony*

- The most common cause of PPH is uterine atony. The diagnosis of atony is obtaine by the inability to contract the uterine myometrium in the third stage of labor.
- A history of PPH at previous birth and prolonged delivery are the best known risk factors for PPH due to atonia.
- With diffuse atony, blood loss can be much greater than is observed because a loose, enlarged uterus can contain a significant amount of blood. In focal atony, while the lower uterine segment is enlarged and atonic, the fundal region, which is difficult to understand on abdominal examination but can be detected on vaginal examination, may be well-contracted.
- Although diffuse uterine atony is the most common cause of PPH, it often responds to the administration of additional uterotonic drugs. Therefore, it is not the most common cause of massive transfusion at birth.

### *3.2. Trauma*

- Genital tract lacerations are the most common complication of obstetric trauma.
- It may be due to bleeding due to trauma, laceration, rupture, etc. or surgical incisions. Vaginal, vulvar, periclitoral, perineal and cervical lacerations may develop after delivery. Larations are predominantly venous bleeding. Lacerations should be repaired quickly.
- If a uterine artery injury is suspected, interventional radiology or surgical exploration and ligation should be considered. Repair may require assistance from anesthesia or referral to a better equipped centre.
- Genital system hematomas (labial, vaginal, or retroperitoneal) may be a sign of severe blood loss in sudden uncontrolled labor or operative vaginal delivery. Labial, rectal, pelvic pain or deterioration in general condition may

be the only symptom of genital tract hematomas and may not be noticed immediately after delivery.

- In the presence of abnormal vital signs, incision and drainage should be performed in case of rapid progression and enlargement of the hematoma. Arterial embolization may be an option before the hematoma is opened.
- In bleeding without deterioration in the general condition of the mother, the bleeding team should be ready and it should be kept in mind that intraperitoneal or retropertoneal bleeding may occur.

### *3.3. Rest Placenta*

- A detailed visual inspection of the placenta for completeness should be performed after all deliveries. Inability or incomplete separation of the placenta should bring local/diffuse invasion anomalies to mind. If the rest placenta does not come manually, an ultrasound-guided curette or oval forceps can be used.

### *3.4. Abnormalities of Coagulations*

- An acute coagulopathy may complicate PPH. The major situations are that;
  - o Detachment of placenta
  - o Amniotic fluid embolism
  - o HELLP
  - o Acute fatty liver of pregnancy
  - o Septic abortion
- Placental abruption is often associated with uterine atony due to extravasation of blood into the myometrium.
- Major complications of placental abruption are DIC and hypofibrinogenemia. Placental abruption usually presents as a combination of vaginal bleeding, frequent uterine contractions (tachysystole), and pain.
- Placental abruption constitutes approximately 20% of cases requiring massive transfusion. Given the deep coagulopathy, postpartum hemorrhage is almost always seen with amniotic fluid embolism. Rapid fluid replacement and massive transfusion may be required in the presence of deep coagulopathy.
- Hypothermia and acidosis should be avoided. Hypothermia causes myocardial ischemia, coagulopathy, decreased platelet function and mortality.
- The combination of hypothermia and acidosis significantly increases the risk of bleeding. Therefore, acidosis should be corrected with bicarbonate if necessary.

- Generally, less invasive methods should be used in the treatment of postpartum hemorrhage initially if possible, but if unsuccessful, more aggressive interventions, including hysterectomy, may be required for maternal survival.

## 4. Medical Treatment of PPH

- Uterotonic agents are the first treatment to be used in postpartum hemorrhages caused by atony. If there is no response to uterotonic agents, packing or surgical interventions are required.
- Tranexamic acid is an antifibrinolytic agent. It can be given intravenously. Early use of tranexamic acid is recommended for patients with coagulopathy and DIC.
- The World Maternal Antifibrinolytic Study has shown that tranexamic acid (1 g IV in 10 minutes, then 2 g in 10 minutes if bleeding continues after 30 minutes) reduces death due to bleeding by 20-30% in patients with PPH[4].
- There are also studies that are not directly recommended because the efficacy of tranexamic acid in the treatment of postpartum hemorrhage is unclear in the studies[5-7].

**Table 2. Acute Medical Management of Uterine Atony[8]**

| Drug | Dose and Frequency | Contraindications and adverse effects |
|---|---|---|
| **Oxytocin** | IV: 10-40 units per 500-100ml as continuous infusion or IM: 10 units. Continious | **Contraindications;** Rare, hypersensivity to medication. **Adverse effects;** Nausea, vomiting, hyponatremia with prolonged dosing. Hypotension can result from IV push, which is not recommended. |
| **Methyler-gonovine** | IM: 02.mg Every 2-4 hour | **Contraindications;** Hypertension, preeclampsia, cardiovascular disease **Adverse effects;** Nausea, vomiting |
| **Misoprostol** | 600-1000micrograms oral, sublingual or rectal One time | **Contraindications;** Rare, hypersensivity to medication. **Adverse effects;** Nausea, vomiting, diarrhea, shivering, fever, headache |

## 5. Tamponad Techniques

- Compression can be effective in intrauterine tamponade PPH when uterotonic and bimanual uterine massage fails to maintain uterine contractions and control bleeding.
  - o Bakri Baloon: Inflated with 300-500mL of saline
  - o Ebb uterine tamponade system: Double balon; maximum recomended fill volumes are 750mL fort he uterine balon and 300mL for the vaginal balon.
  - o Foley catheter: Insert one or more 60mL bulbs and fill with 60mL of saline

## 6. Surgical Techniques

- o Vascular ligation
- o uterine compression sutures
- o hysterectomy

## 7. Blood Products and Transfusion Principles

- When an intensive transfusion is required, the recommended initial transfusion ratio for erythrocyte: fresh frozen plasma: platelet is typically 1:1:1 to mimic replacement of whole blood [8].
- In case of PPH, acute changes in Hb or Htc are indicative of blood loss. Emergency preparation for transfusion should be obtained in women with ongoing bleeding equal to 1000-1500 mL or more blood loss, or with abnormal vital signs (tachycardia and hypotension).
- Massive blood loss may cause rapid reduction of coagulation factors and cause the patient to go to DIC. These patients need platelet and coagulation factors in addition to the erythrocyte suspension.

