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Perinatal Journal can be read by perinatal medicine experts, fetal medicine experts, obstetricians, gynecologists, radiologists, pediatricians, sonographers, midwives, radiographers, and scientific members of other related areas, that mainly includes original clinical and experimental research articles, case reports, reviews, technical notes and letters to the editor.

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The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation

Abstract

This practice guideline follows the mission of the World Association of Perinatal Medicine (WAPM) in collaboration with the Perinatal Medicine Foundation (PMF), bringing together groups and individuals throughout the world with the goal of improving the use of antenatal corticosteroids (ACS) for fetal maturation. In fact, this document provides further guidance for healthcare practitioners on the appropriate use of ACS with the aim to increase the timely administration and avoid unnecessary or excessive use. Therefore, it is not intended to establish a legal standard of care. This document is based on consensus among perinatal experts throughout the world and also serves as a guideline for use in clinical practice.

Keywords: Corticosteroids, fetal maturation, guideline, pregnancy, preterm delivery.

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Introduction

According to the WHO International Classification of Diseases 10th revision (ICD-10), a preterm birth (PTB) is one that occurs between 22+0 and before 37+0 weeks of gestation (between 154 and 259 days). Approximately two thirds of preterm deliveries are the consequence of preterm uterine contractions with or without preterm rupture of membranes whereas about one third is medically indicated due to maternal, fetal or placental conditions, including preeclampsia, uterine malformations, multiple gestation, fetal growth restriction, fetal anomalies, placenta previa and placenta accreta spectrum disorders. Preterm neonates have complicated medical issues, the earlier a baby is born, the higher the risk of complications. Thus, timely diagnosis and effective management of preterm labor is essential to improve newborn outcomes. The administration of antenatal corticosteroids (ACS) to accelerate fetal lung maturation is considered as one of the most valuable antenatal therapies. Following the landmark study of Liggins and Howie in 1972, the impact of ACS on fetal lung maturation has been extensively studied.

It is obvious that, in elective cases, the clinicians can administer ACS at the time they expect they will be most effective. However, in many cases i.e. PPROM, the situation is less straightforward as some women will be falsely diagnosed with PPROM, some will deliver before a full course is administered and a substantial proportion will remain undelivered for a period of weeks. The situation is even more difficult in cases of spontaneous labor with intact membranes, i.e. women who present reporting contractions, as most of these women will not deliver prematurely. Importantly, there is no consensus on the definition of true preterm labor and this allows for an arbitrary and often unnecessary use of ACS. In fact, this failure to accurately predict imminent PTB became apparent from the first study by Liggins, as less than half of the women delivered within the predicted timeframe of 2 to 7 days; about one in three cases delivered later than 7 days, most commonly later than 21 days after ACS administration. Almost 50 years later, the successful timing of ACS administration has not improved at all.

Mechanism of Action

As glucocorticoid receptors are expressed in almost every human cell, glucocorticoids exert effects throughout the body, including the placental and fetal tissues to result in pleiotropic effects. The binding of glucocorticoids to these receptors induces a modulation of gene expression, transcription and protein synthesis, therefore it is obvious that this sequence takes some time (hours) before exerting effects.

Considering endogenous corticosteroids, the fetus is exposed to low levels of glucocorticoids during early and mid-gestation. Towards the end of pregnancy, a complex process of organ maturation is triggered including a rise of both maternal and fetal glucocorticoids to transition from in to ex-utero. Both betamethasone and dexamethasone’s most known effect is at the lung through surfactant production; however, their actions will also affect the growth, heart, brain, hypothalamus, kidneys and thyroid, simulating the endogenous corticoid surge and fetal adaptations that occur late in pregnancy.

Fetal lung development can be divided into five stages: embryonic, pseudoglandular, canalicular, terminal sac and alveolar. From 28 to 35 weeks of gestation, the alveoli increase in number and mature. Lamellar bodies, which store surfactant, appear at 22 to 24 weeks. Surfactant is needed to stabilize alveoli and is a complex mixture of lipids and apoproteins.

ACS accelerate the development of type 1 and type 2 pneumocytes, induce pulmonary beta receptors and subsequently are responsible for modifications on alveolar structure, vascularization, surfactant production and airspace fluid clearance. The increase of surfactant production will be achieved through both transcription and post-transcriptional mechanisms, enhancing the rate of phosphatidylycholine and fatty acid biosynthesis in the fetal lung. Animal and human studies have shown that ACS also increase lung compliance and volume and increase response to exogenous surfactant treatment.

The timing of effectiveness of ACS is usually considered to be between 2 and 7 days from administration based on the first paper by Liggins and on a Cochrane review that demonstrated a reduction in RDS in infants treated with ACS in the prior 2 to 7 days. However, observational data suggest that neonatal benefits begin as early as within a few hours of ACS administration and can expand beyond a week. There are studies that have found no differences between those delivered 8–14 days after treatment compared to those delivered within 7 days. This could be explained as 7 days was an arbitrary cut-off and the decline in the effectiveness of antenatal corticosteroids...
over time is gradual. Some authors even postulate that it is likely that this decline is not static across all gestational ages or birthweights.\textsuperscript{[20,21]}

**Considerations in Diagnosing Preterm Labor**

Clinicians should be cautious, especially in cases of suspected preterm labor, to ensure appropriate and timely administration of ACS.

First, the accurate determination of gestational age is crucial. The WAPM supports the sonographic determination of gestational age in the first trimester using the crown-rump length (up to 84 mm). In later gestations, the head circumference should be used; however, this reduces the accuracy of estimation. In settings where ultrasound is not available and the woman is certain of her dates, the gestational age should be based on the last menstrual period, whereas in unknown dates, the best estimate using the fundal-symphysis height should be applied.\textsuperscript{[22,23]}

In cases of suspected preterm labor, the first step is to diagnose regular contractions, either manually or preferably by cardiotocography. A minimum of 6 contractions per 30 minutes may be used as a reasonable threshold. Moreover, it is expected that in cases of true labor, the uterine contractions are regular, with increasing frequency, duration and strength and cause cervical changes. If such contractions are not observed, it is unlikely that it is a case of true labor.

The next step is to assess the cervix for changes. A speculum examination allows the visualization of the external cervical os; a manual examination may assist in determining dilatation, effacement, consistency and position of the cervix, as included in the Bishop score. Depending on the availability of ultrasound and biomarkers, local protocols should be implemented to provide clear pathways in cases of women presenting with reported uterine contractions before 34+0 weeks of gestation to determine if there is a high-risk of PTB within the next 7 days.\textsuperscript{[24–27]} In cases where a first dose of corticosteroids is administered without any of these criteria met, the clinicians are encouraged to discontinue both tocolysis and the administration of subsequent doses of ACS.

**Timing of Administration**

22+0–23+6 weeks

A meta-analysis of observational studies including more than 3,500 neonates assessed the effect of ACS administration before 24 weeks of gestation and proved that the rate of mortality to discharge was reduced by 52% in the ACS group compared to the placebo or no treatment group (aOR: 0.48; 95% CI: 0.38–0.61).\textsuperscript{[28]} Moreover, a multicenter study found that neurodevelopmental impairment or death at 18 to 22 months of age was significantly lower in cases that received ACS and were born at 23 weeks (83.4% vs. 90.5%; aOR: 0.58; 95% CI: 0.42–0.80), 24 weeks (68.4% vs. 80.3%; aOR: 0.62; 95% CI: 0.49–0.78) and 25 weeks of gestation (52.7% vs. 67.9%; aOR: 0.61; 95% CI: 0.50–0.74), but not in neonates born at 22 weeks of gestation (90.2% vs. 93.1%; aOR: 0.80; 95% CI: 0.29–2.21).\textsuperscript{[29]} Neonates born at 22–25 weeks of gestation had higher survival rates post ACS exposure in total (72.3% vs. 51.9%); (aRR: 2.11; 95% CI: 1.68–2.65 at 22 weeks), (aRR: 1.54; 95% CI: 1.40–1.70 at 23 weeks), (aRR: 1.18; 95% CI: 1.12–1.25 at 24 weeks), (aRR: 1.11; 95% CI: 1.07–1.14 at 25 weeks).\textsuperscript{[30]} Furthermore, a meta-analysis of neonates born between 22+0 and 22+6 weeks of gestation found that the administration of ACS doubled the rate of survival when compared to those not receiving corticosteroids (39.0% vs. 19.5%; p<0.01).\textsuperscript{[31]} In any case, for fetuses at the periviable period, appropriate consultation should be provided to the parents by the perinatal specialists and the neonatologists.

**Recommendations**

- A course of ACS should be considered between 22+0 and 23+6 weeks of gestation in women at high-risk of PTB within the next 7 days.
- The decision should be based on local standards regarding periviable neonatal support and availability of neonatal facilities, following appropriate consultation to the parents.

24+0–33+6 weeks

A meta-analysis of 27 randomized controlled trials found that in cases of imminent PTB, the administration of ACS was associated with reduced rates of RDS (RR: 0.71; 95% CI: 0.65–0.78), IVH (RR: 0.58; 95% CI: 0.45–0.75), perinatal (RR: 0.85; 95% CI: 0.77–0.93) and neonatal death (RR: 0.78; 95% CI: 0.70–0.87).\textsuperscript{[32]} Importantly, data from the same meta-analysis showed that treatment with ACS did not increase the risk of chorioamnionitis (RR: 0.86; 95% CI: 0.69–1.08) or endometritis (RR: 1.14; 95% CI: 0.82–1.58).\textsuperscript{[32]} It is worthy of note that this meta-analysis included 27 studies and 11,272 women. Of the 20 studies including women...
between 24 and 34 weeks of gestation, all but one (WHO 2020, in low-income countries only) were conducted between 1972 and 2002. Overall, 17 studies (all up to 2002) were conducted in high-income countries and 10 in middle- and lower-income countries, 15 of 27 included only singleton pregnancies, whereas the rest included multiples as well, 19 studies used a single course of steroids whereas 8 used either single or repeated doses and 16 used placebo whereas the rest compared ACS with no treatment. It should also be noted that this meta-analysis concluded that more detailed data are needed for certain high-risk groups (including multiple pregnancies, diabetes or hypertension).

In 2015, the ACT study raised some concerns regarding the use of steroids in low-income countries as it found that the administration of ACS probably increased neonatal mortality. However, this study received criticism for certain limitations. The WHO study (2020) was subsequently conducted to resolve this issue and concluded that the use of dexamethasone resulted in significantly lower risks of neonatal death (RR: 0.84; 95% CI: 0.72–0.97) and stillbirth or neonatal death (RR: 0.88; 95% CI: 0.78–0.99) than the use of placebo, without an increase in the incidence of maternal bacterial infection. Therefore, current data supports the use of ACS both in high- and low-income countries.

### Recommendation
- A single course of ACS should be administered between 24+0 and 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days.

### 34+0–36+6 weeks

In the first decade of research on ACS (1972–1981), most studies included cases up to 36+6 weeks. Subsequently, all studies focused on cases up to 34+6 weeks. However, between 2010 and 2018, a series of studies looked again at the possible benefit of steroids in late preterm fetuses.

The Antenatal Late Preterm Steroids (ALPS) study was a multicenter prospective randomized controlled study that assessed the impact of ACS between 34+0 and 36+5 weeks of gestation, using strict criteria for the definition of threatened preterm labor. They found a significant reduction in the primary composite adverse outcome (neonatal respiratory treatment in the first 72 hours, stillbirth or neonatal death within 72 hours of birth) (RR: 0.80; 95% CI: 0.66–0.97), TTN, severe respiratory complications, administration of surfactant and bronchopulmonary dysplasia. No significant differences were identified in the incidence of chorioamnionitis or neonatal sepsis. Interestingly, in subgroup analyses, it was found that only female fetuses had benefit from the administration of ACS regarding the primary outcome (RR: 0.64; 95% CI: 0.47–0.87). Moreover, ACS reduced the rate of the primary adverse outcome in cases of elective cesarean section at the late preterm period (RR: 0.62; 95% CI: 0.43–0.90). On the other hand, neonatal hypoglycemia occurred more frequently in the steroids group (24.0% vs. 15.0%; RR: 1.60; 95% CI: 1.37–1.87). It is worthy of note that hypoglycemia may be associated with subsequent neurodevelopmental morbidity in the future.

### Type and Dose of Corticosteroids

The beneficial effects of ACS on fetal lung maturation necessitate placental transfer from the maternal to the fetal compartment. Placental passage of drugs varies extensively, both between compounds, as well as throughout the different stages of pregnancy. This explains why beta- or dexamethasone are administered for fetal lung maturation; no significant differences have been identified in fetal lung maturation between these two steroids.

The most commonly offered regimens are a total of 24 mg divided in either two doses of 12 mg IM of betamethasone or 4 doses of 6 mg IM of dexamethasone; up to 80% of corticosteroid receptors are occupied using these doses, leading to the stimulation of corticosteroid receptors response to the fetus. The shortened dosing interval of corticosteroids may be associated with NEC, therefore it should be avoided.

Regarding the differences between the two options, betamethasone has been associated with a lower risk of chorioamnionitis and RDS compared to dexamethasone. On the other hand, in the dexamethasone group, the risk of IVH was lower (RR: 0.44; 95% CI:
0.21–0.92) and the duration of hospitalization in neonatal intensive care unit (NICU) was shorter (mean difference – MD: -0.91 days; 95% CI: -1.77 to -0.05). Based on the available in vitro and in vivo observations, it is reasonable to state that beta- and dexamethasone display similar biological activity and exposure, so that preferences rather relate to availability or costs.

Based on the available in vitro and in vivo observations, it is reasonable to state that beta- and dexamethasone display similar biological activity and exposure, so that preferences rather relate to availability or costs.\

**Recommendation**

- Either betamethasone (2 doses of 12 mg IM in a 24-h interval) or dexamethasone (4 doses of 6 mg IM at 12-h intervals) may be administered for fetal lung maturation.

**Repeated Courses**

The ACTORDS study reported that the weekly repeated doses of betamethasone, following an initial course in cases remaining undelivered for more than 7 days, were associated with fewer respiratory complications, including RDS. Accordingly, a Cochrane review found that repeated doses were associated with lower rates of RDS (RR: 0.83; 95% CI: 0.75–0.91) and a reduction in the rates of serious adverse neonatal outcomes (RR: 0.84; 95% CI: 0.75–0.94). However, the policy of repeated dose(s) has been linked to a reduction in the mean birthweight (MD: -75.79g; 95% CI: -117.63 to -33.96). Another meta-analysis confirmed these findings and found lower rates of respiratory support in neonates treated with repeated ACS during pregnancy compared to no treatment (RR: 0.91: 95% CI: 0.85–0.97), but the birthweight was lower in the repeated ACS group (MD: -0.12; 95% CI: -0.18 to -0.06). Furthermore, a trial reported increased rates of SGA for the repeated doses group (≥4 courses) (10th centile: 19.3% vs. 8.4%; 5th centile 10.4% vs. 4.7%). Additionally, repeated corticosteroids doses have been correlated with a reduction in the placental weight.

In a pre-planned secondary analysis of data from the ACTORDS study, including neurocognitive function at 6–8 years as primary outcome, it was found that repeated antenatal betamethasone treatment, compared to placebo, was not associated with adverse effects on neurocognitive function at 6 to 8 years of age, even in the presence of FGR. Although there is evidence of a certain short-term respiratory benefit, long-term outcomes remain unclear. It should be noted that the uncertainty on the possible usefulness of repeated ACS doses highlights the continuing failure to accurately predict imminent PTB.

### Scheduled Cesarean Delivery at Term

A meta-analysis showed that ACS administration 48 hours before scheduled cesarean section at term was associated with a lower risk of TTN (RR: 0.38; 95% CI: 0.25–0.57), RDS (RR: 0.40; 95% CI: 0.27–0.59) and need for mechanical ventilation (RR: 0.19; 95% CI: 0.08–0.43), and also a shorter stay in NICU (MD: -7.44 days; 95% CI: -7.44 to -7.43) and higher Apgar scores. However, according to the most recent Cochrane review on this issue, which is based on the data from only one trial (Antenatal Steroids for Term Elective Cesarean Section - ASTECS), it is uncertain if ACS reduces the risk of RDS (RR: 0.34; 95% CI: 0.07-1.65) or TTN (RR: 0.52; 95% CI: 0.25-1.11). On the other hand, ACS probably reduces the risk of admission to neonatal special care for respiratory complications (RR: 0.45; 95% CI: 0.22–0.90), while they have no effect on the risk of needing mechanical ventilation (RR: 4.07; 95% CI: 0.46–36.27).

### Special Populations

#### Multiple gestation

According to data from the EPIPAGE-2 trial, the administration of ACS in twin pregnancies at high-risk of PTB within the next 7 days was significantly associated with a reduced rate of periventricular leukomalacia or IVH grade III/IV (aOR: 0.2; CI 95%: 0.1–0.5) and in-
hospital mortality (aOR: 0.3; 95% CI: 0.1–0.6). Based on a recent Cochrane review, there was no effect of ACS on twin pregnancies regarding the outcomes of fetal death, perinatal death, neonatal death, RDS, and IVH; however, the number of studies and the number of the participants were limited. With regards to the hypothesis that multiple gestations may have higher needs of corticosteroids, it has been proven that cord blood levels of steroids are similar to those observed in singletons.

**Recommendation**

- In multiple pregnancies, ACS should be administered at the same dosage and indications as in singleton pregnancies.

**Obesity**

Some concerns have been raised whether the doses of ACS should be modified according to body mass index. There is limited data to make relevant recommendations; based on a study of 55 participants, cord blood levels of corticosteroids were comparable between the groups of obese and non-obese pregnant women.

**Recommendation**

- In obese women, ACS should be administered at the same dosage and indications as in women without obesity.

**Preterm prelabor rupture of membranes**

There is still no consensus on the criteria to diagnose PPROM and there is very little evidence on the accurate prediction of women with PPROM that are more likely to deliver within 7 days. Moreover, concerns have been raised regarding a possible increase in the incidence of perinatal infection in women with PPROM treated with ACS. A meta-analysis including more than 1,400 women with PPROM found that ACS reduces the risk of RDS (RR: 0.56; 95% CI: 0.46–0.70), IVH (RR: 0.47; 95% CI: 0.31–0.70) and NEC (RR: 0.21; 95% CI: 0.05–0.82) without increasing the risk of maternal infection (RR: 0.86; 95% CI: 0.61–1.20) or neonatal infection (RR: 1.05; 95% CI: 0.66–1.68). Similarly, a subgroup analysis of the latest Cochrane review showed no differences in the effect on perinatal, neonatal and fetal death, RDS, endometritis or chorioamnionitis. A study investigating the effect of a repeat ACS course in cases with PPROM showed that women receiving a repeat course were not at increased risk of chorioamnionitis (aOR: 1.28; 95% CI: 0.69–2.14) or any neonatal morbidity. However, multiple ACS courses may increase the risk of chorioamnionitis.

**Recommendation**

- A single course of ACS is recommended at the time of diagnosis of PPROM when gestational age criteria are met.

**Fetal growth restriction**

There are no randomized studies on the effect of ACS in FGR. It has been proposed that these fetuses may not benefit as much from this therapy as their lung maturation might be physiologically enhanced (given chronic stress and 11-B-HSD II breakdown) or may even be detrimental as shown by some animal studies. Furthermore, some reports have described that ACS can reduce mean birthweight at the expense of the reduction of the cranial perimeter. However, more recent studies have shown that the detrimental effect on weight may only be a consequence of repeat courses and that some poor outcomes associated to these fetuses may have been influenced by maternal comorbidity. Furthermore, a secondary analysis from the ACTORDS trial found that, in 139 FGR fetuses, repeated antenatal betamethasone treatment compared with placebo was not associated with adverse effects on neurocogniive function at 6 to 8 years of age, even in the presence of FGR.