**Table 3. Blood Products and Characteristics**

| Product | Volume per Unit | Content per Unit | Effect on Bleeding |
|---|---|---|---|
| **Whole blood** | ~500 ml, Htc: ~%40 | erythrocytes plasma 600-700 mg of fibrinogen no platelets | It restores blood volume and fibrinogen, increasing Htc by 3-4% volume per unit. |
| **Erythrocyte Suspension** | ~250-300 ml, Htc: ~%55-80 | erythrocytes, minimal fibrinogen, no platelets | Increases Hct by 3-4% volume per unit. |
| **Fresh frozen Plasma** | ~250 ml; 30 minutes dissolution | colloid 600-700 mg of fibrinogen, no platelets | Restores circulating volume and fibrinogen |
| **Cryoprespitate** | ~15 ml; frozen | 1 unit ~200 mg of fibrinogen other coagulation factors no platelets | Increases baseline fibrinogen by ~150 mg by 15-20 units or 3-4 g. |
| **Platelet Suspension** | ~50 ml, It is stored at room temperature. | 1 unit increases the platelet count by approximately 5000 /µl. Single donor apheresis bag is preferred. | 6-10 units are given. A single donor apheresis bag raises ~30000/µl. |

## 8. Defination of Massive Transfusion

- Transfusion of blood equal to the person's total blood volume within 24 hours,
- Transfusion of 5 units or more of erythrocyte suspension within four hours
- Transfusion of more than half of the person's blood volume within 3 hours,
- Transfusion of 3 units or more of erythrocyte suspension within 1 hour,
- Transfusion of blood >150 ml/min in adults.

### *8.1. Massive Transfusion Targets*

- Hemoglobin >7
- Fibrinogen >300

- Platelet count >50,000
- The PT and aPTT value should be aimed at 1.5 times less than the control value.
- We should avoid hypothermia and acidosis in massive blood transfusion. At the same time, we should pay attention to hypocalcemia and hyperkalemia due to massive transfusion.

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# CHAPTER 15

# VENOUS THROMBOEMBOLISM PROPHYLAXIS IN PREGNANCY

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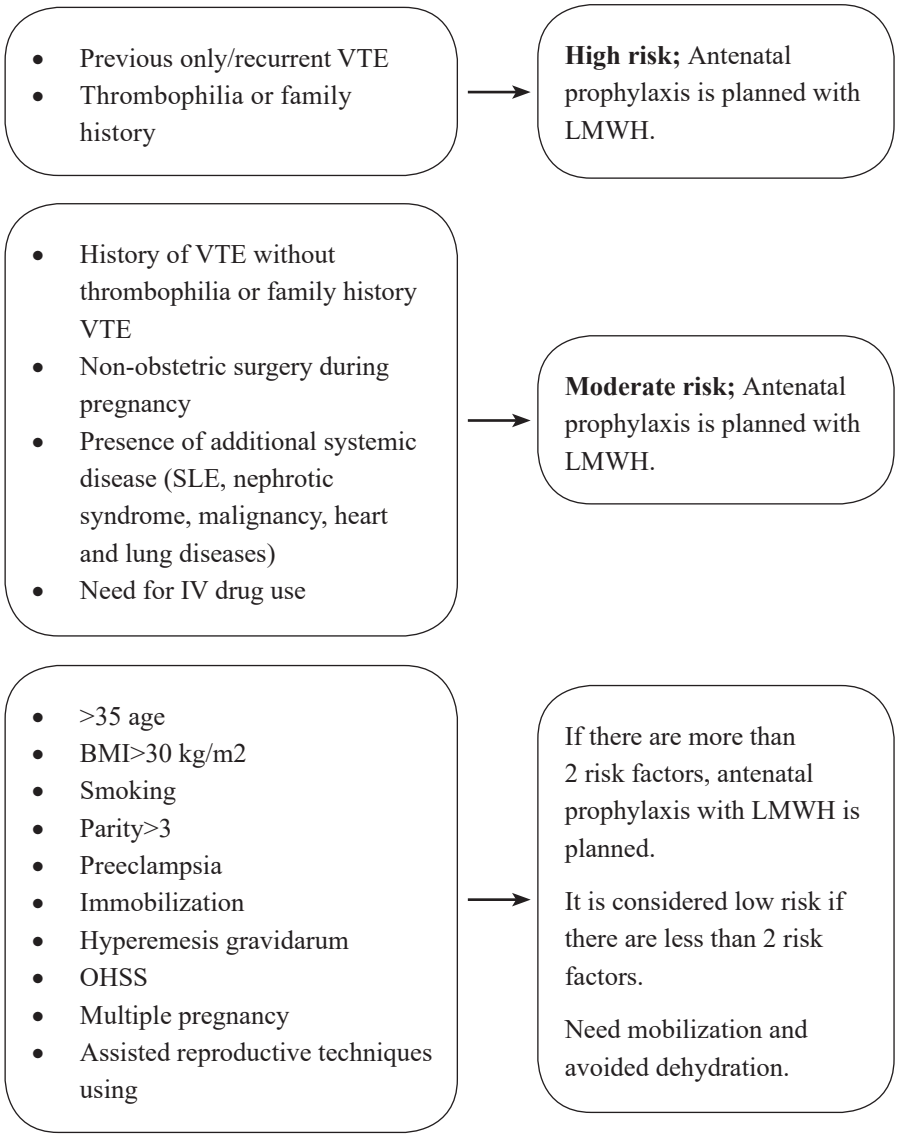
## 1. Introduction

Pregnants have a 5-6 times higher risk of venous thromboembolism (VTE) than non-pregnant womens of the same age.Therefore venous thromboembolic diseases are among the leading causes of maternal death and morbidity.

## 2. Prophylaxis in antenatal period

All pregnant women should be evaluated for risk factorsf or VTE during early pregnancy

**Algorithm 1. Antepartum Risk Factors and Prophylaxis**[1]




## 3. Prophylaxis during delivery and postprtum period[1]

- The most important thing to know is that thrombotic predisposition is the highest level immediately after delivery.
- If vaginal delivery or cesarean section is planned, LMWH use should be discontinued at least 12-24 hours before delivery, depending on the characteristics of the preferred anticoagulant, at the beginning of labor if regional anesthesia is to be applied.

- In pregnant women receiving high prophylactic doses of LMWH/AFH, the heparin dose should be reduced to the dose of thromboprophylaxis one day before induction and, if appropriate, continued throughout delivery.
- Pregnant women who received LMWH in the prenatal period and are likely to have a cesarean section should receive a thromboprophylactic dose of LMWH one day before delivery, but the operation should be performed without taking the morning dose.
- The first thromboprophylactic dose of LMWH should be given as soon as possible after ensuring that there is no postpartum hemorrhage and that regional analgesia is not administered.

**Algorithm 2. Postpartum Risk Factors and Prophylaxis**[1]

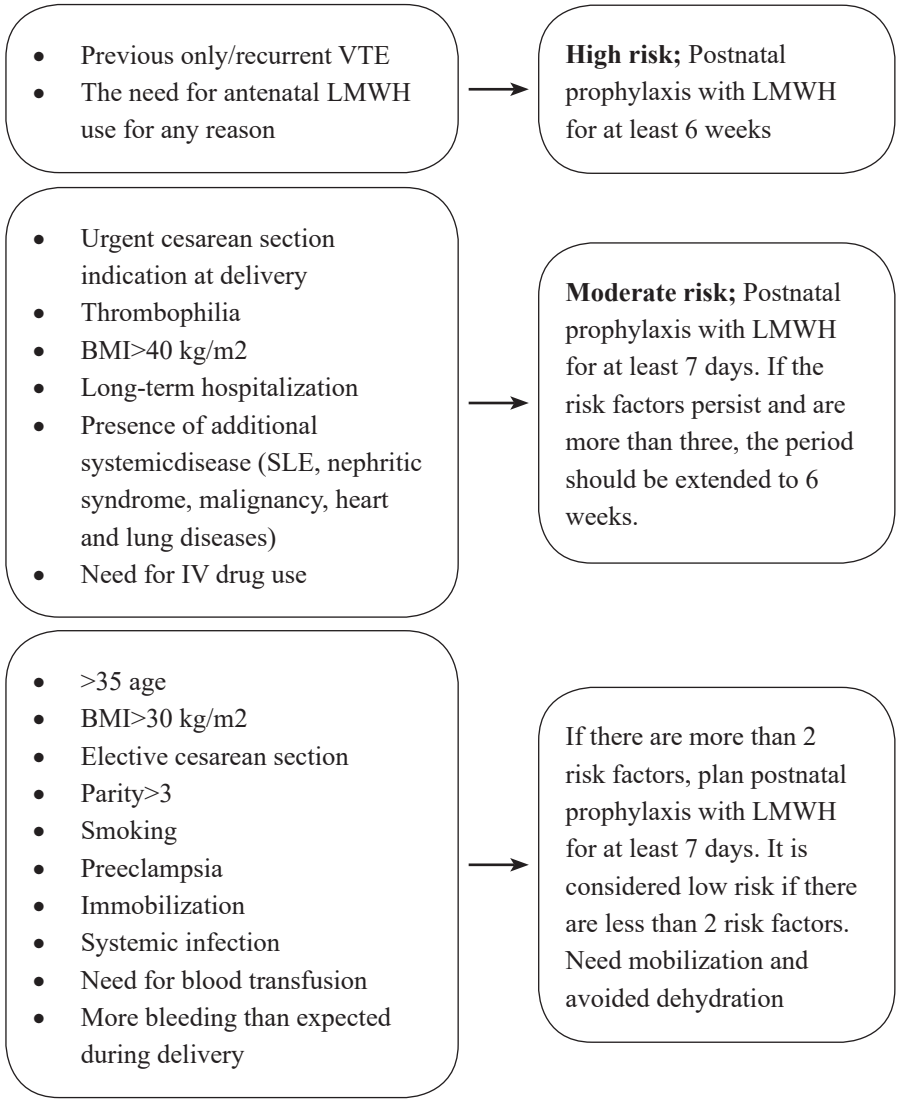


**Table 1. Recommended Doses forLow MolecularWeight Heparin**[1]

| **Maternal weight(kg)** | **Enoxaparin (Oksapar, Clexan, Enox)** | **Dalteparin (Fragmin)** | **Tinzaparin (İnohep)** |
|---|---|---|---|
| <50 | 2000 unit/day | 2500 unit/day | 3500 unit/day |
| 50-90 | 4000 unit/day | 5000 unit/day | 4500 unit/day |
| 91-130 | 6000 unit/day | 7500 unit/day | 7000 unit/day |
| 131-170 | 8000 unit/day | 10000 unit/day | 9000 unit/day |
| **High prophylacticdose** | | | |
| | 2*4000 unit/day | 2*5000 unit/day | 2*4500 unit/day |

## 4. Contraindications of using of LMWH

After a careful bleeding risk assessment, the use of LMWH in pregnant women at risk of bleeding should be delayed until bleeding control is achieved and the patient is stable.

### *4.1. Risk factors for bleeding*

- Active prenatal and postpartum bleeding
- Risk of severe bleeding (placental invasion anomalies and previa etc.)
- Bleeding diathesis (VonWillebrand, hemophilia etc.)
- Thrombocytopenia (platelet count less than 75,000)
- Acute stroke in the last 4 weeks
- Severe renal dysfunction (GFR<30 ml/min/1.73 m2)
- Hepatic dysfunction (prothrombin time above normal limits)
- Uncontrolled hypertension (systolic blood pressure ≥ 200mmHg and diastolic blood pressure ≥120mmHg)

## References

1. T.C. Sağlık Bakanlığı yüksek riskli gebelik yönetim rehberi

# CHAPTER 16

# TRAUMA IN PREGNANCY

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## 1. Introduction

Pregnancy trauma is one of the specialcases in the emergency department and the important cause of non–obstetric related morbidity and mortality.The percentage of trauma during pregnancy is 8-12, and 0.4 percent of these will be hospitalized. The most common blunt trauma is observed.In many studies, blunt traumas due to bruises were most frequently reported as head and neck with 42.2 percent.

- The risk of death was 1.4 maternal deaths and 3.7 fetal deaths per 100,000 pregnancies.
- Car accidents constitute 40-50% of pregnancy-related traumas and even in low speed accidents, placental abruption can occur.
- To reduce possible damage to the airbag, it should increase the distance to the steering wheel (10 cm). Seat belts should be recommended to pregnant women.