A 2009 review that included 5 studies with 664 fetuses found no differences in terms of morbidity, mortality, respiratory distress syndrome, IVH or NEC. These results, however, may have been underpowered to detect differences among outcomes. A more recent meta-analysis conducted in 2020, including 13 studies with 6,387 FGR and small for gestational age infants, found that neonatal mortality was significantly lower among infants who received ACS (12.8% vs. 15.1%; OR: 0.63; 95% CI: 0.46–0.86), with significant heterogeneity between studies (I²=55.1%; p=0.011). There was no significant difference in respiratory distress syndrome, NEC, IVH and periventricular leukomalacia, bronchopulmonary dysplasia or chronic lung disease of prematurity, or neonatal sepsis.

Finally, a small sub-analysis from the TRUFFLE 2 feasibility study found no benefit from ACS administration beyond 32 weeks of gestation. However, in
this matched case-control study, the sample size was too small to enable evaluation of all outcomes.

Therefore, most recent data indicate that ACS reduces neonatal mortality in FGR cases delivered preterm (specially <32+0 weeks of gestational age), with no apparent effect on neonatal morbidity short or long term.

**Recommendation**

- In cases complicated with FGR, ACS should be administered at the same dosage and indications as in appropriate for gestational age fetuses.

**Diabetes mellitus**

Pregnant women with diabetes are usually excluded from studies due to the adverse effects of corticosteroids on glycemic control. Accordingly, a systematic review could not retrieve any comparative studies of ACS in cases of either pregestational or gestational diabetes. An increase in glucose levels is usually identified after ACS administration for up to seven days after the first dose in pregnant women with or without diabetes.

**Recommendations**

- In diabetic women, ACS should be administered at the same dosage and indications as in women without diabetes.
- Close monitoring of the maternal blood glucose levels is recommended for women with diabetes in the following days after the administration of ACS.
- After the administration of ACS, screening with glucose tolerance test should be delayed for at least one week.

**Short- and Long-Term Outcomes of Corticosteroids in the Offspring**

As the primary stress hormone is cortisol, ACS given to women with a singleton or multiple pregnancy prior to PTB interfere with endogenous stress hormone action and thus may have short- and long-term implications. Whereas a single course of ACS is associated with immediate adverse effects such as postnatal hypoglycemia, long-term adverse effects including reduced fetal growth or poor academic performance were only unequivocally documented when ACS have been administered repeatedly. Moreover, according to data from a population-based study in Finland, exposure to ACS was significantly associated with mental and behavioral disorders in children.

The latest Cochrane meta-analysis found that a single course of ACS given to women with a singleton or multiple pregnancy prior to anticipated PTB (elective, or following rupture of membranes or spontaneous labor) leads to a reduction in the incidence of developmental delay in childhood (RR: 0.51; 95% CI: 0.27–0.97). The same meta-analysis found no increase on intellectual impairment, visual impairment, or hearing impairment, neither in childhood nor in adulthood. It is worthy of note that, in this meta-analysis, a large proportion of deliveries occurred at >37 weeks of gestation. Another meta-analysis that included only children born before 34 weeks of gestation and focused specifically on neurodevelopmental outcome after a single course of ACS found an improvement in most neurodevelopmental outcomes in the offspring.

Repeated courses of ACS (a second or weekly doses after an initial ACS course) decreased fetal growth as an indicator of a global effect on the fetus. At 5 years of age, children exposed to repeated ACS that were delivered after 37 weeks of gestation showed a significant increase in neurosensory disability but were otherwise intact. There was also a directional trend for more cerebral palsy at 2–3 years of age following repeat ACS in a National Institute of Child Health and Development trial, but no other abnormalities were identified. In a complex study approach to judge gestational age-specific risks vs. benefits of multcourse ACS for preterm labor, it was found that below 29 weeks of gestation a repeat course in case of anticipated PTB is beneficial whereas after 29 weeks the long-term side effects, including growth retardation and neurodevelopmental delay predominate.

**Conclusion**

Despite the usefulness of ACS in improving neonatal outcomes, there are still certain unresolved issues. The main setback remains the failure to accurately identify which of the women that present with preterm contractions or PPROM are most likely to deliver within the next 7 days. In view of the uncertainty regarding the long-term effects of ACS and neonatal hypoglycemia, especially in late preterm neonates, the WAPM recommends that the use of ACS should adhere to strict guidelines. Thus, until more data are available from prospective studies, the clinicians are advised to administer a single course of ACS in cases that are at high-risk of PTB within the next 7 days and the gestational age is between 22+0 and 33+6 weeks. To achieve that, they should be
supported by comprehensive protocols that describe the diagnosis of preterm labor based on the availability of resources and expertise in their settings.

**Implications for future research**

- Accurate diagnosis of preterm labor with intact membranes
- Accurate prognosis of PTB within the next 7 days in cases with PPROM
- Effectiveness of strict criteria of preterm labor on the timely use of ACS
- Effect of ACS on multiple pregnancies
- Value of administration of ACS in women already on steroids for other indications
- Exact timing of ACS administration in elective cases to maximize their effectiveness
- Cardiovascular long-term outcomes of the offspring following the administration of ACS
- Long-term outcomes in the offspring of women that received ACS but subsequently not delivered preterm

**Summary of recommendations**

- A course of ACS should be considered between 22+0 and 23+6 weeks of gestation in women at high-risk of PTB within the next 7 days. The decision should be based on local standards regarding periviable neonatal support and availability of neonatal facilities, following appropriate consultation to the parents.
- A single course of ACS should be administered between 24+0 and 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days.
- A single course of ACS is not routinely recommended between 34+0 and 36+6 weeks of gestation in women at high-risk of PTB within the next 7 days because of the current uncertainty regarding the benefit to risk ratio.
- Either betamethasone (2 doses of 12 mg IM in a 24-h interval) or dexamethasone (4 doses of 6 mg IM at 12-h intervals) may be administered for fetal lung maturation.
- Repeated doses of ACS following an initial course of ACS are not recommended. A single rescue course of ACS is not routinely recommended. It may be administered up to 33+6 weeks of gestation in women at high-risk of PTB within the next 7 days when a course of ACS has been administered at least 14 days before.
- ACS is not routinely recommended before scheduled cesarean section at term because of the current uncertainty regarding the benefit to risk ratio. In the absence of other indications, a scheduled cesarean section should not be performed before 39+0 weeks of gestation.
- In multiple pregnancies, ACS should be administered at the same dosage and indications as in singleton pregnancies.
- In obese women, ACS should be administered at the same dosage and indications as in women without obesity.
- A single course of ACS is recommended at the time of diagnosis of PPROM when gestational age criteria are met.
- In cases complicated with FGR, ACS should be administered at the same dosage and indications as in appropriate for gestational age fetuses.
- In diabetic women, ACS should be administered at the same dosage and indications as in women without diabetes. Close monitoring of the maternal blood glucose levels is recommended for women with diabetes in the following days after the administration of ACS.
- After the administration of ACS, screening with glucose tolerance test should be delayed for at least one week.

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Abstract

This statement follows the mission of the World Association of Perinatal Medicine (WAPM) in collaboration with the Perinatal Medicine Foundation (PMF), bringing together groups and individuals throughout the world with the goal of improving the use of antenatal corticosteroids (ACS) for fetal maturation in Coronavirus Disease 2019 (COVID-19). Pregnant women with COVID-19 are at increased risk of hospitalization, admission to intensive care unit and mechanical ventilation compared to non-pregnant patients. Thus, obstetricians may face the dilemma of initiating maternal corticosteroid therapy for maternal indication while weighing its potential adverse effects on the fetus. As there is no evidence on the effect of betamethasone in pregnant women with COVID-19, dexamethasone should be preferably used for fetal maturation, if available. As a recommendation, for pregnant women with COVID-19 who are oxygen dependent or under mechanical ventilation and meet the criteria for ACS, the usual doses of dexamethasone should be administered, followed by oral prednisolone 40 mg OD or intravenous hydrocortisone 80 mg BD for up to 10 days.

Keywords: Corticosteroids, fetal maturation, COVID-19.
Pregnant women with Coronavirus Disease 2019 (COVID-19) are at increased risk of hospitalization, admission to intensive care unit and mechanical ventilation compared to non-pregnant patients. Thus, obstetricians may face the dilemma of initiating maternal corticosteroid therapy for maternal indication while weighing its potential adverse effects on the fetus. On the other hand, the neonatal benefits of antenatal corticosteroids (ACS) in women at high risk of preterm birth within the next 7 days have been well established.

The use of glucocorticoids as a means of immune-modulatory therapy in oxygen dependent COVID-19 patients is supported by the results of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial; the use of dexamethasone for up to 10 days significantly reduced 28-day mortality in COVID-19 patients receiving invasive mechanical ventilation or oxygen without invasive mechanical ventilation (29.3% vs. 41.4%; RR: 0.64; 95% CI: 0.51–0.81) and in those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; RR: 0.82; 95% CI: 0.72–0.94). Conversely, there was a trend towards increased mortality in those patients receiving no respiratory support at randomization (17.8% vs 14.0%; RR: 1.19; 95% CI: 0.91–1.55). It is worthy of note that only six pregnant women were included in the RECOVERY trial and, as per protocol for pregnant women, they received either oral prednisolone or intravenous hydrocortisone instead of dexamethasone, as these, contrary to dexamethasone, do not cross the placenta in significant quantity. Based on this safety signal of possibly increased mortality among patients with mild COVID-19 receiving dexamethasone, the indications for ACS should be limited to obstetrical indications with expected preterm delivery within the next 7 days. As there is no evidence on the effect of betamethasone in pregnant women with COVID-19, dexamethasone should be preferably used for fetal maturation, if available.

### Recommendation

- For pregnant women with COVID-19 who are oxygen dependent or under mechanical ventilation and meet the criteria for ACS, the usual doses of dexamethasone (4 doses of 6 mg IM at 12 h intervals) should be administered, followed by oral prednisolone 40 mg OD or intravenous hydrocortisone 80 mg BD for up to 10 days.

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### Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

### Conflicts of interest

Authors state no conflict of interest.

### Informed consent

Not applicable.

### Ethical approval

Not applicable.

### References


Evaluation of early pregnancy risk factors for venous thromboembolism in Turkish pregnant women: a prospective study

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Abstract

Objective: Venous thromboembolism (VTE), a condition during pregnancy that manifests as deep vein thrombosis and pulmonary embolism, is the third most common cause of death in 0.01–0.2% pregnant women worldwide each year. Because this risk has increased in pregnant women and is treatable, early diagnosis and treatment would save lives. The aim of this study was to evaluate the early pregnancy risk factors for VTE in Turkish pregnant women.

Methods: In this prospective study, 480 pregnant women between the ages of 18 and 45 years and who applied to our clinic within their first trimester (4–14 weeks) of pregnancy were enrolled in the study. Because the risk factors of the patients were to be determined, there were no exclusion criteria. The antepartum thromboembolism risk parameters were determined according to Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines.

Results: There were 336 (70%) pregnant women in the low-risk group, 62 (12.9%) in the medium-risk group, and 82 (17.1%) in the high-risk group. The permanent parameters within the groups that determined the risk factors were individually evaluated.

Conclusion: Our results indicated that 30% of the study population needed low-molecular-weight heparin (LMWH) prophylaxis, of whom 12.9% were in the medium-risk group, and 17.1% were in the high-risk group. VTE risk occurs from a combination of minor factors, rather than one high-risk factor. In addition, most of these VTE risk factors can be easily corrected and prevented in the pre-gestational phase or first trimester.

Keywords: Venous thromboembolism, low-molecular-weight heparin, LMWH, pregnancy, first trimester.

Introduction

Venous thromboembolism (VTE), a condition that includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 0.1–0.2% of pregnant women each year and is the third most common cause of death of these women worldwide.1,2 The risk factors for VTE are generally classified as patient-related and environment-related or reversible,3 for which pregnancy is a well-known environmental risk factor. The risk to pregnant women of developing VTE is four to five times greater than that for non-pregnant women. These risk factors include increasing age (>35 years), obesity, hereditary thrombophilia, and grand multiparity; however, the leading causes of VTE in these women are immobility and bed rest caused by preterm birth, premature rupture of membranes, or preeclampsia.4

The increased risk of VTE comes from a variety of factors that result from the physiological and anatomical changes that occur during pregnancy. These include blood clotting factors VII, VIII, X, von
Evaluation of early pregnancy risk factors for venous thromboembolism in Turkish pregnant women

Willebrand disease and fibrinogen increase, and a decrease in free protein S levels with a five-fold increase in the levels of plasminogen activator inhibitor type I. As a result, thrombogenic properties increase because of changes in the balance between procoagulants and anticoagulants.\(^5\) The mainstay of VTE treatment is anticoagulant therapy and the main anticoagulants used are unfractionated heparin and low-molecular-weight heparin (LMWH), with LMWH being the preferred choice.\(^6\) Because the risk in pregnant women increases and it is treatable, early diagnosis and treatment would save lives. The aim of the current study was to evaluate the VTE risk factors early in pregnancy in Turkish pregnant women.

**Methods**

The current study was conducted at Gynecology and Obstetrics Clinic of Tuzla State Hospital using a cross-sectional design. The Ethics Committee of Faculty of Medicine of Marmara University gave approval for the study (Approval no: 09.2020.1145) which was conducted in accordance with the Declaration of Helsinki.

We evaluated 480 pregnant women who applied to the outpatient clinic between January 1 and October 1, 2021. All pregnant women between the ages of 18 and 45 years and who applied to our clinic within the first trimester (4–14 weeks) were included in the study. Because the risk factors for these women were to be determined, there were no exclusion criteria for the study. The demographic data on the women such as age, height, weight, gravidity, parity, abortion, and the number of living children were recorded. In addition, the antepartum thromboembolism risk parameters presented in **Fig. 1** were considered according to Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines\(^7\) as follows: VTE history, presence of thrombophilia, presence of maternal comorbidity, relative history, smoking, presence of large varicose veins, any assisted reproduction technology, presence of a multiple pregnancy, or previous surgery during the current pregnancy. The risk factors of the women were determined by assessing the presence of hyperemesis gravidarum, systemic infection requiring intravenous medication, immobilization status, and any travel history ≥4 h. Scoring was obtained according to VTE risk analyses and classified as follows: low risk, ≤2 points; medium risk, 3 points; and high risk, ≥4 points. Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines uses data from The Royal College of Obstetricians & Gynecologist (RCOG) as a source, and the table in **Fig. 1** is a modified version of the RCOG recommendations.\(^8\) Data were analyzed using Minitab\(^\text{®}\) 16 (Minitab Inc., State College, PA, USA). The patient analyses based on risk factors for VTE and their parameters were calculated as n%.

**Results**

We evaluated 480 pregnant women during their first trimester. The mean maternal age was 29±4.2 years, mean body mass index (BMI) was 27±3.2 kg/m\(^2\), and nulliparity rate was 26.7%. **Fig. 2** illustrates the ratio of patients according to the risk factors for VTE. According to their total scores, there were 336 (70%) pregnant women in the low-risk group, 62 (12.9%) in the medium-risk group, and 82 (17.1%) in the high-risk group (**Fig. 2**).

When the permanent parameters within the groups determining the risk factors in pregnancy were individually evaluated, we found that 5 women had a history of VTE, 12 women had thrombophilia (presence of antithrombin-3 deficiency, protein C and S deficiency, factor V Leiden heterozygous and homozygous mutation, and prothrombin PT G20210A mutation), 22 women had medical comorbidity (heart failure, cancer, active systemic lupus erythematosus, inflammatory polyarthropathy, sickle cell anemia, inflammatory bowel disease, type 1 and 2 diabetes mellitus, nephrotic syndrome, or disease requiring continuous intravenous drug use), 8 women had triggered or estrogen-related VTE, 82 women were ≥35 years old, 68 women had BMI ≥30 kg/m\(^2\), 6 women had BMI ≥40 kg/m\(^2\), 69 women had parity ≥3, 32 women smoked more than 10 cigarettes per day, 22 women had large varicose veins, and 9 women had a multiple pregnancy (**Fig. 3**).

Considering the distribution of obstetric and transient risk factors within the first trimester, we found that 12 women became pregnant by assisted reproductive technology, 4 women underwent surgical intervention within the first trimester of pregnancy, 28 women had hyperemesis gravidarum, 72 women were immobilized and dehydrated, and 68 women traveled for ≥4 h (**Fig. 4**).
Discussion

Pregnancy-related VTE is a leading cause of death in pregnant women at a mortality of 1.1–1.5 deaths per 100,000 deliveries in North America and Europe. The risk of VTE also increases during the postpartum period. The reported incidence of VTE ranges from 0.7 to 1.3 per 1000 deliveries, which is four to five times higher than that in non-pregnant women. The aim of the current study was to determine the risk of early pregnancy-related VTE in Turkish pregnant women. We first determined that 30% of the study population required LMWH prophylaxis, with 62 (12.9%) in the medium-risk group and 82 (17.1%) in the high-risk group. Second, the risk of VTE occurs from a combination of minor factors such as advanced maternal age, obesity, increased parity, and smoking, rather than one factor alone. Third, we considered the major transient risk factors in pregnancy such as immobilization, dehydration, and traveling for ≥4 h. Fourth, and most impor-
tant, most of these risk factors for VTE are those that can be easily corrected and prevented in the pre-gestational stage or during the first trimester.

We examined the risk factors for VTE in Turkish pregnant women during the first trimester. In the literature, the authors preferred to examine the increased

![First trimester VTE risk evaluation](image)

**Fig. 2.** Ratio of pregnant women according to the risk factors for venous thromboembolism (VTE).

![Evaluation of risk factor](image)

**Fig. 3.** Ratio of pregnant women with permanent risks for venous thromboembolism (VTE) in the first trimester.
risk of VTE during the postpartum period; however, many fatal VTE events occur during the first trimester; therefore, prophylaxis for women who had previous VTE should be initiated early in pregnancy. The incidence of VTE in women during their first trimester of pregnancy is higher than that in non-pregnant women and gradually increases thereafter. VTE occurs with increased coagulation factors II, VII, VIII, X, and fibrin, decreased protein S production, and suppression of systemic fibrinolytic activity during the first trimester. In the later weeks of pregnancy, more anatomical factors come into play. As the uterus presses on the inferior vena cava and pelvic veins during pregnancy, venous blood flow slows and venous stasis in the lower extremities increases, which increases the risk of VTE. This becomes even more important in the later stages of pregnancy in cases of complications such as the threat of premature birth, premature rupture of membranes, preeclampsia, and increased inactivity and bed rest. The risk of VTE increases during the postpartum period when a cesarean delivery prevents early mobilization compared to that in normal delivery.

The Royal College of Obstetricians & Gynecologist (RCOG) recommends that all women be evaluated either before or early in pregnancy for risk factors for VTE. Risk assessment should be also repeated during delivery or the postpartum period if the woman is hospitalized for any reason or other problems. Based on the risk factors, prophylactic LMWH should be considered during the antenatal period, which requires prophylactic LMWH for 6 weeks postpartum. This protocol is controversial with pregnant women at risk of VTE; therefore, the reasons for individual recommendations should be explained. When the American College of Gynecology (ACOG), Society of Obstetricians and Gynecologists of Canada, and RCOG consider the timeframe of thrombophilia treatment, antepartum care, and VTE-related complications, antiphospholipids, including Factor V Leiden, prothrombin G20210A gene variant, antithrombin III, protein C, and protein S deficiencies recommend screening every pregnant woman with a history of VTE for antibody syndrome and hereditary thrombophilia. The risks for VTE are increased by 15 times in pregnant women with hereditary thrombophilia compared to that in normal pregnant women, although even among those without a history of VTE, the magnitude of risk varies with specific thrombophilia and family history of VTE. The risks for VTE also increase with a deficiency of endogenous anticoagulants such as protein C, protein S, and antithrombin III (4.8, 3.2, and 4.7, respectively). A family history of VTE also increases the risk by up to 4 times, even in the absence of thrombophilia. In their studies on in vitro fertilization pregnancies, Sennstrom et al., have shown that assist-
ed reproduction technology increases the risk of VTE by two to three times during ovarian stimulation compared to that in the general pregnant population. As a result of previous studies, it is believed that estradiol levels that abnormally increase can cause hemoconcentration, activation of coagulation, and fibrinolytic systems. In their study of the risk for VTE in multiple pregnancies, Rova et al. have shown in an antepartum trial that multiple pregnancy increases the risk for VTE by 2.1 to 2.6 times compared to that in normal pregnant women. In another prospective cohort study involving 1.3 million pregnant women in Denmark, the authors have shown that hospitalization for hyperemesis and multiple pregnancy within the last trimester.