- Complications of trauma during pregnancy are associated with preterm delivery, premature rupture of membranes, placental abruption, fetal maternal hemorrhage, uterine rupture, cesarean section, and pregnancy loss.
- The most common cause of fetal death is maternal death.The second cause of fetal death is placental abruption. For maternal and fetal health, it requires the joint effort of prehospital, emergency department, trauma, delivery and neonatal intensive care unit teams[1].
- The chances of fetal survival depend on them other. For this reason, resuscitation of the mother is always a priority[2].

## 2. Anatomic and Physiologic Changes of Pregnancy

- Blood pressure drops in the first trimester of pregnancy and returns to the level of non-pregnan twomen in the third trimester. During pregnancy, blood volume can increase up to 50 percent.
- Cardiac output increases by up to 50%. Even with a loss of 2L, vital signs may not deteriorate but the fetus cannot tolerate it. Uterine blood supply increases during pregnancy, so injury to the uterus can lead to serious bleeding.
- The uterine fundus is preserved in the pelvis until the 12th week, so fetal injury is rare in the first trimester. If the maternal pelvis is fractured, fetal injury may occur. A history of pelvic fracture is not a contraindication for vaginal delivery and the patient should be consulted at this time.
- Even a slow blunt trauma directly to the abdomen after 20 weeks can cause placental separation. It should not be forgotten that the diaphragm rises 4 cm during pregnancy so tube thoracostomy should be applied 1-2 ribs above.

## 3. Management of Trauma[2,3]

- The trauma resuscitation algorithm for the pregnant patient is almost the same as for the non-pregnant patient.
- In resuscitation, priority is given to the mother, because the chance of fetal survival depends on early and aggressive maternal resuscitation.
- All women of child bearing age should be asked about their pregnancy. If possible, a known pregnant woman at >20 weeks of gestation should be triaged in a hospital with trauma, obstetric and neonatal skills. Pregnant women who require pinalim mobilization should be placed in the semi-left lateral decubitus position to prevent compression of the inferior vena cava of the uterus.

### *3.1. Primary Survey*

- Maternal airway safety and ventilation should be ensured.
- Oxygen should be administered to keep the pulse oximeter >95%.
- Early intubation should be kept in minddepending on the severity of the injury.
- Mucosa can be edematous, hyperemic, fragile. Care should be taken in terms of difficult intubation(especially in inhalation burns).
- Maintain cervical spine immobilization and the patient should be in the semi-left lateral decubitus position. Provide extensive peripheral IV access above the diaphragm if possible.
- Since hypovolemia is harmful to both mother and fetus, attention should be paid to bleeding sites. The crystalloid infusion volume should be increased by 50% to account for the patient's additional plasma volume. Vasopressors should not be administered without volume replacement.
- A brief neurological evaluation should be made and the patient should be protected from hypothermia.
- The mothers hould be monitored and close vital follow-up should be done.
- Aspiration risk is high. A nasogastric tube should be inserted to reduce the risk of aspiration. An extended FAST should be performed to identify abdomen and thorax injury.

### *3.2. Secondary Survey*

- Evaluation of all systems is the same as in adults.
- A detailed history and physical examination should be performed in the secondary evaluation.
- Uterin erupture is common in patients with previous cesarean section. It is seen with a frequency of 1%. The uterus and abdomen are sensitive. Some patients may experience vaginal bleeding. Fetal structures are palpable. Uterine contours are irregular on examination. Fetal death rate is high. Amniotic membrane rupture can be evaluated by looking at the liquid pH paper in the vagina. Amniotic fluid is compatible with pH 7 and vaginal secretions with pH 5.

## 4. Cardiotocographic Monitoring and Obstetrical Ultrasound

- For pregnant patients who come with trauma, obstetrician and obstetrics nurse should be present in the emergency room. As soon as the mother returns to life after the 20th week of pregnancy, fetal heart rate and cardiotocography evaluations should be performed quickly. If there is more

than 3 uterine contractions per hour after trauma, placental abruption should be considered.

- A normal fetal heart rate is between 120 and 160 beats/min. If fetal cardiac activity is absent, then directhe remainder of treatment efforts solely at maternal resuscitation. With obstetric ultrasound, fetal heart rate, gestational age, presentation, placenta, abruption, evidence of fetal injury, and intra-abdominal/pelvic fluid are evaluated.
- In order to reduce fetal radiation, the mother should not be afraid to perform the necessary examinations. The specificity of the diagnosis of placental separation with CT of the abdomen is 98, and the sensitivity is 86. In order to reduce the effect of fetal radiation, the dose can be reduced by protecting the uterus and pelvis. IV and oral contrast media are safe both during pregnancy and lactation.
- All women of child bearing age should have a pregnancy test. Hemogram, biochemistry, coagulation factors, blood groups tests should be done. If possible, perform a Kleihauer-Betke analysis in women>12 weeks pregnant. It is a test that shows the mixing of maternal blood and fetal blood cells. It may be useful for patients that are Rh negative.
- Administer Rho(D) immunoglobulin to all Rh-negative pregnant women with abdominal trauma. A 300-microgram dose protects for up to 30 μL of fetomaternal hemorrhage. The immunoglobulin should be given within 72 hours. Tetanus vaccine should be administered.
- Emergency laparotomy indications are the same for pregnant and non-pregnantwomen.
- Cesarean section in the emergency room should be performed with in the first 4 minutes of maternal arrest.
- The condition of the patient after trauma depends on the severity of the injury.At least 4 hours of monitorized follow-up is required in pregnant traumas older than 20 weeks. Monitoring is not indicated for a non viable fetus. If there are signs of fetal distress, they should be followed up for at least 24 hours.

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# CHAPTER 17

# CLASSIFICATION AND MANAGEMENT OF MATERNAL HEART DISEASES IN PREGNANCY

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## 1. Introduction

- Maternal heart disease is one of the most important causes of maternal death both in antepartum and postpartum period. Advance maternal age, hypertension and obesity are the most important risk factors that increase morbidity and mortality in patients with cardiac disease.
- It is well known that physiological hemodynamic cardiac changes occur during pregnancy. Pregnancy causes a sustained increase in cardiac output and plasma volume and a decrease in maternal systemic vascular resistance. Dramatic changes occur in heart rate, cardiac output, plasma volume and blood pressure both in intrapartum and postpartum period. Maternal hemodynamic usually returns to its pre-pregnancy state 3-6 months after

delivery. Physiological anemia occurs during pregnancy. Severe anemia will worsen the prognosis of maternal heart diseases, patients should be followed every trimester with laboratory tests for anemia.