In their study, Saltan et al. have shown that the incidence of VTE within the first trimester is 0.26 per 1000 births. In that study, four (80%) of the five DVTs occurred within the first trimester, and one occurred within the last trimester.

In the risk analyses published in accordance with the Turkish Ministry of Health (Fig. 1), it is recommended that those scoring >4 points should begin LMWH prophylaxis, and those with >3 points should begin LMWH at 28 weeks of gestation. As a result of the current study, 62 (12.9%) patients scored >3 points and were in the medium-risk group and LMWH was recommended beginning from the 28th week of gestation, 82 (17.1%) scored >4 and it was recommended beginning LMWH after evaluation. We concluded that approximately one out of every three women should begin LMWH treatment. The clinical significance of this study showed an increase risk for VTE with pregnancy. In line with the current findings, we believe that one out of every three pregnant women is at risk for VTE. This is a key factor for examining risk factors and beginning early prophylaxis to prevent VTE within the first trimester. The risks for VTE increase during both antepartum and postpartum periods with increasing maternal age, obesity, and smoking, therefore, VTE prophylaxis is becoming increasingly important. In addition, at each visit in the presence of increased risk for the development of VTE, the patients should be informed and their awareness should be raised, thereby eliminating the risk factors by providing education before certain conditions occur.

Study limitations
There were some limitations to this study. First, it was a single-center observational study and did not reflect the entire population. As the criteria for the risk for VTE were obtained using the Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines, some undiagnosed conditions such as a mild DVT or PE could have been missed because the diagnoses were made using patient information accompanied by questions and answers. Some factors such as immobilization were observed more frequently because of the increased barrier to mobility within the society from the COVID-19 pandemic. One of the limitations is that the cost of anticoagulant prophylaxis to be used to reduce the risk of VTE during pregnancy and puerperium has not been calculated.

Conclusion
Our results indicated that 30% of the population needed LMWH prophylaxis according to Risky Pregnancies Management Guide of Turkish Ministry of Health Guidelines, of whom 12.9% were in the medium-risk group, and 17.1% were in the high-risk group. The risk for VTE occurs from a combination of minor factors such as advanced maternal age, obesity, increased parity, and smoking, rather than only one factor that causes an elevated risk. Immobilization, dehydration, and traveling for ≥4 h were the major transient risk factors for VTE during pregnancy. Additionally, it is noteworthy to mention that many of these factors are those that can be prevented in the pre-pregnancy period.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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Multifetal pregnancy reduction outcomes from triplets to singletons and twins

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Abstract

Objective: To study the obstetric and neonatal outcomes of reduction to singleton and twin pregnancies by multifetal pregnancy reduction (MPR) in patients with triplet pregnancies.

Methods: The multifetal reduction was performed in 27 patients with triplet pregnancies. Fourteen patients were reduced to singleton pregnancies and 13 patients to twin pregnancies. Obstetric and neonatal outcomes were compared between the two groups.

Results: The mean gestational age at the time of the procedure was 12.43±0.76 weeks in patients reduced to singleton pregnancies and 12.08±0.64 weeks in those reduced to twin pregnancies. The most common complications of the procedure were abdominal pain (21.4%) in women with singleton pregnancies and both the presence of abdominal pain and vaginal bleeding (30.8%) in women with twin pregnancies. Gestational age at birth (33.07±5.73 versus 35.78±6.14 weeks, p=0.009) and neonatal birth weight (1998.46±808.07 versus 2765±803.03 gram, p=0.003) was significantly higher in the group reduced to singleton pregnancies than in twin pregnancies.

Conclusion: The MPR procedure is a good and acceptable option for patients with multiple pregnancies of three or more children. Multifetal pregnancy reduction of triplets to singletons is associated with better pregnancy outcomes such as birth at higher weeks of gestation and higher neonatal birth weight than MPR of triplets to twins.

Keywords: Multiple pregnancies, multifetal pregnancy reduction.

Introduction

The widespread use of ovulation induction agents and assisted reproductive technologies have significantly increased the incidence of multiple pregnancies in recent years. Efforts are being made to reduce the incidence of these multiple pregnancies by limiting the number of embryos transferred in women undergoing assisted reproductive technologies. However, this situation cannot be completely avoided, as a triplet or multiple pregnancies with monozygotic twins may occur after single or double embryo transfer, or multiple pregnancies with triples or more may occur after ovulation induction. Although good clinical practice in multiple pregnancies has increased in recent years, multiple pregnancies with triplets or more, in particular, are associated with an increased number of adverse obstetric and perinatal outcomes and these risks increase with the number of fetuses. To reduce the increased maternal and perinatal risks associated with multiple pregnancies, fetal reduction has been incorporated into the management of multiple pregnancies. The most commonly used multifetal pregnancy reduction (MPR)
method is intrathoracic potassium chloride (KCl) injection, administered transabdominally at 11–14 weeks of gestation.\textsuperscript{[1]} The other alternative methods for MPR are transvaginal fetal aspiration in 6–8 weeks of gestation, intrafetal laser embryo reduction, radiofrequency ablation, and microwave ablation.\textsuperscript{[11–13]}

Maternal and perinatal outcomes have improved after fetal reduction in multiple pregnancies.\textsuperscript{[11]} Specifically, it has been reported that reduction from triplet pregnancies to twin pregnancies is associated with better pregnancy outcomes such as higher perinatal survival and lower preterm birth compared to triplet pregnancies.\textsuperscript{[8,14]} However, few studies are investigating obstetric and perinatal outcomes after reducing triplet pregnancies to twins or singletons.\textsuperscript{[1,15,16]} This study aimed to compare the obstetric and perinatal outcomes of triplet pregnancies after reduction to singleton or twin pregnancies in a single tertiary center.

**Methods**

This retrospective cohort study was conducted between June 2016 and October 2018 at Istanbul Kanuni Sultan Suleyman Training and Research Hospital, a prenatal diagnosis and treatment center. After approval from the ethics committee of our hospital, data were collected from all triplet pregnant women who underwent elective fetal reduction to twin or singleton pregnancy in our hospital during the study period.

The study group included triplet pregnancies (n=27) in which MPR was performed between 11–14 weeks of gestation. Before the procedure, all patients were informed about the expected risks and benefits in triplet pregnancies and after MPR in singleton or twin pregnancies. The patients were offered the option to reduce the number of embryos based on the current literature on expected outcomes in triplet pregnancies compared to outcomes after MPR. The decision to reduce to twins or a single embryo was based on the patients’ personal preferences and the technical feasibility of fetal reduction. Fetuses to be reduced were selected primarily on the basis of the presence of fetal abnormalities, chorionicity, and ease of use of the procedure. According to this, all dichorionic triamniotic (DCTA) triplet pregnancies (n=11) were reduced to singleton pregnancies to avoid the adverse outcomes of monochorionic twin pregnancies. Of the 16 trichorionic triamniotic (TCTA) triplet pregnancies, 13 were reduced to dichorionic diamniotic twin pregnancies and 3 to singleton pregnancies. Written informed consent was obtained from all patients undergoing the procedure.

All procedures were performed by perinatal specialists with experience in invasive procedures. An ultrasound scan was performed before the procedure to assess the chorionicity, number, location, size, and cardiac activity of the embryos. The entire procedure was performed under the guidance of a transabdominal ultrasound (Voluson 730 Expert; General Electric Healthcare, Milwaukee, WI, USA). After cleaning the mother’s abdominal skin with an antiseptic solution, a 20-G spinal needle was used to penetrate first through the anterior uterine wall into the targeted gestational sac and then into the fetal thorax. 1–3 ml of 10% KCl (2 meq/ml) was injected into the fetal thorax. Cardiac activity was observed for at least 2 minutes. If cardiac activity persisted, additional KCl was injected. Reduction of other fetuses was performed with the same needle puncture or, less frequently, with a separate needle puncture. The total duration of the procedure was less than 10 minutes. After the procedure, the women were clinically observed for an average of two hours for pain, water leakage, and bleeding. The patients were discharged after a follow-up ultrasound to confirm the presence of asystole in the reduced fetus and cardiac activity in the others. An ultrasound was performed in all patients 1 week after the procedure to check fetal viability.

The demographic, obstetric, and neonatal clinical data of all patients included in the study were evaluated using electronic archives or patient records. The study patients were divided into two groups: Triplet pregnancies reduced to singletons (n=14) and triplet pregnancies reduced to twins (n=13). The demographic data, complications related to the reduction procedure (post-procedure complications), various pregnancy complications such as early spontaneous abortion (pregnancy loss before 24 weeks), preterm birth (≤32, <34, and <37 weeks), gestational diabetes mellitus (GDM), gestational hypertensive disorders, preterm premature rupture of membranes (PPROM), and intrauterine growth restriction (IUGR) were compared in both groups. GDM was diagnosed with a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. The threshold values for fasting, 1-h and 2-h plasma glucose levels were 92 mg/dl, 180 mg/dl, and 153 mg/dl, respec-
tively. If at least one of these values was reached or exceeded, the pregnant woman was diagnosed with GDM.\textsuperscript{17} Preeclampsia was identified as maternal hypertension >140/90 mmHg without a previous history of hypertension and 300 mg/L proteinuria without a history of renal disease.\textsuperscript{16,19} PPROM was described as a rupture of the fetal membranes before 37 weeks of completed gestation.\textsuperscript{20} IUGR was defined as EFW < 3rd centile based on sonographic measurements of fetal biparietal diameter, head circumference, AC, and femur length, and no end-diastolic flow loss on Doppler examination.\textsuperscript{21,22}

Statistical analysis

Pregnancy reduction was determined as the primary outcome variable for this descriptive study, which was retrospectively planned. SPSS 20.0 (IBM Corp., released in 2011. IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY, USA) was used to analyze the data obtained in the study. Student’s t-test and Mann-Whitney U-test were applied to compare the continuous variables in the study where groups were formed by reducing triplet pregnancies to twin and singleton pregnancies. The group-specific assumptions about normal distribution were tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. These results were used to decide whether parametric or nonparametric hypothesis tests should be used for comparison. The chi-square test or Fisher’s exact test was performed to examine the difference between the distributions of the categorical variables. The p-values of the exact test were used when the number of cells with an expected value of less than 5 was more than 25% of the total number of cells. Mean-standard deviation, median-range, and frequency distributions-percentiles were used as descriptive statistics to summarize the results. Statistical significance was taken as p-value <0.05.

Results

During the study period, 27 patients with triplet pregnancy between 11–14 weeks of gestation underwent reduction. Of these 27 triplet pregnancies, 14 were reduced to singleton pregnancies and 13 to twin pregnancies. The comparison of patients’ demographic and clinical data including maternal age, number of pregnancies, type of pregnancy, gestational age at the time of the procedure, and post-procedure complications are given in Table 1.

At the time of the procedure, the mean gestational age was 12.43±0.76 weeks for singleton pregnancies and 12.08±0.64 weeks for twin pregnancies. Of the 27 patients, 22 (81.48%) developed triplet pregnancies after an in vitro fertilization (IVF) treatment, 3 (11.1%) after ovulation induction with gonadotropin, and 2 (7.4%) were naturally occurring triplet pregnancies. One of the triplet pregnancies that occurred after ovulation induction was a pregnancy by intrauterine insemination (IUI). Of the 27 triplet pregnancies in which a reduction procedure was performed, 16 (59.3%) were TCTA pregnancies and 11 (40.7%) were DCTA pregnancies. The most common complication of the procedure was abdominal pain in singleton pregnancies (21.4%), and both the presence of abdominal pain and vaginal bleeding (30.8%) in twin pregnancies.

Table 1 shows obstetric complications by procedure MPR. There was no significant difference between the two groups in obstetric complications including the prevalence of GDM, gestational hypertensive disorders, PPROM, and IUGR.

A comparison of the perinatal outcomes of patients reduced from triplet pregnancies to singletons and twins is given in Table 2. Compared to singleton pregnancies, twin pregnancies had significantly earlier weeks of gestation (33.07±5.73 weeks versus 35.78±6.14 weeks, p=0.009) and lower birth weight (1998.46±808.07 g versus 2765±803.03 g, p=0.003). It was also observed that the rate of births before 37 weeks of gestation (46.2% versus 28.6%, p=0.440) was higher in pregnancies reduced to twins than in pregnancies reduced to singletons, although this was not statistically significant. In the group reduced to singleton pregnancies, no delivery occurred before 34 or 32 weeks of gestation. In addition, in the group reduced to twin pregnancies, 2 (15.4%) patients delivered at less than 34 weeks of gestation and 1 (7.7%) patient delivered at less than 32 weeks of gestation.

Before 24 weeks of gestation, pregnancy loss was 7.1% and 15.4% in the groups reduced to singletons and twins, respectively. One patient who was reduced to twin pregnancy after fetal reduction experienced premature rupture of membranes and was delivered at 33 weeks and 4 days of gestation. Intrauterine fetal demise occurred at 15 weeks of gestation in one patient who was reduced to a singleton pregnancy. Postneonatal death occurred in two patients in the group reduced to twins,
and both patients were at <25 weeks of gestation (18 and 24 weeks of gestation). There was no significant difference between the two groups in terms of the type of birth. The most preferred birth method was cesarean section (92.9% versus 84.6%). The need for a neonatal intensive care unit (NICU) was not significant between the two groups (p=0.209).

**Discussion**

Multiple pregnancies are taking an increasingly important place in obstetrics due to the increasing advances in assisted reproductive technologies. Reduction of multiple pregnancies is a widely used procedure to reduce the risk of perinatal morbidity and mortality.\(^1\) Although the reduction is a therapeutic option in the management of multiple pregnancies, it should not be the first choice to prevent multiple pregnancies. Patients undergoing assisted reproductive techniques such as IVF should be recommended a single embryo transfer as a priority.\(^{2,3}\) Single embryo transfer has been shown to significantly reduce the incidence of multiple pregnancies\(^{24}\) but does not completely eliminate them. Therefore, MPR is an alternative option for multiple pregnancies with three or more fetuses because it improves pregnancy outcomes. The main goal of fetal reduction is to reduce preterm birth and associated neonatal morbidity.

Our study shows that the group reduced to a twin pregnancy delivered at an earlier week of gestation and

| Table 1. Comparison of the demographic and clinical data of patients reduced from triplet pregnancies to singletons and twins. |
|---------------------------------|----------------------------------|---------------------------------|
|                                  | Triplet pregnancies reduced to singletons (n=14) | Triplet pregnancies reduced to twins (n=13) |
|                                  | Mean±standard deviation | Median– range | Mean±standard deviation | Median– range | p-value  |
| Age, years                       | 32.71±6.58 | 30–23 | 33.31±6.1 | 31–22 | 0.810*  |
| Gravidity, n                    | 1.57±0.85 | 1–3  | 1.46±0.88 | 1–3  | 0.569†  |
| Gestational age at reduction     | 12.43±0.76 | 12–3  | 12.08±0.64 | 12–2  | 0.223†  |
| Nulliparity                     | 10 | 71.4 | 11 | 84.6 | 0.648 |
| Mode of conception               | 0.162 |
| Spontaneous                      | 2 | 14.3 | 0 | 0.0 |
| Ovulation induction             | 0 | 0.0 | 2 | 15.4 |
| Ovulation induction / Intrauterine insemination | 0 | 0.0 | 1 | 7.7 |
| In vitro fertilization           | 12 | 85.7 | 10 | 76.9 |
| Number of procedures            | 1 | 92.9 | 1 | 100.0 |
| 1                               | 13 | 7.1  | 13 | 0.0  |
| 2                               | 1 | 7.1  | 0 | N/A  |
| Procedure complications         | 3 | 21.4 | 5 | 38.5 |
| Abdominal pain                  | 2 | 14.3 | 0 | 0.0 |
| Vaginal bleeding                | 0 | 0.0  | 0 | 0.0 |
| Amniotic fluid leakage          | 0 | 0.0  | 1 | 7.7  |
| Abdominal pain + vaginal bleeding | 1 | 7.1  | 4 | 30.8 |
| Gestational diabetes mellitus   | 0 | 0.0  | 2 | 15.4 |
| Gestational hypertensive disorders | 2 | 14.3 | 5 | 38.5 |
| Preterm premature rupture of membranes | 0 | 0.0  | 1 | 7.7  |
| Intrauterine growth restriction  | 1 | 7.1  | 2 | 15.4 |
| Cerclage                        | 0 | 0.0  | 0 | N/A  |
| Antepartum hemorrhage           | 0 | 0.0  | 3 | 23.1 |

\(^*\)Refers to Student’s t-test and \(^†\)for Mann-Whitney U test, all others from Fisher’s exact test p-values.
Multifetal pregnancy reduction outcomes from triplets to singletons and twins

had a lower birth weight than the group reduced to a singleton pregnancy. These results indicate positive outcomes after reduction to a singleton pregnancy similar to previous studies.[15,16] In contrast, there was no statistically significant difference between groups in preterm birth rate and pregnancy loss before 37, 34, and 32 weeks of gestation. The rate of births below 37 weeks of gestation was 28.6% in the group reduced to a singleton pregnancy and 46.2% in the group reduced to a twin pregnancy. Moreover, in our study, no deliveries were observed at <34 weeks or <32 weeks in all pregnant women reduced to a singleton pregnancy.

The risk of miscarriage before 24 weeks of gestation after the MPR procedure is controversial. While previous studies reported that the risk of miscarriage increased after the procedure,[11] more recent studies report that the risk of pregnancy loss before 24 weeks is similar in pregnancies with and without reduction.[23] Some studies have reported that the risk of miscarriage is higher with the reduction from triplets to singleton pregnancies than with reduction to twin pregnancies (62% versus 4%).[12,28] There are studies suggesting that this may be due to the resorption of the remaining dead fetoplacental tissue rather than the procedure itself.[9,10,27,28] However, more recent studies have shown that reduction of triplet pregnancies to singleton rather than twin pregnancies is associated with higher weeks of gestation and better perinatal outcomes.[15,16,29] In our study, the overall pregnancy loss rate was 3.7%. Similar to the literature, the fetal loss rate below 24 weeks was not significantly different between the two groups (7.1% in singleton pregnancies, 15.4% in twin pregnancies, p=0.596), which may be due to the small number of patients in both groups in the present study. Also, our study concluded that one patient with singleton pregnancy experienced in utero death at 15 weeks of gestation and two patients with twin pregnancy delivered at <25 weeks’ gestation (18 and 24 weeks of gestation). It was observed that the group reduced to singleton pregnancy had higher gestational weeks and birth weights.

Belogolovkin reported that pregnancy reduction did not seem to increase the IUGR incidence after adjusting for potential confounders, including placental pathology and the use of assisted reproduction, where available.[30] However, Audibert et al. concluded that embryo reduction was the only significant risk factor for the development of birth weight discordance.[11] In our cohort, the IUGR prevalence in triplet pregnancies reduced to twins was 15.4%, and in triplet pregnancies reduced to twins was 7.1%. We found no significant difference

Table 2. Comparison of the perinatal outcomes of patients reduced from triplet pregnancies to singletons and twins.

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<thead>
<tr>
<th>Table 2. Comparison of the perinatal outcomes of patients reduced from triplet pregnancies to singletons and twins.</th>
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<tr>
<td><strong>Triplet pregnancies reduced to singletons (n=14)</strong></td>
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<tr>
<td><strong>Week of gestation at birth</strong></td>
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<td><strong>Birthweight, g</strong></td>
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<td><strong>Neonatal intensive care unit admission, days</strong></td>
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</table>

| Miscarriage <24 weeks | 1 | 2 |
| Live birth | 13 | 11 |
| <32 weeks preterm birth | 0 | 2 |
| <34 weeks preterm birth | 0 | 1 |
| ≤37 weeks preterm birth | 4 | 6 |
| Cesarean delivery | 13 | 11 |
| Neonatal intensive care unit admission | 2 | 5 |
| Surviving neonates | 13 | 11 |

*Refers to Mann-Whitney U test, all others from Fisher’s exact test p-values.
between the groups regarding IUGR, but the sample size of 27 patients was low to draw any conclusion.