## 2. Heart Disease Symptoms and Signs[1]

- In the follow-up of normal pregnancy cardiac problem should be considered in symptoms such as chest pain, palpitation, shortness of breath, syncope, and cough.
- On physical examination, findings such as pretibial edema, jugular venous engorgement, murmur, wheezing in the lung, and decreased breath sounds can be observed. Tachycardia, hypertension, increased respiratory rate and decreased oxygen saturation may be observed.
- Patients with high risk cardiovascular disease should be managed with a multidisciplinary Pregnancy Heart Team (obstetricians, maternal-fetal medicine subspecialists, cardiologists, anesthesiologists) during pregnancy, delivery and postpartum period in medical centers.
- Cardiac diseases that cause maternal mortality and morbidity need to be identified.
- The modified WHO pregnancy risk classification separate cardiovascular diseases into 5 categories. These categories provide information on how often patients will be called for examination. Health care provider do not suggest pregnancy for women in the Modified World Health Organization (WHO) pregnancy risk category IV.
- Symptoms suggestive of peripartum cardiomyopathy in a pregnant or postpartum woman are dispnea, angina, palpitations, rhythm disorder, or edema. The echocardiogram is often foremost diagnostic test. Consultation with cardiologist is recommended. The patient should be referred by a pregnancy heart team to a proper level of facility for multidisciplinary care.

## 3. Antepartum, intrapartum and postpartum management and mode of delivery[1]

- Pregnant women with heart disease should delivery in the hospital with a multidisciplinary team.
- If the mother has congenital heart disease, the probability of having it in the fetus is 4-10%. Echocardiogram is indicated in these fetuses between 18-22 weeks.
- Fetal growth reterdation should be evaluated by serial clinical examination or ultrasonography.

- Women with stable cardiac disease can deliver vaginally at 39 weeks of gestation, and cesarean delivery can be planned if there is an obstetric indication. Cardiac output changes during vaginal delivery. Valsalva maneuver may be required. High-risk heart patients may not tolerate it.
- Regional anesthesia during labor may provide sufficient analgesia to enable vaginal delivery. Patients who cannot have a vaginal delivery and who will need help in the second stage of labor should be determined.
- Low molecular weight heparin should be discontinued 12 hours before cesarean or normal delivery.
- Pulmonary edema and arrhythmia are the most common cardiac complications in intrapartum period. Intrapartum cardiac observation should be recommended in pregnant women with arrhythmia. Modification of neuraxial anesthesia management should also be considered for patients at risk for cardiovascular decompensation (left ventricular outflow tract obstruction or cyanotic congenital heart disease) due to decreased systemic vascular resistance.
- It is necessary to minimize the risk of venous thromboembolism in the postpartum period. Institutions should implement venous thromboembolism risk assessment protocols.
- Cardiology outpatient control is recommended within 7-10 days after parturition for women with hypertensive disease, and within 7-14 days after parturition for women with cardiovascular disease.
- Postpartum follow-up is significant in pregnant women with high-risk cardiovascular disorder. After 3 months, control is suggested.

### 4. Acute Myocardial Infarction and Acute Coronary Syndrome

- Acute coronary syndrome refers to clinical conditions that may result in myocardial damage and necrosis as a result of myocardial oxygen deprivation. Acute coronary syndrome contains stable angina, unstable angina, myocardial infarction and death.
- Risk factors for acute coronary syndrome in pregnancy; maternal age above 30, obesity, diabetes mellitus, smoking, hyperlipidemia, cardiovasculer genetic predisposition, hypertensive diseases of pregnancy, previous coronary artery dissection, blood transfusion and peripartum infection. Acute coronary syndrome may consequence from coronary atherosclerosis, dissection, embolism, spasm, arteritis, and coronary artery occlusion due to aortic dissection.

- Findings occur in pregnancy or preeclampsia can also be accur in acute coronary syndrome (typical; chest pain or dispnea, atypical; vomiting, reflux or sweating).Some patients attends with hemodynamic instability, arrhythmia or cardiogenic shock.
- Etiology-based treatment should be applied. Mother's condition during treatment should be considered first. An unstable patient should be placed in a left lateral tilt ranging from 30 to 90 degrees.
- Fetal monitoring and corticosteroids are suggested to assure fetal lung maturation at proper weeks of gestation.
- First medical treatment usually contains oxygen supplementation, nitrates, aspirin, intravenous unfractionated heparin, and beta-blocker therapy.
- If symptoms sustain, coronary angiography is recommended and should be applied without delay. Data on timing and type of birth are ambiguous.

**5. Maternal Cardiac Arrest**

- Bleeding is the most common cause of cardiac arrest during delivery (38.1%), followed by amniotic fluid embolism (13.3%).
- There are six key concepts to highlight for the pregnant cardiac arrest patient:

**Table 1. Management ofCardiac Arrest**[1]

| |
|---|
| Intubation should be done quickly with a small endotracheal tube against the increased oxygen demand and risk of aspiration. |
| Aortocaval pressure of a uterus greater than 20 weeks gestations should be decrease by a manual left uterine replacement maneuver early in the resuscitation process, while the patient stay in a fully supine position on the back board to maximize cardiac compression efficiency. |
| Synchronous interventions are suggested as opposed to a sequential approach used in non-pregnant patients. |
| Preparations for delivery in a viable fetus should be initiated simultaneously with the mother's efforts to resuscitate. |
| When performing left lateral uterine displacement, high-quality chest compressions of 100-120 perminute should be performed using the same markings on the mid-lower sternum. |
| Oxygenation should continue to be the primary goal, using a 30:2chest compression/ventilation ratio initially provided by bag-mask ventilation with 100% oxygen. |

- The patient should be monitored with a defibrillator. Rhythm analysis is monitored. Chest compressions are paused every two minutes to monitor the suitable shockable rhythm.

### 6. Perimortem Cesarean Delivery / Resuscitative Hysterotomy[1]

- The patient should be monitored with a defibrillator. Rhythm analysis is monitored. Chest compressions are paused every two minutes to monitor the suitable shockable rhythm. The fetus should be delivered as soon as possible after cardiac arrest. This should be done within 4-5 minutes. It has a significant impact on maternal and infant survival.
- It is not recommended to delay delivery for 4-5 minutes when in situations where spontaneous circulation is unlikely to be achieved or cardiac arrest is not witnessed.
- Perimortem cesarean section after 25 minutes after maternal cardiac arrest has 50% undamaged survival rates and may be beneficial even if delivery does not occur within 4 minutes.
- Perimortem cesarean delivery should to be at the area of the cardiac arrest. This does not lead further delay and does not compromise cardiopulmonary resuscitation. The abdomen is entered with a midline incision. Open heart massage can be done.
- The rarity of maternal cardiac arrest creates the need to practice resuscitation skills and scenarios through regular team training and simulation training.

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CHAPTER 18

# FETAL CHROMOSOMAL ANOMALY SCREENING

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## 1. Introduction

There are many screening tests to evaluate fetal chromosomal abnormalities, these tests have advantages and disadvantages, and the patient undergoing screening should be informed about the performance and limitations of the tests.Chromosomal anomalies occur at a rate of approximately one in 150 births. The prevalence is higher in early pregnancy and generally results in pregnancy loss. The most common autosomal chromosomal anomaly in live-born babies is trisomy 21. The most common sex chromosome aneuploidy is Kleinefelter Syndrome.Advanced maternal age, having a genetic condition such as translocation in the parents, detecting anomaly in ultrasonography during pregnancy follow-up, and having a positive screening test during pregnancy are important risk factors for chromosomal anomalies.

## 2. Screening Methods[1]

First trimester screening tests: NT and serum analysis
Second trimester screening tests: triple or quadruple test
Integrated testing: sequential or conditional
Cell free DNA test

### *2.1. First trimester screening tests: NT and serum analysis*

- It is a test performed when the CRL is between 38-84 mm (10-14 weeks of gestation).
- It may contain serum analytes (PAPP-A and free hCG) with or without NT measurement.
- Estimate risk for common trisomies 21, 18, and 13.
- NT measurement above 3 mm is an independent risk factor, and it has been observed that it may be associated with structural malformations such as cardiac anomalies, apart from chromosomal anomalies.
- Early screening is the biggest advantage of the first trimester screening test.

### *2.2. Second trimester screening tests: triple or quadruple test*

- Quadruple screening test can be done up to 15 0/7- 22 6/7 weeks.
- Analyte components; hCG, alpha fetoprotein, dimeric inhibin-A and unconjugated estriol (uE3) together with analytes make a risk estimation together with factors such as maternal age, weight, diabetes.
- It has an 80% detection rate for trisomy 21.
- The triple test uses hCG, AFP and uE3, and has a sensitivity of 69%.

### *2.3. Integrated testing: sequential or conditional*

- Combining the first and second trimester tests provides a higher detection rate for trisomy 21, 18 and 13.
- Integrated screening is performed with first trimester NT and analytes. For analytes in the 2nd trimester, blood is drawn and given to the patient as a single result.
- As expected, the result is achieved in a late period.
- For this reason, sequential tests have come to the fore. Sequential tests are performed in two ways;
- Sequential screening: If there is a high risk as a result of the 1st trimester screening, diagnostic testing is recommended. In case of low risk, the result is reported to the patient after the second trimester screening.

- Dependent screening: According to the results of the 1st trimester screening, patients are divided into high, medium and low risk groups. Additional testing is recommended for the high-risk group. (eg amniocentesis). No additional testing is recommended for the low-risk group.
- Intermediate risk patients receive the result after the second trimester test. With this model, the number of 2nd trimester screening tests can be reduced.

### *2.4. Cell free DNA test*

- It can be done in any trimester, starting from the 9th or 10th week of pregnancy.
- The fetal component are trophoblasts undergoing programmed cell death that are released into the maternal blood and are known as the fetal fraction. The fetal fraction increases in maternal law throughout pregnancy.
- The Cell free DNA test is not a diagnostic test and may give false positive and false negative results.
- In current analysis, it has a 99% detection rate for trisomy 21, 98% for trisomy 18, and 99% for trisomy 13.
- It is also possible to screen for some microdeletions but has not been clinically validated.

## Table 1. Characteristics of Commonly Used Screening Tests[1]

| Screening test | Gestational Age | Detection rate of Trisomy 21 | Advantages | Disadvantages | Method |
|---|---|---|---|---|---|
| **Cell free DNA** | 8-10 weeks to term | 99 | High detection rate<br>Can be done at any time<br>Low false positive rate | May be affected by maternal aneuploidy and diseases. | Molecularly |
| **First trimester screening test** | $10^{0/7}$- $13^{6/7}$ | 82-87 | Early screening and outcome | Lower detection rate than integrated tests.<br>NT measurement requirement. | NT, PAPP-A, free hCG |
| **Second trimester quadruple test** | $15^{0/7}$-$22^{0/7}$ | 81 | No special ultrasound skills required | Lower detection rate than first trimester and integrated testing. | hCG, AFP,D-Inhibin A, uE3 |
| **Integrated testing** | 10-$13^{6/7}$ after $15^{0/7}$-$22^{0/7}$ | 96 | High detection rate | Requirement to take two samples and measure NT | NT+ PAPP-A after hCG, AFP,D-Inhibin A, uE3 |
| **Serum Integrated testing** | 10-13 $^{6/7}$after 15-$22^{0/7}$ | 88 | First trimester close detection rate<br>No specialized ultrasound required | Requirement to take two samples | PAPP-A+ hCG, AFP,D-Inhibin A, uE3 |
| **Sequential–gradual** | 10-13 $^{6/7}$ sonra 15-$22^{0/7}$ | 95 | First trimester test result required. | Requirement to take two samples<br>NT measurement requirement | NT+ free Hcg + PAPP-after hCG, AFP, D-Inhibin A, uE3 |
| **NT alone** | 10- 13 $^{6/7}$ | 70 | Useful in multiple pregnancies, Scan feature for additional structural anomalies | Low sensitivity, expertise for measurement | Ultrasound |