The frequency of maternal morbidity is greater in higher-order pregnancies. Gestational hypertensive disorders are observed in 12.7% to 19.6% of multiple pregnancies compared with 6.5% of singletons.\(^{(12)}\) Moreover, compared with mothers of twins, mothers of triplets and quadruplets were more likely to be diagnosed with PPROM, GDM, and antepartum and postpartum hemorrhage, to require tocolytic agents, and to be delivered by cesarean section.\(^{(11)}\) In our study, the prevalence of gestational hypertensive disorders, GDM, PPROM, and antepartum hemorrhage was higher in triplet pregnancies reduced to twins (38.5%, 15.4%, 7.7%, and 23.1%, respectively) than in triplet pregnancies reduced to singletons (14.3%, 0%, 0%, and 0%, respectively). However, these differences were not statistically significant. We consider that the lack of statistically significant difference was due to the low sample size.

There are some limitations to this study. The main limitation is the low sample size. The fact that the decision MPR was difficult for these patients because this is a retrospective study, multiple pregnancies are rare, and these patients became pregnant after long-term infertility treatment may not be sufficient to detect the differences between the perinatal outcomes of the two groups. There are also no long-term neonatal outcomes.

**Conclusion**

We indicated that reducing triplet pregnancies to singleton pregnancies instead of twin pregnancies leads to better obstetric outcomes such as higher birth weights and further birth weeks. However, prospective studies with a larger number of patients are needed to contribute more to the literature on the clinical significance of this difference and to better counsel parents on the risks and benefits of MPR.

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**Compliance with Ethical Standards:** The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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Clinical characteristics and perinatal outcomes of pregnant women with Coronavirus-19 disease

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Abstract

Objective: The aim of this study was to evaluate the maternal and perinatal outcomes of COVID-19 infection during pregnancy.

Methods: We performed a retrospective review of medical records of 37 pregnant women with the diagnosis of COVID-19. The clinical characteristics, laboratory results, perinatal and neonatal outcomes were analyzed.

Results: The majority of cases with COVID-19 were evaluated as mild (97.3%). None of the women needed intensive care unit or invasive mechanical ventilation and mortality were not observed. The most common symptoms were fever (62.2%) and cough (40.5%). Of all the pregnancies, 5.4% ended with abortion, 2.7% with stillbirth, and 10% of the infants were hospitalized in the neonatal intensive care unit. Neonatal mortality was not observed.

Conclusion: In our study, none of the pregnant women with SARS-CoV-2 infection had severe illness. Vertical transmission of SARS-CoV-2 which was possible in several studies is not observed in our patient population.

Keywords: Coronavirus-19, pregnancy outcome, newborn.

Introduction

Emerging in China, Wuhan at the end of 2019, the outbreak of novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly spread to become a pandemic leading to a global public health crisis. The spectrum of the disease severity ranges from mild to critical. Because of this pandemic, many researchers shifted their interest to investigate the possible impact of this infection on vulnerable groups like pregnant women and their fetuses. Pregnancy is a state that is particularly susceptible to infectious diseases primarily because of an altered immune response. Along with it, due to the physiologic changes in their cardiopulmonary systems, pregnant women are prone to develop severe pneumonia.

As previously stated, infections especially of viral origin may affect pregnancy outcomes. Most infectious diseases may increase complications during pregnancy and lead to extremely detrimental effects on the fetus and the mother. However, there also have been studies showing that pregnant women are not found to be more susceptible to SARS-CoV-2 than non-pregnant women. One of the largest series on both pregnancy and neonatal outcomes, including a total of 99...
SARS-CoV-2-infected pregnant women, demonstrated that this infection during pregnancy was not associated with an increased risk of adverse outcomes, such as spontaneous preterm birth.\(^{14}\) When we investigate different time frames, as seasonal flu is known to be associated with higher rates of miscarriage for the period of early pregnancy (first trimester), there is little evidence about the possible impact of SARS-CoV-2 infection on this period of pregnancy.\(^{15}\) When we search for evidence about the impact of SARS-CoV-2 infection on late pregnancy (third trimester), the majority of studies have been reassuring and the risk of severe disease and mortality due to SARS-CoV-2 infection in pregnancy appears to be no greater than the general population.\(^{16}\) On the other hand, considering the severity of the disease, limited data suggest that pregnant women may present with severe symptoms which can provoke fetal distress, preterm labor, miscarriage, or even fetal death.\(^{17,18}\)

As for the fetus, the risk of perinatal transmission of SARS-CoV-2 infection is unknown and the risk of postnatal transmission remains to be clarified.\(^{19,19}\) Yan et al. stated that none of the 100 neonates born to women with COVID-19 was infected with SARS-CoV-2.\(^{14}\) However, data to date is scarce and there are conflicting results according to several case reports and studies. Until recently, 15 studies presented the neonatal test results for SARS-CoV-2\(^ {20-23}\) but positive cases were reported only in the minority.\(^ {20,21,23}\) Furthermore, significant neonatal respiratory diseases appear to be rare, even in the presence of SARS-CoV-2 positivity.

There is still a need to accumulate and analyze each data to further elucidate the course of COVID-19 infection during pregnancy and clarify possible perinatal outcomes.\(^ {24}\) Therefore, our study aimed to unravel meaningful factors which have a possible impact on how COVID-19 affects pregnant women and their babies.

**Methods**

**Study design and patients**

We performed a retrospective review of medical records of pregnant women with the diagnosis of COVID-19 admitted to Tepecik Training and Research Hospital, Izmir, Turkey from March 15, 2020 to January 31, 2021. Diagnosis and management of pregnant women with possible COVID-19 infection were based on the “Diagnosis and Management Guideline for COVID-19 Infection” published by the Turkish Ministry of Health. All 37 pregnant women with COVID-19 infection were tested positive for SARS-CoV-2 by the use of reverse transcriptase-polymerase chain reaction (RT-PCR) on samples from the respiratory tract. This study was reviewed and approved by the Medical Ethical Committee of Tepecik Training and Education Hospital (approval number 2021/02-27).

**Data collection**

Clinical characteristics, laboratory results, and treatment courses were extracted from the medical records of patients. We collected data regarding maternal age, parity, blood type, medical history of other underlying conditions, presenting signs and symptoms (fever, cough, shortness of breath, fatigue, loss of taste and smell, nausea and vomiting, and arthralgia), the timing of infection, laboratory tests, imaging results, duration of hospitalization, gestational age at delivery, intensive care unit admission and use of mechanical ventilation. We also analyzed gestational and neonatal outcomes, including mode of delivery (cesarean or vaginal delivery), miscarriage indication for cesarean delivery, the time between COVID-19 diagnosis and delivery, fetal distress, APGAR scores, birth weight of the fetus, and neonatal morbidities including respiratory distress syndrome, neonatal intensive care unit (NICU) admission, meconium aspiration syndrome, stillbirth, and mortality. Samples of nasopharyngeal and pharyngeal swabs were tested for SARS-CoV-2 by using a kit (Bioeksen, Istanbul, Turkey), following the World Health Organization guidelines for RT-PCR. Amniotic fluid, cord blood, placental swab, or human milk samples could not be analyzed for any of the patients.

**Statistical analysis**

Statistical analysis was done with IBM SPSS Statistics 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA). Continuous data are shown as mean ± standard deviation and categorical data are given as percentage (%). The Shapiro-Wilk test was used to investigate the compatibility of the data to normal distribution. For the comparison of groups showing normal distribution, independent sample t-test analysis was used for cases with two groups, and one-way analysis of vari-
ance (one-way ANOVA) for cases with three or more groups. In a comparison of the groups that did not conform to a normal distribution, the Mann-Whitney U test was used for cases with two groups and the Kruskal-Wallis H test for cases with three or more groups. Determining the direction and size of the relationship (correlation) between variables, regression analysis was performed for variables with normal distribution, and lines were drawn. Pearson’s chi-square, Pearson’s exact chi-square, and Fisher’s exact chi-square analyzes were used in the analysis of the cross tables created. A p-value of less than 0.05 was considered significant for the statistical tests.

Results
We have studied 37 pregnant women who were diagnosed with confirmed SARS-CoV-2 infection during the period of nearly 11 months. None of the pregnant women were vaccinated as data collection was carried out in the first wave of the pandemic. The median age of the women was 25 years (22–31). Three (8.1%) of them had multiple pregnancies. Of these 37 women, 2 (15.4%) had coexisting preeclampsia, 1 (7.7%) had asthma, 2 (15.4%) had cholestasis, 5 (38.5%) had gestational diabetes, 2 (15.4%) had hypothyroidism and 1 (7.7%) had gestational hypertension. Demographic characteristics and comorbid diseases of pregnant women with confirmed SARS-CoV-2 infection are shown in Table 1. Thirty-four of the women had a diagnosis of SARS-CoV-2 infection during the third trimester (median: 38.0 [range 38.0–39.0] weeks) while only 2 had this diagnosis during the first trimester (median: 11.0 [range 10.5–11.5] weeks) and 1 had it during the second trimester (median: 22.0 weeks). The mean time between the time of diagnosis and delivery is 8.08±7.94 weeks (8.41±8.17 weeks for single and 4.33±3.21 weeks for multiple pregnancies). The most common symptom was fever in 23 (62.2%) patients, cough in 15 (40.5%) patients, then arthralgia in 7 (18.9%) patients, fatigue in 7 (18.9%) patients, loss of taste and smell in 7 (18.9%) patients, nausea in 3 (8.1%) patients and diarrhea in 1 (2.7%) patient. Mean white blood cell count was 9180±4100/mm$^3$, absolute lymphocyte count was 1320±570/mm$^3$, median C-reactive protein was 21.0 (range 3.40–54.0) mg/l, and D-dimer was 1120 (range 540–2860) ng/ml. No thrombocytopenia was observed. Thrombocyte values were lower (p=0.019) and ferritin values were higher (p=0.001) in multiple pregnancies. Lopinavir was used for only one case who was in the third trimester of pregnancy. Clinical characteristics, laboratory findings, pregnancy and neonatal outcomes of pregnant women are shown in Tables 2 and 3.

Out of the 37 women, 17 (47.2%) had cesarean section, 18 (47.2%) had a vaginal delivery, and 2 (5.6%) had an abortion. Cesarean section indication was mostly due to repeat cesarean section with a ratio of 70.6%. One out of 37 women had to undergo a cesarean section due to fetal distress. The mean gestational age at birth was 36.4±6.88 weeks and the mean birth weight was 3148±428 g. In 5 cases, women gave birth to a baby with a birth weight <2500 g and 1 of them was multiple pregnancy.

Median APGAR scores were 7 (IQR: 7–7) for the 1-minute and 8 (IQR: 8–8) for the 5-minute. Four (11.8%) of the babies were admitted to the neonatal intensive care unit. Three (8.8%) of them had the diagnosis of RDS, one (2.9%) of them had meconium dyed

| Table 1. Demographic characteristics and baseline comorbidities of pregnant women infected with SARS-CoV-2. |
|---------------------------------|----------|
| **Characteristics**             | **n (%)** |
| Maternal age, years (median, IQR) | 25.0 (22.0–31.0) |
| **Blood type**                  |          |
| A+                              | 15 (40.5%) |
| A-                              | 1 (2.7%)  |
| O+                              | 8 (21.6%) |
| O-                              | 0 (0%)    |
| B+                              | 6 (16.2%) |
| B-                              | 0 (0%)    |
| AB+                             | 5 (13.5%) |
| AB-                             | 2 (5.4%)  |
| **Gravidity**                   |          |
| Single pregnancy                | 34 (91.9%) |
| Multiple pregnancy              | 3 (8.1%)  |
Table 2. Clinical characteristics, laboratory findings, and gestational and neonatal outcomes of pregnant women infected with SARS-CoV-2.

<table>
<thead>
<tr>
<th></th>
<th>All pregnant women (n=37)</th>
<th>Single pregnancy (n=34)</th>
<th>Multiple pregnancy (n=3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age at diagnosis, weeks (median, IQR)</strong></td>
<td>38.0 (38.0–39.0)</td>
<td>38.0 (38.0–39.0)</td>
<td>38.0 (34.0–38.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Duration of hospitalization, days (mean, SD)</strong></td>
<td>4.43±7.60</td>
<td>14.0±18.5</td>
<td>4.33±3.21</td>
<td>0.478</td>
</tr>
<tr>
<td><strong>Drug therapy - lopinavir</strong></td>
<td>1 (2.7%)</td>
<td>0 (0%)</td>
<td>1 (100.0%)</td>
<td>0.317</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>23 (62.2%)</td>
<td>21 (61.8%)</td>
<td>2 (66.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>7 (18.9%)</td>
<td>5 (14.7%)</td>
<td>2 (66.7%)</td>
<td>0.152</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (18.9%)</td>
<td>6 (17.6%)</td>
<td>1 (33.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cough</td>
<td>15 (40.5%)</td>
<td>15 (44.1%)</td>
<td>0 (0%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Malaise</td>
<td>7 (18.9%)</td>
<td>6 (17.6%)</td>
<td>1 (33.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (8.1%)</td>
<td>3 (8.8%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.7%)</td>
<td>1 (2.9%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>16 (43.2%)</td>
<td>14 (41.2%)</td>
<td>2 (66.7%)</td>
<td>0.393</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>21 (56.8%)</td>
<td>20 (58.8%)</td>
<td>1 (33.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood count, ×10^9/mL, (median, IQR)</td>
<td>8300 (6700–10700)</td>
<td>8350 (6700–10,500)</td>
<td>8300 (7250–9600)</td>
<td>0.198</td>
</tr>
<tr>
<td>Lymphocyte, ×10^9/mL, (median, IQR)</td>
<td>1300 (900–1600)</td>
<td>1250 (900–1580)</td>
<td>1300 (1050–1950)</td>
<td>0.095</td>
</tr>
<tr>
<td>Neutrophil, ×10^9/mL, (median, IQR)</td>
<td>6300 (4500–7500)</td>
<td>6300 (4500–7500)</td>
<td>7200 (5550–7350)</td>
<td>0.120</td>
</tr>
<tr>
<td>Platelet, ×10^9/mL, (median, IQR)</td>
<td>223,000 (181,000–249,000)</td>
<td>224,000 (186,000–470,000)</td>
<td>180,000 (180,000–224,000)</td>
<td>0.019</td>
</tr>
<tr>
<td>CRP, mg/mL, (median, IQR)</td>
<td>21.0 (3.40–54.0)</td>
<td>16.8 (3.33–47.7)</td>
<td>55.4 (45.3–80.2)</td>
<td>0.948</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL, (median, IQR)</td>
<td>0.0200 (0.0100–0.0300)</td>
<td>0.0200 (0.0100–0.0300)</td>
<td>0.0300 (0.0200–0.0300)</td>
<td>0.93</td>
</tr>
<tr>
<td>ALT, U/L, (median, IQR)</td>
<td>19.0 (14.0–28.0)</td>
<td>18.5 (14.0–27.5)</td>
<td>19.0 (16.0–33.5)</td>
<td>0.839</td>
</tr>
<tr>
<td>AST, U/L, (median, IQR)</td>
<td>27.0 (19.0–34.0)</td>
<td>26.5 (18.3–33.8)</td>
<td>27.0 (24.0–38.0)</td>
<td>0.799</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L, (median, IQR)</td>
<td>200 (150–220)</td>
<td>191 (150–212)</td>
<td>252 (228–260)</td>
<td>0.903</td>
</tr>
<tr>
<td>D-Dimer, ng/mL, (median, IQR)</td>
<td>1120 (540–2860)</td>
<td>1090 (526–2810)</td>
<td>2370 (1950–4230)</td>
<td>0.471</td>
</tr>
<tr>
<td>Blood urea nitrogen, mol/L, (median, IQR)</td>
<td>15.0 (14.0–18.0)</td>
<td>15.0 (14.0–17.5)</td>
<td>18.0 (16.5–21.0)</td>
<td>0.898</td>
</tr>
<tr>
<td>Albumin, g/dL, (median, IQR)</td>
<td>3.10 (2.73–3.14)</td>
<td>3.10 (2.74–3.14)</td>
<td>2.90 (2.00–3.00)</td>
<td>0.499</td>
</tr>
<tr>
<td>Creatinine, mg/dL, (median, IQR)</td>
<td>0.600 (0.510–0.800)</td>
<td>0.600 (0.503–0.700)</td>
<td>0.800 (0.700–1.41)</td>
<td>0.804</td>
</tr>
<tr>
<td>Ferritin, mg/L, (median, IQR)</td>
<td>55.0 (36.0–122)</td>
<td>51.4 (33.3–121)</td>
<td>70.0 (57.5–153)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gestational age at birth, weeks, (median, IQR)</td>
<td>38.0 (38.0–39.0)</td>
<td>38.0 (38.0–39.0)</td>
<td>38.0 (34.0–38.0)</td>
<td>0.793</td>
</tr>
<tr>
<td>Week between diagnosis and birth, (median, IQR)</td>
<td>5.00 (3.00–8.00)</td>
<td>5.50 (3.25–8.75)</td>
<td>3.00 (2.50–5.50)</td>
<td>0.478</td>
</tr>
<tr>
<td><strong>Delivery method</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section (C/s)</td>
<td>17 (47.2%)</td>
<td>15 (44.1%)</td>
<td>2 (66.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>18 (47.2%)</td>
<td>17 (50%)</td>
<td>1 (33.3%)</td>
<td>0.512</td>
</tr>
<tr>
<td>Abortion</td>
<td>2 (5.6%)</td>
<td>2 (5.9%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Indication for C/s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal distress</td>
<td>1 (5.9%)</td>
<td>1 (6.7%)</td>
<td>0 (0.0%)</td>
<td>0.515</td>
</tr>
<tr>
<td>Repeat C/s</td>
<td>12 (70.6%)</td>
<td>11 (73.3%)</td>
<td>1 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Cephalopelvic disproportion</td>
<td>3 (17.6%)</td>
<td>2 (13.3%)</td>
<td>1 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Labor arrest</td>
<td>1 (5.9%)</td>
<td>1 (6.7%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight &lt;2500 g</td>
<td>5 (13.5%)</td>
<td>4 (11.8%)</td>
<td>1 (33.3%)</td>
<td>0.171</td>
</tr>
<tr>
<td>Birth weight ≥2500 g</td>
<td>32 (86.5%)</td>
<td>30 (88.2%)</td>
<td>2 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight, g (mean, SD)</td>
<td>3148±428</td>
<td>3119±601</td>
<td>2543±748</td>
<td>0.059</td>
</tr>
<tr>
<td>APGAR score (median, IQR) 1-min</td>
<td>7 (7-7)</td>
<td>7 (7-7)</td>
<td>7 (7–7)</td>
<td>0.650</td>
</tr>
<tr>
<td>APGAR score (median, IQR) 5-min</td>
<td>8 (8-8)</td>
<td>8 (8-8)</td>
<td>8 (8–8)</td>
<td>0.556</td>
</tr>
<tr>
<td><strong>Neonatal morbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU admission</td>
<td>4 (11.8%)</td>
<td>3 (9.7%)</td>
<td>1 (33.3%)</td>
<td>0.783</td>
</tr>
<tr>
<td>RDS</td>
<td>3 (8.8%)</td>
<td>2 (6.5%)</td>
<td>1(33.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Meconium aspiration syndrome</td>
<td>1 (2.9%)</td>
<td>1 (3.2%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1 (2.7%)</td>
<td>1 (2.9%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Table 3. Clinical characteristics, laboratory findings, and gestational and neonatal outcomes of pregnant women infected with SARS-CoV-2 (according to the time of diagnosis).