### 3. Ultrasonographic Screening[1]

- Fetuses with trisomy 21 have fewer structural anomalies than those with trisomy 13 and 18.
- In the first trimester, NT measurement, absence or hypoplasia of the nasal bone, and detection of an inverted ductus venosus wave also increase the risk of aneupliodia.
- Second trimester ultrasound scanning is recommended for all patients to screen for structural anomalies.
- Ideally, it should be done between 18-22 weeks of pregnancy.
- Although major structural anomalies are screened in the 2nd trimester ultrasound, soft markers indicating the risk of aneuploidy can also be detected.
- These markers are generally nonspecific and have non-pathological findings.
- However, it is more frequently associated with trisomy 21.
- The most common soft markers are; echogenic cardiac focus, nuchal translucency, renal pelvis dilatation, and echogenic bowel.
- Choroid plexus cysts are more common with trisomy 18.
- If these markers are detected, additional tests should be offered to the patient if they have not been done before.
- Screening or diagnostic testing should be offered to all patients, regardless of maternal age and existing risks.
- Patients should be given the necessary information about the performance and limitations of the tests.
- The patient with a positive test result should be informed about diagnostic tests and detailed ultrasound.
- Although positive screening test or ultrasonographic findings indicate the risk of chromosomal abnormality, tests such as CVS or amniocentesis are needed for definitive diagnosis.
- Cell-free DNA testing may be an option for patients who have a positive screening test and do not want to perform diagnostic tests. However, a residual risk of 2% still needs to be disclosed to the patient in a negative cellfree DNA test following a positive screening test.
- A negative screening test means that the risk is low, but not completely absent, and patients who want it done should still be offered the option of diagnostic tests.
- The main factor affecting the success of the cell free DNA test is the fetal fraction. A minimum fetal fraction of 2-4% is required for an accurate test result.

- Factors such as early gestational week, maternal BMI, advanced maternal age, ivf pregnancy, and medications used by the mother affect the test success.
- First rimester ultrasound: NT is the primary ultrasound marker. Increased NT is an indicator of increased risk for structural anomalies such as cardiac defects, abdominal wall defects and diaphragmatic hernia, as well as chromosomal anomalies. In case of increased NT, the patient should be offered diagnostic testing and detailed ultrasound.
- Second trimester ultrasound: All patients should be offered 2nd trimester ultrasound regardless of the screening test result. While more major structural anomalies are observed in trisomy 18 and 13, only 27% major structural anomalies are observed in trisomy 21. Soft markers are associated with trisomy 21 at varying rates and cannot be used for diagnostic purposes. In the presence of multiple soft markers, diagnostic testing should be considered to exclude chromosomal anomaly.
- In twins, as in singleton pregnancies, there is no reliable method of serum testing for aneuplioid screening. Second trimester screening tests have a sensitivity of approximately 60% in twins. The same cutoff values for NT can also be used in twins.

## 4. Important summary information

- Prenatal tests (screening and diagnostic tests) should be offered to all pregnant women regardless of age and risk.
- More than one prenatal test should not be done at the same time and should start with a single test.
- Cell free DNA test is the test with the highest sensitivity and specificity. However, it should be noted that it is not a diagnostic test.
- Ultrasonographic examination for fetal structural anomaly should be recommended to all pregnant women in the second trimester.
- Detailed ultrasonography, diagnostic tests and genetic counseling should be offered to patients with a positive screening test.
- A negative screening test does not completely eliminate the risk for fetalaneuploidy. Patients should be offered a diagnostic test option.
- Patients who fail the cell free DNA test should be informed of a possible risk of aneuploidy.
- In case of increased NT or other anomaly detection, the patient should be offered diagnostic tests and detailed ultrasound.

- Cell-free DNA testing may be an option for a patient with a positive serum screening test, but the patient should be informed about the risk of aneuploidy.
- If an isolated soft marker is detected, the patient should be offered screening or diagnostic tests. If it has been done and low risk has been identified, no further investigation is required.
- There is no reliable serum screening method in twin pregnancies.
- Cellfree DNA test in twin pregnancies is a promising test for the future.

**Referances**

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CHAPTER 19

# COVID-19 VACCINE USING IN OBSTETRICS AND GYNECOLOGY

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## 1. Introduction

TheSARS-Cov-2 commonly know as Covid-19 virus has been the cause ofa respiratory infective syndrome which was declared a pandemic by WHO on March 11, 2020. The vaccine studiesstarted rapidly all over the world together with start of pandemic. There are currently three vaccines approved by the FDA[1];

- Pfizer BioNtech mRNA vaccine: It is administered in two doses, at least 3 weeks apart, in individuals aged 12 years and older.
- Moderna mRNA vaccine: It is administered in two doses, one month apart, in individuals aged 18 years and over.
- Janssen Biotech Inc. (Johnsson&Johnsson) vaccine: Ad26.Cov2.S vaccine: It is administered as a single dose to individuals aged 18 years and over.

## 2. Vaccines[1]

### *2.1. mRNA Vaccines (Pfizer- BioNtech and Moderna vaccines)*

- mRNA vaccines contain mRNA packaged with a lipid nanoparticle for delivery to the host cell.
- These vaccines use the body's own cells to produce the corona spike protein.
- As with all other vaccines, they activate the immune system and stimulate the production of antibodies.
- mRNA vaccines are not live virus vaccines and do not contain adjuvants.
- These vaccines do not enter the cell nucleus and do not cause changes in DNA.
- In phase-2 and phase-3 studies, the safety and efficacy of vaccines were found to be similar in pregnant women to non-pregnant women.
- In addition, observational data show that there is no safety concern for pregnant women.

### *2.2. Adenovirus vector vaccine (Janssen Biotech Inc.)*

- Janssen vaccine is a monovalent vaccine containing recombinant replication of a human incomplete adenovirus type 26 (Ad26).
- By means of this vector, the spike (S) protein of SARS Cov-2 is encoded.
- Ad26.Cov2.S vaccine is not a live virus vaccine and does not contain preservatives and does not multiply in the cell.
- According to the available data, it is rapidly cleared from the tissues after application (FDA 2021).
- Again, in the light of the data, Ad26-based vaccines have acceptable safety and are not a concern for use in pregnancy (FDA 2021).