<table>
<thead>
<tr>
<th></th>
<th>1st trimester (n=2)</th>
<th>2nd trimester (n=1)</th>
<th>3rd trimester (n=34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational week at diagnosis, (median, IQR)</strong></td>
<td>11.0 (10.5–11.5)</td>
<td>22.0 (22.0–22.0)</td>
<td>38.0 (38.0–39.0)</td>
<td>-</td>
</tr>
<tr>
<td>Single pregnancy</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>31 (91.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (8.8%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Duration of hospitalization, days (mean, SD)</strong></td>
<td>3.00±4.24</td>
<td>3.00±0.0</td>
<td>4.56±7.89</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Drug therapy - lopinavir</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>1 (50%)</td>
<td>1 (100%)</td>
<td>21 (61.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Loss of smell</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>6 (17.6%)</td>
<td>0.481</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>19 (55.9%)</td>
<td>0.511</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>6 (17.6%)</td>
<td>0.481</td>
</tr>
<tr>
<td>Malaise</td>
<td>1 (50.0%)</td>
<td>0 (0%)</td>
<td>6 (17.6%)</td>
<td>0.481</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>31 (91.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>33 (97.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Symptomatics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single symptom</td>
<td>1 (50%)</td>
<td>1 (100%)</td>
<td>14 (41.2%)</td>
<td>0.712</td>
</tr>
<tr>
<td>Multiple symptoms</td>
<td>1 (50.0%)</td>
<td>0 (0.0%)</td>
<td>20 (58.8%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood count, ×10^9/mL, (median, IQR)</td>
<td>4900 (4850–4950)</td>
<td>13,400 (13,400–13,400)</td>
<td>8400 (6730–10,500)</td>
<td>0.759</td>
</tr>
<tr>
<td>Lymphocyte, ×10^9/mL, (median, IQR)</td>
<td>500 (300–700)</td>
<td>1100 (1100–1100)</td>
<td>1300 (950–1680)</td>
<td>0.450</td>
</tr>
<tr>
<td>Neutrophil, ×10^9/mL, (median, IQR)</td>
<td>3600 (3550–3650)</td>
<td>11500 (11,500–11,500)</td>
<td>6550 (4580–7500)</td>
<td>0.859</td>
</tr>
<tr>
<td>Platelet, ×10^9/mL, (median, IQR)</td>
<td>213,000 (189,000–236,000)</td>
<td>87,000 (87,000–87,000)</td>
<td>224,000 (186,000–247,000)</td>
<td>0.748</td>
</tr>
<tr>
<td>CRP, mg/mL, (median, IQR)</td>
<td>26.8 (19.1–34.4)</td>
<td>31.2 (31.2–31.2)</td>
<td>19.8 (3.33–55.1)</td>
<td>0.327</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL, (median, IQR)</td>
<td>0.0150 (0.0125–0.0175)</td>
<td>0.0200 (0.0200–0.0200)</td>
<td>0.0200 (0.0100–0.0300)</td>
<td>0.472</td>
</tr>
<tr>
<td>ALT, U/L, (median, IQR)</td>
<td>17.5 (16.3–18.8)</td>
<td>26.0 (26.0–26.0)</td>
<td>18.5 (13.3–33.3)</td>
<td>0.931</td>
</tr>
<tr>
<td>AST, U/L, (median, IQR)</td>
<td>17.5 (16.3–18.8)</td>
<td>33.0 (33.0–33.0)</td>
<td>27.0 (19.0–34.0)</td>
<td>0.953</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L, (median, IQR)</td>
<td>174 (155–194)</td>
<td>210 (210–210)</td>
<td>198 (150–222)</td>
<td>0.223</td>
</tr>
<tr>
<td>D-Dimer, mg/mL, (median, IQR)</td>
<td>495 (473–518)</td>
<td>560 (560–560)</td>
<td>1330 (960–3170)</td>
<td>0.375</td>
</tr>
<tr>
<td>Blood urea nitrogen, mol/L, (median, IQR)</td>
<td>16.0 (15.0–17.0)</td>
<td>14.0 (14.0–14.0)</td>
<td>15.0 (14.0–18.0)</td>
<td>0.156</td>
</tr>
<tr>
<td>Albumin, g/dL, (median, IQR)</td>
<td>3.07 (3.05–3.08)</td>
<td>3.51 (3.51–3.51)</td>
<td>3.03 (2.72–3.13)</td>
<td>0.216</td>
</tr>
<tr>
<td>Creatinine, mg/dL, (median, IQR)</td>
<td>0.550 (0.525–0.575)</td>
<td>0.600 (0.600–0.600)</td>
<td>0.600 (0.518–0.800)</td>
<td>0.384</td>
</tr>
<tr>
<td>Ferritin, mL/ng, (median, IQR)</td>
<td>361 (293–428)</td>
<td>56.0 (56.0–56.0)</td>
<td>46.9 (33.3–114)</td>
<td>0.735</td>
</tr>
<tr>
<td>Week between diagnosis and birth, (median, IQR)</td>
<td>3.00 (2.50–3.50)</td>
<td>2.00 (2.00–2.00)</td>
<td>6.00 (3.25–8.75)</td>
<td>0.401</td>
</tr>
<tr>
<td><strong>Delivery method</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section (C/s)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>17 (50%)</td>
<td>0.615</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>17 (50%)</td>
<td>-</td>
</tr>
<tr>
<td>Abortion</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Indication for C/s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal distress</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5.9%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Repeat C/s</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>12 (70.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Cephalopelvic disproportion</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (17.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Labor arrest</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5.9%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Birth weight, g</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 g</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>2 (94.1%)</td>
<td>0.086</td>
</tr>
<tr>
<td>≥2500 g</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>32 (9.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Mean (SD), g</td>
<td>-</td>
<td>-</td>
<td>3148±428</td>
<td>-</td>
</tr>
<tr>
<td>APGAR score (median, IQR) 1-min</td>
<td>-</td>
<td>-</td>
<td>7 (7–7)</td>
<td>-</td>
</tr>
<tr>
<td>APGAR score (median, IQR) 5-min</td>
<td>-</td>
<td>-</td>
<td>8 (8–8)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Neonatal morbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU admission</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (11.7%)</td>
<td>-</td>
</tr>
<tr>
<td>RDS</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (8.8%)</td>
<td>-</td>
</tr>
<tr>
<td>Meconium aspiration syndrome</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
</tbody>
</table>
amniotic fluid and there was no neonatal death. One (2.7%) woman experienced stillbirth. All the live-born babies were tested negative for SARS-CoV-2 and none of the mothers needed intensive care unit admission. There was a positive correlation between the time of diagnosis and the time of birth. This correlation was more prominent in multiple pregnancies (Fig. 1).

**Discussion**

The present study is a descriptive study on both maternal and neonatal clinical features as well as outcomes of pregnancies complicated with SARS-CoV-2 infection. We found that the most common symptoms in our patient population were fever and cough. This finding is concordant with the findings of previous studies that found fever and cough as the most common symptoms in pregnant women having the diagnosis of COVID-19. But on the contrary, one study revealed that the majority of women were asymptomatic at presentation. As we did not perform routine screening for all the pregnant women except the ones who had signs and symptoms of SARS-CoV-2 infection or who were admitted to the hospital for a planned cesarean delivery, we could not diagnose most of the asymptomatic cases. We speculate that, in a cross-sectional study where all the pregnant women are screened at once in a population, different results regarding signs and symptoms would be observed.

In our study, the most common comorbidity in pregnant women with COVID-19 was gestational diabetes. 13.5% of the pregnant women with COVID-19 were associated with gestational diabetes. The International Diabetes Federation suggests that 1 in 6 (16.8%) preg-

![Fig. 1](image-url)
nancies are affected by diabetes. 13.6% of them are pregestational diabetes and 86.4% are gestational diabetes. Although the relationship between gestational diabetes and SARS-CoV-2 infection during pregnancy has been documented in many studies, SARS-CoV-2 infection did not increase the frequency of gestational diabetes in our cases and was consistent with the gestational diabetes prevalence rate in the literature.\(^\text{[21]}\) The majority of the pregnant women (40.5%) had a blood type of A (+) which was concordant with the general population (39%).\(^\text{[26]}\)

Previous studies showed that most of pregnant women with COVID-19 were diagnosed during the late second or third trimester of pregnancy.\(^\text{[19,26]}\) Besides, a prospective cohort study found that pregnant women hospitalized were in their third trimester of pregnancy.\(^\text{[25]}\) When we evaluated our findings according to the time of diagnosis, the majority of cases were diagnosed during the third trimester of pregnancy. This was partly attributed to the fact that most of the pregnant women in the early trimester remain undiagnosed as they may prefer not to search for medical assistance in case of minor signs of COVID-19. Moreover, some of the pregnant women were diagnosed by routine PCR testing just when they were admitted to the hospital for delivery. Cosma et al. recruited 138 pregnant women attending the first-trimester screening in Italy and found 10.1% of cumulative COVID-19 incidence during the first trimester with a high prevalence of asymptomatic patients (42.8%).\(^\text{[39]}\) Therefore, our study, as well as many other similar studies, most probably underestimate both the real incidence of SARS-CoV-2 infection in pregnancy and also the real distribution of COVID-19 incidence according to different trimesters of pregnancy.

In the present study, the pregnant women who had the diagnosis during the first trimester had slightly lower total lymphocyte values but this did not reach statistical significance. Pregnant women in the third trimester had higher values of CRP compared to other trimesters of pregnancy and those with multiple gestations also had higher values of CRP compared to the singleton pregnancies, none of which approached statistical significance. The same association was also observed for D-dimer values. Therefore, due to the hypercoagulable state in pregnancy, monitoring of D-dimer should be included in the management of pregnant women with COVID-19.\(^\text{[30]}\)

In our study, none of the women required intensive care unit or invasive mechanical ventilation and the majority had a mild form of COVID-19. This result was similar to the course of the disease in non-pregnant adults.\(^\text{[29]}\) Previous studies show similar results regarding intensive care unit admission and mortality rates for both pregnant women and the general population with COVID-19.\(^\text{[14,25]}\) In contrast, a systematic review of 108 cases of pregnancies complicated with confirmed SARS-CoV-2 infection reported the possibility of increased risk of severe disease among pregnant women.\(^\text{[10]}\) In our study, we found favorable outcomes for pregnant women with SARS-CoV-2 infection. Maternal mortalities have been rarely reported so far in the literature.\(^\text{[13]}\) D’Antonio et al. reported that the rate of critical care need in pregnant women over 35 years of age with SARS-CoV-2 infection was 7.7%.\(^\text{[31]}\) This difference in results is attributed to the variations in sample sizes and characteristics of different centers.

According to our results, 47.2% of neonates were delivered by cesarean section. These findings are similar to the findings of previous studies.\(^\text{[19]}\) Previous cesarean delivery was the most common cesarean indication (70.6%). Of our patients, which are unrelated and/or not specific to COVID-19 infection, only one mother underwent cesarean delivery because of fetal distress and one for labor arrest. Several studies reported that the majority of pregnant women delivered by cesarean section to prevent neonatal transmission of the virus.\(^\text{[1,17]}\) Pierce-Williams et al. revealed higher cesarean delivery rates for pregnant women with COVID-19 (53% for severe and 94% for critical cases) compared to the general pregnant population.\(^\text{[14]}\) Another review about the outcomes of COVID-19 disease in pregnancy showed that cesarean delivery rates are 80% in total in observational studies.\(^\text{[15]}\) Our study emphasized that maternal SARS-CoV-2 infection itself is not an absolute contraindication for vaginal delivery.

Among the neonates of 37 women with confirmed COVID-19 infection, none of them were diagnosed with SARS-CoV-2 infection. Even if there are studies with similar results, this does not support the findings of previous studies suggesting vertical and intrapartum transmission.\(^\text{[1,16]}\) On the other hand, a case report showed that virus-specific antibodies were detected in serum samples of some neonates born to pregnant
women with COVID-19, although SARS-CoV-2 infection was undetected by PCR tests. As IgM is known to be too large to cross the placenta, detection of IgM was interesting and this may imply the possible vertical transmission of SARS-CoV-2 infection from mother to fetus. However, in another study, transplacental passage of IgM was detected in cases of severe COVID-19. So, detection of IgM in neonates may not precisely mean that IgM in neonates was produced by fetuses after vertical transmission. It may also be transferred from the mother due to severe COVID-19.

In this study, 5.4% of pregnancies resulted in abortion, and 2.7% resulted in stillbirth. Although 10% of infants were hospitalized in the NICU, infant mortality was not observed. A multinational cohort study of all consecutive pregnant women with COVID-19 from 22 different countries and 73 centers analyzed 251 newborns born to women with SARS-CoV-2 infection and found the neonatal mortality rate 2%. A comprehensive meta-analysis by Allotey et al. reported that stillbirth incidence was 0.9%, NICU admission was 25.6% and neonatal death was 0.4%. In a systemic review in which nine studies and 92 cases were analyzed, Smith et al. declared that 76.9% of newborns born to mothers diagnosed with COVID-19 infection required admission to NICU. As most newborns are expected to be asymptomatic, this number may vary quite a lot according to the individual guidelines of each hospital. There still is not a universal consensus about how the newborn born from a SARS-CoV-2 infected or suspected mother should be followed up right after the delivery. In our hospital, newborns are admitted to an isolation room in NICU if they have any indication for hospitalization in level I-II or III NICU, and asymptomatic newborns are followed up in an isolated room in the Obstetrics ward with a healthy attendant. If the mother is asymptomatic, we also recommend placing the newborn at least 2 meters away from the mother with a barrier in between or in an incubator. If the mother is clinically symptomatic and there is no healthy attendant in the family, then the newborn is admitted to NICU as well. Neonates whose mothers have confirmed or suspected SARS-CoV-2 infection must be isolated and clinically monitored, but this does not necessarily require NICU admission. These newborns might be followed up in a single room without full NICU capabilities according to local settings.

The retrospective nature of the study design and small sample size are the main limitations of our study which limit the capability to generalize the results. Furthermore, only oropharyngeal and nasal swabs were collected for the detection of COVID-19 from newborns. Antibody testing for SARS-CoV-2 may prevent incorrect COVID-19 diagnoses. However, our study provides essential information about the prognosis of COVID-19 both for pregnant women and their fetuses.

Conclusion
Our study demonstrated that clinical and laboratory findings in pregnant women with COVID-19 are mild as non-pregnant women. Furthermore, we did not observe mother-to-fetus vertical transmission of SARS-CoV-2 infection, which was possible in several studies, in our patient population. This study may help healthcare professionals to better deal with the disease in this vulnerable population. Besides, it will also contribute to the continuous update in guidance for SARS-CoV-2-positive pregnant women and their neonates about complications of COVID-19 in pregnancy as well as the possibility of vertical transmission and perinatal complications.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

References


Assessment of the roles of ABO blood types and Rh factors in gestational diabetes mellitus

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Abstract

Objective: Gestational diabetes mellitus (GDM) is a leading cause of both maternal and neonatal morbidity and mortality, the frequency of which is increasing gradually because of the increasing age and obesity of the pregnant woman. The aim of the present study was to evaluate ABO blood types and Rh factors and their roles in GDM prevalence.

Methods: This retrospective study was conducted in the Obstetrics & Gynecology Clinic of Tuzla State Hospital. Between January 1, 2015 and May 1, 2021, 1017 pregnant women who were admitted to our clinic were evaluated according to the presence of GDM using the hospital database system. The ABO blood types and Rh factors were determined in all patients and GDM prevalence was compared among the groups.

Results: The 1017 pregnant women had single- and double-step oral glucose tolerance tests and the ABO blood type results were included in the study. Of the 1017 women, 241 (23.70%) had GDM and 776 (76.30%) were normal. The mean maternal age of the group with GDM was 30.9±4.8 years and it was 27.8±5.4 years in the normal group, which was a statistically significant difference (p<0.001). Of the 1017 pregnant women, 474 (46.61%), 162 (15.93%), 316 (31.07%), and 65 (6.39%) had the blood types A, B, 0, and AB, respectively, with no difference observed among them in terms of the presence of GDM (p=0.592). There were 886 (87.12%) pregnant women in the Rh(+) group and 131 (12.88%) in the Rh(-) group; the groups were similar in terms of the presence of GDM (p=0.503).

Conclusion: Our results indicated that ABO blood types and Rh factors were not risk factors for GDM.

Keywords: ABO blood groups, Rh factors, gestational diabetes mellitus, GDM prevalence.

Introduction

Gestational diabetes mellitus (GDM) is a leading cause of both maternal and neonatal morbidity and mortality, the frequency of which is increasing gradually because of the increasing age and obesity of the pregnant women, which complicates ~10–15% of all pregnancies.[1,2] It is well documented that GDM is associated with preeclampsia, fetal anomaly, macrosomia, fetal death, and increased cesarean delivery rates, and it is a risk for the development of DM during the postpartum period.[3]

The presence of A and B antigens determine the ABO blood types.[4] The results of studies showed the association between ABO blood types and infections, cancer, cardiovascular diseases, and nervous system diseases; however, a potential relationship between ABO blood types and negative perinatal outcomes are controversial.[5-9] ABO antigens are responsible for the regulation of factors such as tumor necrosis factor (TNF)-alpha E-selectin, sICAM-1, P-selectin, and interleukin (IL)-6 that cause type 2 DM.[10] In some studies, the ABO blood types were observed to be a protective factor for GDM; however, it was observed to be a risk factor in others, and some reports reported that there is no association between GDM and blood types.[11-15] The

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ORCID ID: M. M. Kirlangıç 0000-0002-9750-1594; M. Eraslan Şahin 0000-0001-6484-9132
The purpose of the current study was to evaluate the roles of ABO blood types and Rh factors in GDM prevalence.

**Methods**

In this retrospective study, we evaluated 1017 pregnant women who underwent single- and double-step oral glucose tolerance tests (OGTTs) during the 24–28 weeks of follow-up at the Obstetrics & Gynecology Clinic of Tuzla State Hospital between January 1, 2015 and May 1, 2021, using data from the hospital database. The study was approved by the Ethics Committee of the Faculty of Medicine of Marmara University (decision no: 09.2021.872) and was conducted in accordance with the Declaration of Helsinki.

GDM was screened using a single-step (75-g OGTT) or double-step (50- to 100-g OGTT) test at 24–28 weeks of gestation. For single step screening, the patients screened at 24–28 weeks of gestation using the single-step 75-g oral glucose tolerance test (OGTT) according to the criteria of the International Association of Diabetes and Pregnancy Study Group (IADPSG) were analyzed. One or more higher values in the patients who underwent the 75-g OGTT test (i.e., fasting ≥92 mg/dL, first hour ≥180 mg/dL, and second hour ≥153 mg/dL) were considered to be GDM.

For double-step screening, a 3-h diagnostic test was conducted using a 100-g OGTT in patients with glucose >140 mg/dL. Two or more higher values in the patients who underwent a 100-g OGTT test (e.g., fasting ≥95 mg/dL, first hour ≥180 mg/dL, second hour ≥155 mg/dL, third hour ≥140 mg/dL) were considered to be GDM. ABO blood types and Rh factors were also recorded from the hospital database for each pregnant woman. The women were compared according to these blood types and factors for GDM and other demographic characteristics.

**Statistical analyses**

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they are normally distributed or not. Descriptive analyses were presented using means and standard deviations for normally distributed variables. The Pearson’s chi-squared test or Fisher’s exact test was used to compare the groups. One-way ANOVA was used to compare parameters among the blood groups. Levene test was used to assess the homogeneity variances. An overall p-value of less than 0.05 was considered statistically significant.

**Results**

We evaluated 1017 pregnant women in the present study. GDM was diagnosed in 241 (23.70%) of these women; 776 (76.30%) of them were considered normal. Of the 1017 pregnant women, 474 (46.61%) had blood type A, 162 (15.93%) had blood type B, 316 (31.07%) had blood type 0, and 65 (6.39%) had blood type AB. There were 886 (87.12%) pregnant women with Rh(+) factor and 131 (12.88%) pregnant women with Rh(-) factor.

For maternal characteristics and GDM prevalence, ABO blood types and Rh factors were also recorded from the hospital database for each pregnant woman. The women were compared according to these characteristics and GDM prevalence.

**Table 1.** Comparison of ABO blood types with maternal characteristics and GDM prevalence.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>A (n=474)</th>
<th>B (n=162)</th>
<th>0 (n=316)</th>
<th>AB (n=65)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>28.66±6.83</td>
<td>27.95±4.76</td>
<td>29.03±6.32</td>
<td>28.97±5.61</td>
<td>0.358</td>
</tr>
<tr>
<td>BMI at screening, kg/m²</td>
<td>26.85±6.84</td>
<td>27.01±3.15</td>
<td>26.98±4.31</td>
<td>27.96±5.01</td>
<td>0.754</td>
</tr>
<tr>
<td>Nulliparity, n (%)</td>
<td>154 (32.49)</td>
<td>51 (31.48)</td>
<td>98 (31.01)</td>
<td>23 (35.38)</td>
<td>0.741</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>449 (94.73)</td>
<td>153 (94.44)</td>
<td>299 (94.62)</td>
<td>61 (93.85)</td>
<td>0.888</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>43 (9.07)</td>
<td>11 (6.79)</td>
<td>34 (10.76)</td>
<td>8 (12.31)</td>
<td>0.735</td>
</tr>
<tr>
<td>Personal or family history of diabetes, n (%)</td>
<td>25 (5.24)</td>
<td>10 (6.17)</td>
<td>19 (6.01)</td>
<td>8 (12.31)</td>
<td>0.658</td>
</tr>
<tr>
<td>GDM prevalence, n (%)</td>
<td>116 (11.41)</td>
<td>40 (3.93)</td>
<td>67 (6.59)</td>
<td>18 (1.77)</td>
<td>0.592</td>
</tr>
</tbody>
</table>

BMI: body mass index; GDM: gestational diabetes mellitus.
GDM was detected in 116 (11.41%), 40 (3.93%), 67 (6.59%), and 18 (1.77%) patients in blood type groups A, B, 0, and AB, respectively. A positive GDM test result was observed to be similar among the blood types (p=0.592).

A comparison between the Rh factors and maternal characteristics and GDM prevalence is shown in Table 2. Maternal age, nulliparity, BMI at screening, personal or family history of diabetes, smoking, and ethnicity were observed to be similar among the groups (p=0.800, p=0.711, p=0.745, p=0.314, p=0.668, and p=0.689, respectively). Of the 1017 pregnant women, 886 (87.12%) had the Rh(+) factor and 131 (12.88%) had the Rh(-) factor. Of these, 213 (20.94%) with Rh(+) and 28 (2.75%) with Rh(-) factor had GDM, and GDM prevalence was similar between the groups (p=0.503).

A comparison among the ABO blood types with the Rh factor subgroups and the maternal characteristics and GDM prevalence is provided in Table 3. When we subclassified the women into subgroups A Rh(+), A Rh(-), B Rh(+), B Rh(-), 0 Rh(+), 0 Rh(-), AB Rh(+), and AB Rh(-), 100 (9.83%), 16 (1.57%), 33 (3.24%), 7 (0.68%), 63 (6.19%), 4 (0.39%), 17 (1.67%), and 1 (0.09%), respectively, were identified and no statistical difference was observed among the groups based on the presence of GDM (p=0.691).

**Discussion**

The aim of the present study was to evaluate the ABO blood types and Rh factors and their roles in GDM. The key findings were as follows: (i) GDM was diagnosed in 241 (23.70%) of the pregnant women, (ii) ABO blood types were not risk factors for GDM, and (iii) Rh factors were not risk factors for GDM.

Although the underlying mechanism has not been fully elucidated, recent studies on the genome-wide association between ABO blood types and various diseases have reported that genetic variation in the ABO locus is related with sE-selectin, ICAM-1, P-selectin, associated with type 2 diabetes and hypertension.\[^{[19–21]}\]

From their genome-wide association study, Qui et al.\[^{[19]}\] declared that the ABO locus is a critical determinant

### Table 2. Comparison of Rh blood factors with maternal characteristics and GDM prevalence.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rh(+) (n=886)</th>
<th>Rh(-) (n=131)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>28.65±6.27</td>
<td>28.79±5.16</td>
<td>0.800</td>
</tr>
<tr>
<td>BMI at screening, kg/m²</td>
<td>26.88±5.66</td>
<td>27.33±4.48</td>
<td>0.745</td>
</tr>
<tr>
<td>Nulliparity, n (%)</td>
<td>280 (31.60)</td>
<td>45 (34.35)</td>
<td>0.711</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>784 (88.49)</td>
<td>117 (89.31)</td>
<td>0.689</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>75 (8.47)</td>
<td>14 (10.71)</td>
<td>0.668</td>
</tr>
<tr>
<td>Personal or family history of diabetes, n (%)</td>
<td>43 (5.32)</td>
<td>12 (9.16)</td>
<td>0.314</td>
</tr>
<tr>
<td>GDM prevalence, n (%)</td>
<td>213 (20.94)</td>
<td>28 (2.75)</td>
<td>0.503</td>
</tr>
</tbody>
</table>

BMI: body mass index; GDM: gestational diabetes mellitus.

### Table 3. Comparison of ABO blood types and Rh factor subgroups with maternal characteristics and GDM prevalence.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>A Rh(+) (n=411)</th>
<th>A Rh(-) (n=63)</th>
<th>B Rh(+) (n=135)</th>
<th>B Rh(-) (n=27)</th>
<th>O Rh(+) (n=278)</th>
<th>O Rh(-) (n=38)</th>
<th>AB Rh(+) (n=62)</th>
<th>AB Rh(-) (n=3)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>26.85±8.2</td>
<td>27.71±4.7</td>
<td>26.87±4.7</td>
<td>28.99±4.9</td>
<td>28.99±5.4</td>
<td>28.85±6.3</td>
<td>32.67±1.5</td>
<td>0.576</td>
<td></td>
</tr>
<tr>
<td>BMI at screening, kg/m²</td>
<td>26.85±8.2</td>
<td>27.42±3.4</td>
<td>26.87±4.7</td>
<td>28.85±6.3</td>
<td>28.85±6.3</td>
<td>32.67±1.5</td>
<td>0.687</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparity, n (%)</td>
<td>391 (95)</td>
<td>58 (92)</td>
<td>128 (95)</td>
<td>25 (93)</td>
<td>265 (95.5)</td>
<td>34 (90)</td>
<td>3 (100)</td>
<td>0.758</td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>38 (9)</td>
<td>5 (8)</td>
<td>8 (6)</td>
<td>3 (11)</td>
<td>29 (10)</td>
<td>5 (13)</td>
<td>7 (11)</td>
<td>0.645</td>
<td></td>
</tr>
<tr>
<td>Personal or family history of diabetes, n (%)</td>
<td>21 (5)</td>
<td>4 (6)</td>
<td>7 (5)</td>
<td>3 (11)</td>
<td>15 (0.05)</td>
<td>4 (11)</td>
<td>7 (11)</td>
<td>0.495</td>
<td></td>
</tr>
<tr>
<td>GDM prevalence, n (%)</td>
<td>100 (24.3)</td>
<td>16 (25.4)</td>
<td>33 (24.4)</td>
<td>7 (25.9)</td>
<td>63 (22.66)</td>
<td>4 (10.5)</td>
<td>17 (27.4)</td>
<td>0.691</td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; GDM: gestational diabetes mellitus.
for plasma sE-selectin levels and the genetic-inferred ABO blood types are related with the risk of type 2 diabetes. They also showed that the blood type B is associated with a lesser risk than the blood type O. In their high-resolution genome-wide association study of serum sE-selectin patients with type 1 diabetes, Paterson et al. identified the major loci influencing levels. They observed highly significant evidence for an association \((p=10^{-12})\) with rs579459 near the ABO blood type gene, which accounts for 19% of the variance in E-selectin levels and stated that ABO is an important locus for serum sE-selectin levels.

The results of the present study indicated that ABO blood types and Rh factors were not risk factors for GDM. The results of recent studies that have investigated a possible relationship between ABO blood types and GDM risk have been variable, inconsistent, and different from one region to another. In their study on Iranian pregnant women, Seyfizadeh et al. reported that those with blood type AB have higher blood glucose than those with blood type A during their second trimester. In their study, Karagöz et al. evaluated 233 Turkish pregnant women who were diagnosed with GDM and found a significant difference among the women with GDM and control groups by the distribution of ABO blood types. In that study, there was an increased percentage of blood type AB in women with GDM than in the control group. When the women were compared according to the DM, the ratio of those with blood type O was higher than that of other blood types, while the ratio of those with blood type B was lower. A comparison of ABO blood types and Rh factors found a significant difference in the ratio of those who develop DM, which is higher in patients with Rh(+) factor among all, except blood type B. The authors suggested that pregnant women with blood type AB have an increased risk of GDM, which indicates that clinicians must ensure that those women are followed up.

Similarly, Shimodaira et al. suggested that Japanese pregnant women with blood type AB are at risk for GDM; however, Zhang et al. reported that women with blood type A, B, or O (i.e., non-AB) have an higher risk of developing GDM than those with blood type AB. Sensitivity analyses showed that their results were consistent using criteria from the World Health Organization. The adjusted OR comparing those with non-AB blood types with those with blood type AB for the development of GDM was occurred among women with a family history of diabetes (OR: 2.69; CI: 1.21–5.96) and attenuated among those without it (OR: 1.33; CI: 1.03–1.71). The authors declared that blood type AB is a protective factor against GDM in Chinese pregnant women. The study by Fagherrazzi et al. on the association between blood types and type 2 DM showed that specific ABO blood types are related with a risk of the disease, and that those with blood type O have the lowest risk of occurring type 2 DM. The results of their study also indicated that those with blood types A Rh(+), A Rh(-), B Rh(+), and AB Rh(+) have a higher risk of type 2 DM than those with blood type O; however, the difference among all the of results of these studies were interpreted in another study as being the difference between a diversity of races, ethnic origins, and socioeconomic groups.

**Study limitations**

There were some strengths and limitations to the present study. First, the retrospective design of the study and the fact that GDM screening was conducted using both single- and double-step OGTTs (although both are recommended and accepted methods in screening) can be suggested to be important study limitations. Second, the large sample size and family history, BMI at the time of screening, smoking, gravida, and parity information enabled us to analyze these variables as risk factors; however, because the study was conducted at a single center, it is not appropriate to compared the results for the entire Turkish population, and it is well known that the prevalence of GDM varies among different regions of Turkey. Third, our study also suffers from the common problems with retrospective studies in that there was a lack of data, and the reliability of the results are associated with classification bias. Different results have been produced from different studies; therefore, we suggest that generalizations cannot be made on diseases by selecting a specific sample because these different studies were not screened as a whole.

**Conclusion**

Our results indicated that ABO blood types and Rh factors are not risk factors for GDM. Additional studies with predetermined subclasses within specific populations would help to demonstrate whether blood types, including the Rh factors, are risk factors for GDM within the current population or not.
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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

References

Prenatal attachment in the pregnancy: its relationship with fear of childbirth

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Abstract

Objective: The aim of this study was to determine the level of prenatal attachment of pregnant women and its relationship with fear of childbirth.

Methods: This descriptive and cross-sectional study was conducted with a total of 125 pregnant women who applied to outpatient obstetric unit of a training and research hospital in Ankara between September 2019 and March 2020. The data were collected using the “Participant Information Form”, “Wijma Delivery Expectation Questionnaire Version A (W-DEQ A)” and “Prenatal Attachment Inventory (PAI)”.

Results: The average PAI score of pregnant women is 67.19±9.56. It was found that there was a significant relationship between the education level of pregnant women and the average PAI score (p=0.002). There was no significant difference between the gestational age, income level, education level, working status, obstetric characteristics of pregnant women, and average PAI score (p>0.05). A negative, weak, and significant relationship was found between W-DEQ A and PAI scores (r=-0.183, p=0.041). According to the linear regression model, it was found that the age, duration of the marriage, and fear of childbirth of pregnant women had a significant effect on the total score of PAI (p=0.001, p=0.018, p=0.019, respectively).

Conclusion: The high fear of childbirth, young age and short marriage time may decrease prenatal attachment. As the fear of childbirth of pregnant women increases, the level of prenatal attachment decreases.

Keywords: Pregnancy, prenatal attachment, fear of childbirth.

Introduction

Pregnancy and childbirth are defined as the transitional stage of an existential process that women of reproductive age have to go through. The expectations and experiences of women regarding childbirth can be experienced as positive and negative at the same time and can be seen as happiness, faith, anxiety or fear.

According to the attachment theory first put forward by John Bowlby in the early 1960s, an adult willing to take care of and protect themselves is essential for newborn babies to maintain their lives. Attachment bond, which takes shape at an early stage of life and is assumed to be continuous throughout life, is a conceptualized phenomenon that shapes the pattern of individuals forming relationships with other people.

Prenatal attachment is the bond between parents and their babies during the prenatal period. It is suggested that mother-infant bonding during pregnancy can be seen as an emotional bond that has similarities with attachment but is not the same as traditional infant-adult bonding. The prenatal attachment consists of three essential components: cognitive (the ability to accept the fetus as a person and give it personality), emotional (the empathic bond established with the fetus), and behavioral (interaction and role-playing with the fetus). Prenatal attachment is crucial since it is the first cognitive, emotional, and behavioral relationship between the mother and fetus. Feelings related to attachment begin to be observed from the first trimester of pregnancy, increase with the progression

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ORCID ID: M. Uğurlu 0000-0002-9183-219X; Z. Çoban 0000-0002-8393-5332
of pregnancy and intensify, especially in the last trimester.\textsuperscript{9–12}

It is reported that the concept of prenatal attachment introduced by Rubin, a nurse, is also a strong predictor of postpartum mother-baby attachment today.\textsuperscript{8,9,13} Many studies have investigated factors contributing to and preventing prenatal attachment. It has been determined that some psychosocial variables such as socio-demographic characteristics of individuals, risky situations related to pregnancy, obstetric characteristics, anxiety, depression, and fear of childbirth may be related to prenatal attachment.\textsuperscript{9,11,13,14} It is stated that the fear of childbirth is experienced for various reasons such as pain during childbirth, the thought that harm may occur to the baby or herself, or the risk of losing control also affects the prenatal attachment of pregnant women.\textsuperscript{8,13,15}

Strong prenatal attachment during pregnancy is vital for maternal and infant health. While a positive prenatal attachment facilitates psychological adaptation to the parenting role during pregnancy, excessive stress, inability to adapt to the motherhood role, and difficulties that harm the mother and her health during childbirth can lead to poor prenatal attachment.\textsuperscript{8,11}

Nurses’ and midwives’ ability to manage the caring process by identifying prenatal attachment between mother and fetus and situations that may affect it can positively contribute to increasing the attachment levels of pregnant women by making appropriate interventions for women at risk of weak attachment. Of the healthcare professionals, nurses and midwives are the closest ones to women during the pregnancy and postpartum periods, and they are the most important sources of support for pregnant women. In this context, this study has been planned to evaluate prenatal attachment and the factors affecting prenatal attachment in pregnancy, develop recommendations for providing the necessary support to pregnant women with weak attachment, and provide educational counseling services.

**Methods**

Our study’s sample, which is planned in descriptive and cross-sectional type, consists of 125 pregnant women who applied to outpatient obstetric unit of a training and research hospital in Ankara. Research data were collected between September 2019 and March 2020. The study inclusion criteria were the women over 18 who are literate in Turkish, those willing to participate in the study, and the exclusion criteria were multiple pregnancies, risky pregnancies and the women diagnosed with a psychiatric illness.

Three questionnaires were used for data collection: Participant Information Form (PIF), Wijma Delivery Expectation Questionnaire version A (W-DEQ A) and Prenatal Attachment Inventory (PAI). PIF consists of 16 questions including pregnant women’s socio-demographic characteristics (age, income level, education level, family type, employment status, chronic disease) and obstetric characteristics (week of gestation, pregnancy planning status, regular antenatal follow-up, participation in training about birth and pregnancy, number of pregnancies, experiencing dilation/curettage, type of delivery in a previous pregnancy, having problems in a previous pregnancy, planned delivery type).

W-DEQ A is a standard form to assess fear of childbirth during pregnancy.\textsuperscript{16} The scale consists of 33 items in 6-point Likert type, each of which is answered between 0 “extremely” and 5 “not at all”. The total score obtained from the scale varies between 0 and 165. Some items on the scale (2, 3, 6–8, 11, 12, 15, 19, 20, 24, 25, 27, 31) are scored inversely. The scores obtained from the scale below 37 indicate low-level fear, 38–65 points indicate medium-level fear, 66–84 points indicate high-level fear and >85 points indicate clinical-level fear. The Turkish validity and reliability study of the scale was conducted by Korukcu et al. in 2012.\textsuperscript{17}

PAI was developed by Muller and Mercer, to explain the thoughts, feelings, and situations experienced by women during pregnancy and determine the level of attachment to the baby during the prenatal period.\textsuperscript{18} The scale consists of 21 items in 4-point Likert type, each of which is answered between 1 “sometimes” and 4 “always”. The total score obtained from the scale varies between 21 and 84. Yılmaz and Beji conducted the Turkish validity and reliability study of the scale in 2013.\textsuperscript{7}

The ethical approval of the study was obtained from the Ethics Committee of the University of Health Sciences for Non-Interventional Research (Ethics Committee protocol code: 25.09.2019-19/295). The study was conducted in accordance with the Helsinki declaration. The participants were informed about the purpose of the study and informed that personal information would be kept confidential and used only for research. Then, the consents were obtained from the women who volunteered to participate in the study and were included in the sample. Data collection forms were
distributed to the women, and they were asked to fill them out. It took an average of 15–20 minutes for the participants to complete the data collection forms.

The data were analyzed with SPSS 20.0 package program (IBM SPSS Statistics for Windows, Armonk, NY, USA). Number, percentage, mean, standard deviation, minimum, and maximum values were used for descriptive statistics. The Kolmogorov-Smirnov test was used to evaluate the suitability of the data for normal distribution. In comparing PAI score averages according to pregnant women’s descriptive and obstetric characteristics, two independent sample T-tests and one-way ANOVA test were used for the normally distributed data. Pearson’s correlation test was used to compare the scale scores. Multiple linear regression analysis evaluated the effect of independent variables on the PAI score average. In order to include variables in the model, the enter model was used. The level of error for all analyses was determined 0.05.

Results

First, the demographic data of the study are presented. The mean age of the pregnant women was 28.20±70 years, and the mean gestational age was 31.51±22 weeks. 51.2% of women are at the undergraduate and higher education level, 56.8% are not working, and 68.8% have an income equivalent to expenses. 86.4% of women stated that they had a planned pregnancy, 80% participated in regular antenatal follow-up, 48.8% participated education about pregnancy and childbirth, and 68% stated that the planned mode of delivery was a vaginal birth. 37.6% of women were primigravida, and 62.4% were multigravida.

It was found that there was no statistically significant difference between the PAI score averages of pregnant women according to gestational age, income level, family type, working status, and chronic disease status (p>0.05). It was found that there was a statistically significant difference between the education level of the participants and the PAI score averages (p=0.002). After further analysis, it was found that those at the undergraduate and higher education level score the highest in PAI; and those who are literate score the lowest; the difference between the average scores is due to these groups (Table 1).

Table 2 shows the distribution of PAI score averages according to some obstetric characteristics of pregnant

<table>
<thead>
<tr>
<th>Table 1. Comparison of the pregnant women’s mean scores of PAI according to socio-demographic characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week of gestation</strong></td>
</tr>
<tr>
<td>20–28</td>
</tr>
<tr>
<td>≥29</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td><strong>Income level</strong></td>
</tr>
<tr>
<td>Income less than expenses</td>
</tr>
<tr>
<td>Income equivalent to expense</td>
</tr>
<tr>
<td>Income more than expenses</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td><strong>Education level</strong></td>
</tr>
<tr>
<td>Elementary school</td>
</tr>
<tr>
<td>High school</td>
</tr>
<tr>
<td>Undergraduate and masterz</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td><strong>Family type</strong></td>
</tr>
<tr>
<td>Nuclear</td>
</tr>
<tr>
<td>Extended</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td><strong>Working status</strong></td>
</tr>
<tr>
<td>Working</td>
</tr>
<tr>
<td>Not working</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td><strong>Chronic disease</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
</tr>
</tbody>
</table>

*Student’s t-test. †ANOVA. ‡p<0.050. ANOVA: analysis of variance. x-z: there is no difference between groups with the same letter (Tukey HSD).
women. It was found that there was no statistically significant difference between the obstetric characteristics of pregnant women and the PAI score averages (p<0.05) (Table 2).