## 3. Effectiveness of Vaccines

- It has been proven that individuals who receive the vaccine are more likely to contract the disease asymptomatically and are less likely to infect others. In clinical trials, 95% effectiveness of two doses of Pfizer-BioNtech vaccine has been confirmed by laboratories. Likewise, it was found that the Moderna vaccine was 94% effective, the Janssen vaccine was 66.9% effective in preventing moderate-to-severe disease, and 76.7% in preventing severe-critical illness. It also prevents hospitalizations by 93.1% (Janssen 2021).
- In a prospective cohort study, it was observed that pregnant women who were vaccinated produced higher levels of antibodies than those who had

the disease. In addition, the antibody is also found in cord blood and breast milk detected (Gray 2021, Prabhu 2021,Juncker 2021).

- All vaccines showed high efficacy in people of different age groups, gender, race and ethnicity.

## 4. Safety of Vaccines

- Expected side effects are the body's usual response to the vaccine and should be explained to patients. Flu-like symptoms may occur after Pfizer-BioNtech and Moderna vaccines.
- Between the ages of 18-55, those who have received the Pfizer BioNtech vaccine may experience a fever of 38 ºC and above in 3.7% after the first dose and 15.8% after the second dose (FDA 2020).
- In the Moderna vaccine, a fever of 38ºC and above was observed in 0.8% after the first dose and 15.6% after the second dose.
- Side effects in the Janssen vaccine are mild and transient, with a fever of 38ºC and above in 9% (FDA 2021).

**Table1. Common side effects after vaccination**

| Side effects | Pfizer- BioNTec | Moderna | JanssenBiotechInc. |
|---|---|---|---|
| Injection site reactions | %84.1 | %91.6 | %48.6 |
| Tiredness | %62.9 | %68.5 | %38.2 |
| Shake | %31.9 | %43.4 | None |
| muscle pain | %38.3 | %59.6 | %33.2 |
| combined pain | %23.6 | %44.8 | None |
| Headache | %55.1 | %63 | %38.9 |

- Allergic reactions, including anaphylaxis, have been rarely reported following Covid-19 vaccine. For the Pfizer-BionTech vaccine, there were 50 cases of anaphylaxis per 10 million doses (one in 1 million doses). For the Moderna vaccine, 2.8 cases per million doses have been reported. No cases of anaphylaxis have been reported for the Janssen vaccine. Anaphylaxis is managed in pregnant women similarly to non-pregnant women.
- A warning regarding Thrombotic Thrombocytopenic Syndrome (TTS) has been added to the Janssen vaccine by the FDA.Most cases of TTS have been reported in women of reproductive age. None of them were pregnant. It should be emphasized to patients that this is a rare clinical condition (8.9 per 1 million doses). However, if patients do not wish to receive the Janssen

vaccine, they should be encouraged to have other FDA-approved vaccines. Patients should be informed about TTS symptoms.

- In case of symptoms such as blurred vision, severe headache, abdominal pain, vomiting, backache, shortness of breath, pain or swelling in the legs, petechiae, easy bruising or bleeding, they should be advised to visit an emergency service. Symptoms usually appear 6-14 days after vaccination. The American Society of Hematology (ASH) stated that TTS cannot be treated like other coagulation conditions. In particular, heparin should not be used for therapeutic purposes.
- More than expected Gullian-Barre Syndrome has been reported after the Janessen vaccine. Still, more data is needed to learn about the connection of the syndrome to the Janssen vaccine. The absolute risk for developing Gullian-Barre syndrome after vaccination is extremely low.

## 5. Pregnancy and Covid-19 vaccine[1]

- Vaccination is recommended by ACOG to all eligible people, including pregnant and lactating women.
- A pregnancy test is not required prior to vaccination.
- The connection of vaccines with infertility is not based on any scientific data.
- Vaccines can be made in health facilities, as well as in any place where vaccine administration centers are available.
- Those planning a future pregnancy can also be vaccinated.
- Side effects are normal body reactions and are related to the formation of antibodies by the defense system.
- Obstetricians and gynecologists should encourage their patients to be vaccinated.
- Covid-19 vaccines can be given at the same time as other vaccines (including another vaccine administered within the last 14 days, eg flu or Tdap vaccine).
- Despite ACOG's recommendations, none of the FDA-approved vaccines have been tested in pregnant women.
- In animal studies, pregnancy, embryo-foetal development, parturition and postnatal development were not directly or indirectly affected by the Pfizer-BioNtech vaccine (EMA).
- Similarly, animal studies for the Moderna vaccine did not show significant effects on the reproductive process (FDA 2021).
- Acceptable side effects were also observed in studies in rabbits for the Janssen vaccine (FDA 2021).

## 6. Obstetric Care Recommendations[1]

- Available data indicate that pregnant women are at greater risk of contracting Covid-19 disease (Ellington MMWR 2020, Collin 2020, Delahoy MMWR 2020, Han 2021). These data indicate an increased risk of need for intensive care, need for mechanical ventilation, and death.
- Obstetricians and gynecologists and other health professionals should encourage pregnant women to be vaccinated. There is no evidence of adverse effects on the fetus.
- Approved vaccines can be offered to pregnant and breastfeeding women. Those who prefer the Janssen vaccine under the age of 50 should be informed about TTS.
- Pregnant women can get their vaccinations at the hospital or at any vaccination center, similar to non-pregnant women. Pregnant women can use paracetamol for fever that may occur after vaccination. Pregnant women who are vaccinated in the near future or who are planning to get vaccinated and who need anti-D immunoglobulin do not have to postpone their anti-D immunoglobulin administration. The vaccine is considered safe in breastfeeding

## 7. General Recommendations and Considerations[1]

- It is recommended that all individuals aged 12 years and older have the Covid-19 vaccine.
- There is no preference for vaccines over each other, only individuals between the ages of 12 and 17 can only receive the Pfizer-BioNtech vaccine.
- Those who choose the Pfizer-BioNtech or Moderna vaccine must complete a two-dose series of vaccines.
- Covid-19 vaccines can be given at the same time as other vaccines (including another vaccine in the last 14 days). This includes vaccines such as flu and tetanus that are routinely given during pregnancy.
- Those who have a history of allergic reaction to any vaccine should be informed about emergency measures.
- Obstetricians and gynecologists should encourage patients to vaccinate.
- Vaccinators do not need to stop breastfeeding (ABM 2020).

## References

1. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care