The data of fear of childbirth at clinical level according to subgroups are reflected in Fig. 1. It was found that the mean W-DEQ-A score of pregnant women was 52.01±22.32, and the mean PAI score was 67.19±9.56. It was found that there was a negative significant relationship between the mean W-DEQ-A score and the mean PAI score of pregnant women (r=−0.183; p=0.041). Accordingly, prenatal attachment levels decrease as the fear of childbirth of pregnant women increases (Table 3).

The effects of age, gestational age, educational status, working status, income level, marriage period, regular antenatal check-up, participation in birth preparation training, planned pregnancy status, dilation & curettage (D&C) history, currently having problems

### Table 2. Comparison of the pregnant women’s mean scores of PAI according to obstetrics characteristics.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>PAI score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>108</td>
<td>86.4</td>
<td>67.50±9.25</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>13.6</td>
<td>65.23±11.50</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.366*</td>
</tr>
<tr>
<td>Regular antenatal follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>80.0</td>
<td>67.39±9.68</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>20.0</td>
<td>66.38±9.25</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.636*</td>
</tr>
<tr>
<td>Education about pregnancy and childbirth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61</td>
<td>48.8</td>
<td>67.37±9.84</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>51.2</td>
<td>67.00±9.34</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.833*</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>37.6</td>
<td>67.75±9.62</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>36.8</td>
<td>66.93±9.84</td>
</tr>
<tr>
<td>≥3</td>
<td>32</td>
<td>25.6</td>
<td>66.75±9.33</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.879†</td>
</tr>
<tr>
<td>D&amp;C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34</td>
<td>27.2</td>
<td>66.97±8.77</td>
</tr>
<tr>
<td>No</td>
<td>91</td>
<td>72.8</td>
<td>67.27±9.89</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.874*</td>
</tr>
<tr>
<td>Type of previous delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>43</td>
<td>64.2</td>
<td>6.23±9.54</td>
</tr>
<tr>
<td>C/S</td>
<td>24</td>
<td>35.8</td>
<td>69.79±9.14</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.061*</td>
</tr>
<tr>
<td>Problem in previous pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
<td>18.0</td>
<td>66.50±11.16</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>82.0</td>
<td>66.84±9.38</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.905*</td>
</tr>
<tr>
<td>Planned mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>85</td>
<td>68.0</td>
<td>67.10±9.72</td>
</tr>
<tr>
<td>C/S</td>
<td>40</td>
<td>32.0</td>
<td>67.37±9.35</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td>0.886*</td>
</tr>
</tbody>
</table>

*Student’s t-test. †ANOVA. ANOVA: analysis of variance; C/S: cesarean section; D&C: dilatation & curettage.

### Table 3. The correlation between W-DEQ-A and PAI scores.

<table>
<thead>
<tr>
<th></th>
<th>Min–max</th>
<th>Mean±SD</th>
<th>Correlation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>W-DEQ-A-total</td>
<td>0–165</td>
<td>52.01±22.32</td>
<td>r=−0.183</td>
</tr>
<tr>
<td>PAI-total</td>
<td>21–84</td>
<td>67.19±9.56</td>
<td>p=0.041</td>
</tr>
</tbody>
</table>

The bold values represent the p<0.05, and show that the item has statistical difference. *Pearson’s correlation coefficient was used to analyze the relationship of two quantitative variables in data with normal distribution.
with pregnancy, and W-DEQ A total score variables on the total score of PAI were examined in the multiple linear regression analysis applied in our study. As a result, it was found that age, duration of the marriage, and fear of childbirth had a significant effect on the total score of PAI (p=0.001, p=0.018, p=0.019, respectively). According to the model, when there is one unit decrease in age, there will be an increase of 0.728 in the pregnant woman’s score. It was determined that when there is an increase of one unit in the marriage period, there will be an increase of 2.612 in the pregnant woman’s score. When there is one unit decrease in fear of childbirth, there will be an increase of 0.097 in the pregnant woman’s score. The model describes 13.3% of the PAI score of pregnant women (Table 4).

**Discussion**

This study is planned to determine the factors affecting prenatal attachment during pregnancy, evaluate the relationship between prenatal attachment and fear of childbirth, and develop recommendations for positive supporting the attachment of pregnant women in the prenatal period.

Our study determined that the prenatal attachment level of pregnant women was high (67.19±9.56). When the literature is examined, prenatal attachment levels are at a good level,[5,11,19–21] but they are at a lower level than our findings. In our study, we can say that the prenatal attachment levels of pregnant women are high. This may be because the number of pregnant women

---

**Table 4.** Multiple linear regression analysis results on the factors affecting the PAI total score.

<table>
<thead>
<tr>
<th>B (95% CI)</th>
<th>Beta</th>
<th>t</th>
<th>p</th>
<th>Zero-order</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>76.552 (64.543–88.561)</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.728 (-1.15–−0.306)</td>
<td>-0.434</td>
<td>-3.421</td>
<td>0.001*</td>
<td>-0.158</td>
</tr>
<tr>
<td>&gt;29 weeks of gestation</td>
<td>-0.445 (-4.076–3.186)</td>
<td>-0.021</td>
<td>-0.243</td>
<td>0.809</td>
<td>-0.027</td>
</tr>
<tr>
<td>Graduate university degree</td>
<td>2.168 (-3.036–7.371)</td>
<td>0.076</td>
<td>0.825</td>
<td>0.411</td>
<td>0.027</td>
</tr>
<tr>
<td>Income equal to expenses</td>
<td>0.482 (-4.254–5.218)</td>
<td>0.023</td>
<td>0.202</td>
<td>0.841</td>
<td>0.002</td>
</tr>
<tr>
<td>Income more than expenses</td>
<td>1.32 (-5.435–8.074)</td>
<td>0.047</td>
<td>0.387</td>
<td>0.699</td>
<td>0.021</td>
</tr>
<tr>
<td>To be working</td>
<td>0.878 (-3.25–5.007)</td>
<td>0.046</td>
<td>0.422</td>
<td>0.674</td>
<td>0.036</td>
</tr>
<tr>
<td>Marriage time</td>
<td>2.612 (0.457–4.766)</td>
<td>0.307</td>
<td>2.402</td>
<td>0.018†</td>
<td>-0.005</td>
</tr>
<tr>
<td>Regular antenatal follow-up</td>
<td>-0.882 (-5.623–3.86)</td>
<td>-0.037</td>
<td>-0.368</td>
<td>0.713</td>
<td>0.043</td>
</tr>
<tr>
<td>Education about pregnancy and childbirth</td>
<td>-1.2 (-4.859–2.458)</td>
<td>-0.063</td>
<td>-0.650</td>
<td>0.517</td>
<td>0.019</td>
</tr>
<tr>
<td>D&amp;C</td>
<td>-0.311 (-4.102–3.481)</td>
<td>-0.015</td>
<td>-0.162</td>
<td>0.871</td>
<td>-0.014</td>
</tr>
<tr>
<td>W-DEQ A total</td>
<td>-0.097 (-0.178–−0.016)</td>
<td>-0.227</td>
<td>-2.371</td>
<td>0.019†</td>
<td>-0.183</td>
</tr>
</tbody>
</table>

*p<0.001; †p<0.05. B: non-standardized coefficient; Beta: standardized coefficient; f=2.463, p=0.006, Adj.R²=0.133, SE=8.909; D&C: dilatation and curettage.
who have a high fear of childbirth and a low clinical level in our study is low.

In our study, a significant relationship was found between the level of education and the average prenatal attachment score in pregnant women. Pregnant women with a high level of education have a higher average prenatal attachment score. Yilmaz and Beji[22] and Tuncel and Sut[23] have obtained similar results to our findings in their studies. Camarneiro and Justo[6] reported that the quality of attachment in pregnant women did not change according to age, while Yarzheski[24] stated that the level of education had a low effect on maternal-fetal attachment. Elkin[10] also found that educational status had no effect on prenatal attachment. In order to obtain accurate information about the effect of education on prenatal attachment, it is recommended to conduct studies with a high level of evidence.

There was no significant difference between the income level of pregnant women, family type, working status, chronic disease situation, and prenatal attachment. Similarly, it has been determined that there is no difference between family type[10,22] and economic status[22] and prenatal attachment levels of pregnant women in the literature. Differently, Yilmaz and Beji[22] determined that prenatal attachment decreased in pregnant women who did not work, while Tuncel and Sut[23] determined that prenatal attachment decreased in pregnant women who worked. In addition, Elkin[10] found that prenatal attachment was significantly higher in pregnant women whose income was higher than their expenses. A meta-analysis study found that the effect of age and income on maternal-fetal attachment was low.[24]

In the study, there was no difference between the participants’ pregnancy week, pregnancy planning status, regular antenatal follow-up, participation in pregnancy and birth-related education, number of pregnancies, previous delivery, D&C history, and prenatal attachment levels according to the planned delivery type. Similar to our findings, there was no relationship between prenatal attachment and voluntary pregnancies,[10,25] number of pregnancies,[10,22] weeks of gestation,[11] and miscarriage[13] in the literature. However, unlike our findings, there are also studies indicating the prenatal attachment level of those planning a pregnancy[12,22] and primiparas[11,22,26] are higher. On the other hand, Tuncel and Sut[23] and Elkin[10] stated that prenatal attachment increases in pregnant women as the week of gestation increases. According to these findings, socio-demographic and obstetric characteristics affect prenatal attachment, but they vary. It is thought that these changes may be because the studies were conducted with sample groups with different socio-economic, cultural, and social characteristics.

Our study found that the average score of pregnant women’s fear of childbirth was moderate, and in other studies conducted in Turkey, it was partially higher.[7,28] In this study, it was found that pregnant women who experience fear at a high level (25.6%) and a clinical level (5.6%) have a lower rate than the results of similar studies conducted in Turkey.[7,27,28] In a systematic review on the fear of childbirth, it was reported that 6.3–14.8% of pregnant women experience severe levels of fear.[1] Per these data, it was evaluated that the rates of pregnant women who experienced fear at the clinical level were relatively lower.

Our study determined that there is a significant relationship between women’s fears of childbirth and prenatal attachment in the opposite direction, and as women’s fears of childbirth increase, their attachment levels decelerate. Our findings obtained from the regression model support that fear of childbirth has a significant effect on the total score of PAI. Garthus-Niegel et al.[27] found similar results to our finding, but on the contrary, Gürol et al.[14] found a positive relationship between fear of childbirth and prenatal attachment. In our study, it can be interpreted that the reason for finding a significant inverse relationship in our study is that communication between the mother and fetus decays due to high levels of fear of childbirth, and the mother cannot focus on her baby since her mind is busy with fear of childbirth. In this case, to increase the level of prenatal attachment during pregnancy, it is recommended that pregnant women with a high fear of childbirth be identified by nurses and midwives and planned training and counseling for prevention.

According to the multiple linear regression model, we found that apart from fear of childbirth, the duration of marriage and age also had a significant effect on the total score of PAI. According to the model, as age decreases, there is an increase in the level of prenatal attachment. Yilmaz and Beji[22] found that the PAI
scores of thirty-five years of age and older are significantly lower. The results of the study conducted by Camarneiro and Justo also indicated that younger pregnant women had higher attachment quality. Damato reported that younger mothers have more prenatal attachment to their twin babies. These studies support our findings. On the other hand, Elkin found no significant relationship between age and prenatal attachment. At the same time, in this study, it was found that prenatal attachment levels increase as the duration of marriage increases. There is no study in the literature examining the effect of the duration of marriage on prenatal attachment. This finding contributes to the literature.

The study’s limitations should be taken into account when evaluating the results of the study. Our most significant limitation is using rating scales based on participants’ self-reports in the collection of data. Therefore, their answers are the personal statements of pregnant women, and it is not always possible to say that they will be absolutely correct. At the same time, scales can be interpreted differently according to society’s cultural habits and social circles in which they are used. This situation can be considered a limitation on the validity and reliability of the study. In addition, since this study is a cross-sectional study and the number of the participants is limited to 125 pregnant women, studies with larger samples can add new information to the literature.

Conclusion
As a result, in this study, we determined that the prenatal attachment levels of pregnant women were high, and the fear of childbirth was at a moderate level. There was a significant difference between the educational status of women and their PAI score averages. However, there was no significant difference between the other sociodemographic and obstetric characteristics and their mean PAI scores. In our study, we found that prenatal attachment levels decrease as women’s fears of childbirth increase. According to the linear regression model, we found that the age, duration of the marriage, and fear of childbirth of pregnant women had a significant effect on the total score of PAI. If other pregnant women with a clinical level of fear of childbirth and risk of prenatal attachment are detected early, a better level of prenatal attachment can be achieved during pregnancy. In order to identify risky situations, if necessary, it is recommended to use validity-based measurement tools and take the necessary measures to increase prenatal attachment. Increasing the level of prenatal attachment is also essential to help prevent possible problems after childbirth.

Nurses and midwives have important roles while giving care to women during the pregnancy period. For them, knowing the level of women’s prenatal attachment and determining the factors affecting them in the antenatal period is of great significance in planning and implementing their training and care.

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References


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The relationship between first trimester screening test and abruptio placentae

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Abstract

Objective: We compared the first-trimester screening test results and perinatal results of pregnant women to determine the diagnosis of abruptio placentae, one of the essential causes of maternal and fetal mortality and morbidity.

Methods: Between 2019 and 2021, 20 pregnant women diagnosed with abruptio placentae in our hospital and 30 pregnant women who did not develop clinical abruptio placentae during their pregnancy in the same period were included in our study. The relationship between the first-trimester screening test results and the perinatal outcomes of the patients was investigated.

Results: No significant differences were found in maternal age, gravida and parity. Significant difference was found in gestational age at birth, being 33 ± 5.1 weeks in the study group and 38.6 ± 1.48 weeks in the control group. No statistical differences were found at PAPP-A or at β-hCG between the groups (p = 0.219 and p = 0.898, respectively). Nevertheless, a trend of a lower PAPP-A at the study group was noticed (1.03 ± 0.54 MoM vs. 1.28 ± 0.66 MoM). Significant differences were found at fetal birth weight, 1-minute Apgar score and 5-minute Apgar score. When looking at risk factors, no differences between the groups were found at smoking, multiple pregnancy, myoma uteri or diabetes, but preeclampsia and threatened preterm labor were more common at the study group.

Conclusion: When we compared the first-trimester serum biomarkers to predict abruptio placentae, we could not find any significant difference between the two groups. To reach a definite conclusion on this issue, more studies with increasing the number of patients are needed.

Keywords: Abruptio placentae, pregnancy-associated plasma protein A, pregnancy outcome.

Introduction

Abruptio placentae can be explained as the complete or partial separation of the placenta from the place where it was implanted in the uterus before delivery due to bleeding into the decidua basalis. This is one of the most serious causes of third trimester bleeding and it is associated with high mortality and morbidity. It occurs in approximately 0.5–2% of all pregnancies. Its etiology is unknown, but many predisposing risk factors have been described. History of previous abruption of placenta, maternal hypertensive diseases (preeclampsia-chronic hypertension), multiple pregnancies, premature rupture of membranes, chorioamnionitis, trauma, smoking and cocaine use, and maternal age can be listed as risk factors. The usual clinical manifestation of the placenta abruptio is severe abdominal pain, often accompanied by uterine contractions, pathological fetal heart rate, and vaginal bleeding. Pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (β-hCG) are part of the chromosomal anomaly screening test performed between the 11+0 and 14+0 weeks of gestation, combined with maternal age and nuchal translucency. PAPP-A is secreted from trophoblasts, and β-hCG is synthesized by syncytiotrophoblasts. Many studies are investigating the relationship of these markers with pregnancy complications, apart from chromosomal anomaly screening. It has been suggested that PAPP-A may be an important marker in placental pathologies, and low PAPP-A value is associated with preeclampsia.
premature birth, pregnancy loss, and low birth weight. Studies conducted in recent years have also tried to examine first-trimester maternal serum biochemical markers of pregnancies with placental pathologies.

Our study aimed to investigate the relationship between first-trimester maternal serum PAPP-A and $\beta$-hCG values and abruptio placentae.

**Methods**

The research group of our study consists of 20 pregnant women diagnosed with abruptio placentae in our hospital between October 2019 and March 2021 and the control group was composed of 30 pregnant women who did not develop clinical abruptio placentae during their pregnancy in the same time period. All of the patients in both groups had first-trimester screening test results. All procedures in this study were performed according to the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Human Research Ethics Committee of the Sivas Cumhuriyet University approval was received for this study [registry no: 2021-04/54].

While abruptio placentae is considered a clinical diagnosis, the diagnosis was confirmed by histopathological examination of the placenta. Biochemical markers of the patients from first-trimester screening, demographic data including maternal age, parity, type of delivery, gestational age at delivery, fetal weight, Apgar scores (1- and 5-minute were recorded), and results were also compared between the risk factors in vitro fertilization (IVF) pregnancy, smokers, chronic hypertension, preeclampsia, diabetes, gestational diabetes, preterm premature rupture of membranes (PPROM), threatened preterm labor, intrauterine growth retardation (IUGR), uterine myomas and hypothyroidism.

Differences between categorical variables were studied by chi-square analysis. In numerical variables, Shapiro-Wilk normality test was applied to decide which test is appropriate to analyze whether there are differences between the groups. As a result of the analysis, compliance with the normal distribution in all dimensions could not be calculated ($p<0.05$). For this reason, numerical variables were analyzed with the Mann-Whitney U test.

**Results**

Our study was conducted with 50 cases, 20 of them in the study group and 30 in the control group. No significant differences were found in maternal age, gravida, and parity. A significant difference was found in gestational age at birth, 33±5.1 weeks in the study group and 38.6±1.48 weeks in the control group. No statistical differences were found at PAPP-A or at $\beta$-hCG between the groups ($p=0.219$ and $0.898$, respectively). Nevertheless, a trend of a lower PAPP-A in the study group was noticed (1.03±0.54 MoM vs. 1.28±0.66 MoM) (Table 1). Significant differences were found at fetal birth weight, and 1-minute and 5-minute Apgar scores (Table 2). When looking at risk factors, no differences between the groups were found at smoking, multiple pregnancy, myoma uteri or diabetes, but preeclampsia and threatened preterm labor (TPL) were more common at the study group (Table 3).

**Table 1.** Comparison of maternal and pregnancy-related variables between the groups.

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Total</th>
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<td>Mean</td>
<td>Standard deviation</td>
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<td>$\beta$-hCG</td>
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</table>
The relationship between first trimester screening test and abruptio placentae

Discussion

Placental abruption is closely associated with low birth weight, preterm delivery, stillbirth, and early neonatal mortality.\(^ {[11]}\) The incidence of stillbirth and perinatal mortality rates depend on the degree of separation of the placenta and the week of gestation. Particularly, more than 50% separation of the placenta significantly increases stillbirth rates.\(^ {[1]}\) It is very important that placental abruption can be predicted and precautions can be taken.

This study is based on the hypothesis that first trimester maternal PAPP-A or β-hCG serum measurements may be associated with poor perinatal outcomes at the end of pregnancy. If pregnant women with a high risk of obstetric complications can be predicted in the first-trimester, taking the necessary precautions for these patients will prevent possible complications. PAPP-A plays a role in the regulation of fetal growth.\(^ {\[13-16\]}\) In addition, it is estimated that they play a key role in the autocrine and paracrine control of trophoblast invasion of the decidua.\(^ {\[11-16\]}\) Therefore, it is thought that obstetric pathologies associated with insufficient trophoblastic invasion in the first-trimester may be associated with low PAPP-A.

Although the association between low PAPP-A levels and adverse outcomes is statistically significant, the

### Table 2. Comparison of birth weight and Apgar scores between the groups.

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<th>Standard deviation</th>
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sensitivity to individual outcomes is relatively low. Therefore, a low PAPP-A level alone, although strongly associated with a range of adverse obstetric outcomes, is not sufficient for prediction.\textsuperscript{[7]} In some studies in the literature, an inconsistent relationship was detected between first trimester PAPP-A and β-hCG levels and perinatal outcomes.\textsuperscript{[17–22]}

In the study of 137,915 women in California, Blumenfeld et al. reported that PAPP-A ≤5 percentile value was associated with 1.6 times increased risk of abortion.\textsuperscript{[23]} First trimester low PAPP-A, second trimester high AFP, low uE3 and high dimeric inhibin-A levels were found to be associated with placental abruption. PAPP-A has also been shown to be associated with an increased risk of other placental dysfunction disorders, including stillbirth.\textsuperscript{[23–25]}

Smith et al. determined that PAPP-A level, which is ≤5th percentile in the first trimester, increases the risk of stillbirth 60 times due to abruptio placentae.\textsuperscript{[26]} In a similar study, it was reported that the probability of abruptio placentae was 1.8 times higher in women with low PAPP-A (≤5th percentile), but no relationship was found for free β-hCG.\textsuperscript{[7]} In a retrospective study conducted by Kececioglu et al. in 2016, including 120 term pregnant women who gave birth by cesarean section, first- and second-trimester serum biomarker levels were compared. There was no significant difference between the biomarkers examined in the first and second trimesters in predicting cases with abruptio placentae at term without known risk factors.\textsuperscript{[27]} A hospital-based study\textsuperscript{[28]}, in Finland reported no association between low PAPP-A (<1.0 MoM) and abruptio placentae. Another study by Pilalis et al. in Greece\textsuperscript{[29]} reported that the prevalence and risks of abruptio placentae were similar among women with and without low first trimester PAPP-A. A study from Israel also found no association between low PAPP-A MoM values and abruptio placentae.\textsuperscript{[18]}

Our study showed a significant difference between the abruptio placentae and control groups in terms of the weeks of gestation, birth weights, and Apgar scores, consistent with the literature. When we compared the risk factors, there was a significant difference between the abruptio placentae and control groups in preeclampsia and preterm birth threat. However, when we compared the first-trimester serum biomarkers to predict abruptio placentae, we could not find a significant difference between the two groups.

The limitation of our study is the number of patients. But placental abruption is a relatively rare condition. Our hospital’s annual number of births and abruptio placentae rate is 0.85%, compatible with the world literature. As reported in FASTER TRIAL (one of the studies with the largest case series on first trimester maternal serum PAPP-A level and obstetric complications), first trimester low PAPP-A level is associated with significantly spontaneous fetal loss at ≤24 weeks of gestation, preterm birth, gestational, preeclampsia, and low birth weight.\textsuperscript{[7]} However, researchers found some evidence that low PAPP-A levels are also associated with intrauterine fetal death at >24 weeks of gestation, PPROM, and abortion, although this did not meet our strict significance criteria reported. The fact that no decision has been made on this issue has encouraged us to carry out this study. Therefore, we anticipate that any research that will contribute to the literature on this subject can be valuable.

**Conclusion**

Placental abruption still remains an obstetric challenge in terms of prediction and prevention. There is a need for more comprehensive studies on this subject by increasing the number of patients. Future studies aiming to develop predictive models based on Doppler profiling of uterine and umbilical arteries, and maternal early pregnancy serum biomarkers combined with demographic factors may provide clinically relevant information.

**Funding:** This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Compliance with Ethical Standards:** The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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Carrier frequency of spinal muscular atrophy in Turkish population

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2Department of Obstetrics & Gynecology, Memorial Şişli Hospital, Istanbul, Turkey
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4Department of General Surgery, Memorial Bahçelievler Hospital, Istanbul, Turkey

Abstract

Objective: The aim of this retrospective cohort study is to evaluate the carrier frequency of spinal muscular atrophy (SMA) among pregnant women and their partners admitted to our clinic for routine pregnancy follow-up.

Methods: The study included pregnant women and their partners who were informed about SMA disease and screening at first trimester and who accepted to undergo screening for SMA. Carrier screening for SMA was carried out using DNA extracted from peripheral blood with a quantitative real-time polymerase chain reaction (qPCR) assay targeting the recurrent SMN1 exon 7-8 gene deletion. The data of the study were analyzed by the SPSS version 15.0 statistical software package. Descriptive statistical analyses were carried out. Fisher’s exact test was used for intergroup comparisons.

Results: The study included a total of 250 subjects, of whom 182 were female and 68 were male. The carrier frequency of SMN1 deletion was 3.6% (9/250) (95% CI: 1.66–5.54) in the entire study population, with a carrier frequency of SMN1 deletion of 1/27.8. Of 182 female participants, 6 had SMN1 deletion, with a carrier frequency of SMN1 deletion of 3.3% (95% CI: 1.3–6.2). Of 68 male participants, 3 had SMN1 deletion, with a carrier frequency of SMN1 deletion of 4.4% (95% CI: 0.35–9.4). There was no significant difference between female and male participants in terms of SMN1 deletion frequencies (p=0.712). SMN1 duplication frequency was 8% (95% CI: 5.18–10.8) in all gender.

Conclusion: The results of this study demonstrated a carrier frequency of SMN1 deletion of 1/27.7 in the Turkish population, which is higher than in many other countries. The results of the study will be useful for genetic counseling for SMA.

Keywords: Spinal muscular atrophy, SMA, SMN-1, carrier frequency.

Introduction

Spinal muscular atrophy (SMA) is the most common neurodegenerative disease in childhood, characterized by progressive muscle weakness and muscle atrophy.1 SMA is an autosomal recessive single gene disorder caused by homozygous or compound heterozygous mutations in the SMN-1 gene located on the 5q13.2 region of chromosome 5. Approximately 95% of SMA patients, irrespective of their clinical type, have a homozygous deletion of the SMN1 gene (exon 7 and 8).2

The SMN gene has a genomic length of 20 Kb and has 9 exons. It encodes a 32 kD protein consisting of 294 amino acids. This gene has something unique called the survival motor neuron (SMN) gene, which is a copy of this gene located in the telomeric region of the same chromosome (5q11.2-13.3) SMN1 (or SMNt), a pathogenic gene. The other copy of this gene, called SMN2, is located in the centromeric region of the chromosome 5q13.2, and a single nucleotide substitution (840C>T) in SMN2 gene results in different splicing on exon7 and
the production of a less functional protein. The only difference of the SMN2 gene from SMN1 is that thymine replaces cytosine at a single point. Because of this slight difference, the gene produces a transcript that does not contain exon 7. As a result, synthesized protein that is short and unstable breaks down quickly and does not function normally. The low rate (about 10%) of complete protein synthesis from the same gene also plays a role in SMN2 being a determinant of the severity of the disease. Naturally, as the number of SMN2 increases, the amount of normal protein that can be produced will also increase. It has been observed that the more SMN2 copies patient has, the milder disease becomes. For example, SMA type 1 is observed in patients with two SMN2 copies, while SMA type 3 patients have 3 or 4 copies of SMN2. In other words, the severity of the disease is modulated by SMN2, though the SMN1 is the pathogenic one.\(^{[3–7]}\) Adult form of SMA type 4, while less frequent, has also been reported. This group includes patients who are able to walk in adulthood and have no respiratory and nutritional problems.\(^{[8]}\) The remaining 5% of the affected individuals may have compound heterozygote for a deleted gene and an intragenic mutation on the other SMN1 gene.\(^{[6,9]}\)

The aim of this study was to determine the carrier frequency of SMA among pregnant women and their partners admitted to our clinic for routine pregnancy follow-up.

**Methods**

The study included pregnant women and their partners who presented to the department of Obstetrics and Gynecology for pregnancy follow-up between May 1, 2012 and December 30, 2021 and who were informed about SMA disease and carrier screening, and offered SMA carrier screening at first trimester. Informed consent was obtained from all families. Pregnant women and/or their partners who accepted carrier screening test for SMA were included in the study.

Carrier screening test for SMA was carried out using DNA extracted from peripheral blood with a quantitative real-time polymerase chain reaction (qPCR) assay targeting the recurrent SMN1 exon 7-8 gene deletion. All families were informed in detail about the carrier screening results by the Department of Medical Genetics. The approval for the study was obtained from the local Ethics Committee (24.12.2021/008).

SPSS version 15.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used to analyze the statistical data. Descriptive statistical analyses were carried out. Fisher’s exact test was used for intergroup comparisons (male and females). A p-value <0.05 was considered statistically significant.

**Results**

The study included a total of 250 subjects, of whom 182 were female and 68 were male. The carrier frequency of SMN1 deletion was 9/250 in the entire study population, with a carrier frequency of SMN1 deletion of 1/27.8. The frequency of SMN1 duplication was calculated as 20/250 for all participants.

There was no significant difference between female and male participants in terms of SMN 1 deletion (p=0.712) and duplication (p=0.602) frequencies. Of 182 female participants, 6 had SMN1 deletion and 16 had SMN1 duplication, with a carrier frequency of SMN1 deletion of 3.3% (95% CI: 1.3–6.2). Of 68 male participants, 3 had SMN1 deletion and 4 had SMN1 duplication, with a carrier frequency of SMN1 deletion of 4.4% (95% CI: 0.35–9.4). In other words, the carrier frequency of SMN1 deletion was 1/30.3 in female participants and 1/22.7 in male participants (Table 1). There was no couple with both partners identified to be carriers. Considering the diversity of mutations,

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMN1 deletion</strong></td>
<td>6 (3.3%) (95% CI: 1.3–6.2)</td>
<td>3 (4.4%) (95% CI: 0.35–9.4)</td>
<td>9 (3.6%) (95% CI: 1.66–5.54)</td>
</tr>
<tr>
<td><strong>SMN1 duplication</strong></td>
<td>16 (8.8%) (95% CI: 6.1–13.9)</td>
<td>4 (5.9%) (95% CI: 1.37–11.8)</td>
<td>20 (8%) (95% CI: 5.18–10.8)</td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>160 (87.9%)</td>
<td>61 (89.7%)</td>
<td>221 (88.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>182</td>
<td>68</td>
<td>250</td>
</tr>
</tbody>
</table>

Table 1. Analysis of SMN1 Exon7&8 deletion/duplication.
Carrier frequency of spinal muscular atrophy in Turkish population

Discussion

SMA is the most common monogenic cause of infant mortality and is characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem, which results in progressive muscle weakness and atrophy. However, to date, there is a limited number of published studies evaluating the carrier frequency of SMA. The reported incidence of SMA ranges from 4 to 10 in 100,000 live births and the carrier frequency of disease-causing SMN1 mutations ranges from 1/200 to 1/20 among different ethnicities. Since the rate of consanguineous marriage increases from the west to the east of Turkey, the frequency of SMA carriers also increases.

The present study demonstrated a carrier frequency of SMN1 deletion of 3.6% (9/250) in our population, with a carrier frequency of SMN1 deletion of 1/28. Moreover, there was no significant difference between female and male participants in terms of SMN1 deletion frequencies. A study by Prior et al. performed carrier testing on 500 pre-conceptual or pregnant women in the USA and reported a carrier frequency of SMA of approximately 1/31 (95% CI: 1.19–1.54). Zhang et al. performed the largest-scale carrier screening for SMA carriers in 13,069 pregnant women in China. They found that a total of 231 women were carriers (1.77%; 95% CI: 1.56–2.01%), indicating a carrier frequency of approximately 1/56 in the population. In the present study, the carrier frequency of SMA was found to be 1/30.3 in female participants.

Given the carrier frequency studies conducted in various societies, the SMA carrier frequency was reported 1/27 in the Morocco population, 1/49 in the Australian population, 1/56 in the Thai population, 1/38 in the Indian population, 1/34 in the Italian population, 1/48 in the French population and 1/57 in the Swedish population. In a meta-analysis of 10 different publications conducted between 2005 and 2016 in China, random effects models showed an overall carrier frequency of SMA of 2.0% (95% CI: 1.7–2.3%). Sangaré et al. reported that the carrier frequency of SMA was 1/209 in Malians, 1/120 in Kenyans, and 1/60 in Nigerians. They stated that the carrier frequency of SMA was much lower in sub-Saharan Africans than in Eurasians. Hasanzad et al. showed a higher carrier frequency of SMA in Iran (1/20) than in the European population.

Due to the high prevalence of SMA carriers in the United States, the American College of Medical Genetics recommends offering carrier testing to all couples regardless of race or ethnicity. The American College of Obstetricians and Gynecologists (ACOG) recommends that screening for SMA should be offered to all women who are considering pregnancy or are currently pregnant.

Conclusion

This study is the first report addressing the estimation of SMA carrier frequency in Turkish population. Based on the results of the study, the carrier frequency of SMN1 deletion in Turkish population was 1/27.7, which is higher than in many other societies. The limitation of this study is the relatively small number of participants in the study. However, our work will be an inspiration and guide for future studies. Study findings may be useful for genetic counseling about SMA. Moreover, considering the high rate of consanguineous marriage in Turkish population, it will be beneficial for couples to have carrier screening before pregnancy or during pregnancy to prevent SMA disease.

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

Table 2. Distribution of SMN1 carriers by gender and exon.

<table>
<thead>
<tr>
<th></th>
<th>Del exon 7</th>
<th>Del exon 7&amp;8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>
References


Impact of COVID-19 on termination of pregnancy

Cinzia Ferrara, Gabriella Sglavo, Ilaria Morra, Gabriele Saccone, Costantino Di Carlo, Giuseppe Bifulco

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Abstract

Objective: To evaluate the impact of COVID-19 pandemic on termination of pregnancy.

Methods: This was a retrospective study aimed to assess the impact of COVID-19 pandemic on termination of pregnancy in a single center in Italy. Consecutive data on pregnant women who requested induced termination of pregnancy (I-TOP) from February 2018 to December 2021 were included in a dedicated database. The data were divided into two groups according to the COVID-19 outbreak. Women who requested I-TOP from February 2018 to January 2020 were included into the group ‘before COVID-19 pandemic’. Women who requested I-TOP from February 2020 to January 2022 were included into the group ‘during COVID-19 pandemic’. Indications for I-TOP included elective abortion and therapeutic abortion for fetal or maternal indication.

Results: A total of 2578 women were included in the study. Of them, 1637 had I-TOP before COVID-19, and 941 had I-TOP during COVID-19. During the pandemic, the request for elective abortion decreased from 76.2% to 67.7% (p<0.01). Therapeutic abortion were performed in 141/693 cases in the first trimester, and in 552/693 cases in the second trimester. Overall, 91 were for maternal indications and 602 for fetal indications. No differences were noticed between before and during pandemic (p=0.99). Follow-up visits two weeks after abortions were offered to all women. However, only 35.5% women visited for follow-up during pandemic vs. 65.0% before COVID-19 (p<0.01).

Conclusion: The COVID-19 pandemic had impact on access to abortion services, reducing request for elective abortion and post-abortion follow-up visits.

Keywords: COVID-19, induced termination of pregnancy, abortion, miscarriage, curettage.

Introduction

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order. They are enveloped, non-segmented positive-sense RNA viruses. The Novel Coronavirus (2019-nCoV), also known as Wuhan coronavirus, causes the 2019-nCoV acute respiratory disease or COVID-19 or SARS-CoV-2.

The COVID-19 outbreak poses significant risk to public health. In obstetrics and gynecology, COVID-19 pandemic is associated with significantly higher risk of maternal and perinatal complications, but also challenges and issues about organizing labor and delivery unit, training program, and vaccination. Family planning services may be also affected by COVID-19 pandemic. A health system response for family planning services during the pandemic, including telemedicine, is important to avoid unwanted pregnancies and prevent additional mortality and morbidity of women. Currently, there is no lack of information on the impact of the COVID-19 pandemic on abortion access and indications.

Thus, the aim of this study was to evaluate impact of COVID-19 pandemic on termination of pregnancy.
Methods

Study design

This was a retrospective study aimed to assess the impact of COVID-19 pandemic on termination of pregnancy (abortion) performed at a single center in Italy (University of Naples Federico II, Napoli, Italy). Consecutive data on pregnant women who requested induced termination of pregnancy (I-TOP) from February 2018 to January 2022 were included in a dedicated database. The data were divided into two groups according to the COVID-19 outbreak. Women who requested I-TOP from February 2018 to January 2020 were included into the group ‘before COVID-19 pandemic’. Women who requested I-TOP from February 2020 to January 2022 were included into the group ‘during COVID-19 pandemic’. Inclusion criteria were pregnant women undergoing I-TOP. Women with spontaneous abortion or second trimester loss were excluded from the analysis. Indications for I-TOP included elective abortion and therapeutic abortion for fetal or maternal indication. We also evaluated methods of abortion, either surgical or medical.

Elective abortion, or nontherapeutic abortion, was defined as abortion done because a woman chooses to end the pregnancy.[27–31] In Italy, elective abortion is allowed until 12 weeks and 6 days. In our institution, elective abortion was performed either with medical approach or surgical approach. Surgical approach in the first trimester was performed by dilation and curettage with or without vacuum aspiration. Medical approach in the first trimester was performed using oral mifepristone 600 mg followed by oral misoprostol 400 mcg every 4 hours.[32]

Therapeutic abortion is allowed in Italy until 21 weeks and 6 days.[27–31] In our institution, second trimester abortion was performed using oral mifepristone followed by oral or vaginal misoprostol.

Statistical analysis

The data are shown as mean with standard deviation, or as number (percentage). Descriptive statistics were calculated for sociodemographic characteristics. Univariate comparisons of dichotomous data were performed with the use of the chi-square with continuity correction. Comparisons between groups to test group means with standard deviation were performed with the use of the t-test by assuming equal within-group variances. A 2-sided p-value less than .05 was considered significant. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA).

Results

A total of 2578 women were included in the study. Of them, 1637 had I-TOP before COVID-19, and 941 had I-TOP during COVID-19.

During the pandemic, the request for elective abortion decreased from 76.2% to 67.7% (p<0.01). Therapeutic abortion was performed in 141/693 cases in the first trimester, and in 552/693 cases in the second trimester. Overall, 91 were for maternal indications and 602 for fetal indications (Table 1). No differences were noticed between before and during pandemic (p=0.99).

Follow-up visits two weeks after abortions were offered to all women. However, only 35.5% women visited for follow-up during pandemic vs. 65.0% before COVID-19 (p<0.01).

Discussion

This study evaluated impact of COVID-19 pandemic on indication for termination of pregnancy. The study showed that COVID-19 reduced request for elective abortion, while did not impact on therapeutic I-TOP. COVID-19 had also a negative impact on follow-up, reducing post-abortion visits.

This study had several limitations. The sample size is small. The single-center study design raises the question of external generalizability. Because of its retrospective nature, it was not possible to separate the importance of the pandemic versus other confounders that may have affected the results.

The COVID-19 pandemic is a public health crisis that generated social, political, economic, and psychological consequences. In pregnant women, COVID-19 is associated with increased risk of maternal and perinatal complications.[7,33–35] Access to abortion care can be restricted by numerous logistical and financial barriers, and the COVID-19 pandemic may intensify many challenges that abortion service face in providing their services.[16] In our setting, abortion unit remained open during the pandemic proving abortion care, counselling,
and follow-up visits. The reducing request for elective abortion may be caused by different conditions linked to the pandemic. Access to the hospital was restricted to family members and care givers, and visitors. Women can be afraid to go to general medical visit, with less gynecologic visits, including contraception counselling, and missed pregnancy test before 13 weeks, being the gestational age cut-off allowed in Italy for elective abortion.

Prior studies evaluated the impact of COVID-19 on abortion services. [36–40] Tu et al. showed that the pandemic was associated with increased intention of seeking induced abortion due to social factors. [38] Kaller et al. [39] showed that the COVID-19 pandemic caused several disruptions to abortion service availability in India, including lockdowns. To reduce in-person visit time, some clinics shifted to offering medication abortion (versus procedural) or telehealth. In a cohort analysis of abortion requests made through the telemedicine abortion service Women on Web (WoW), almost half of the women and pregnant people having an abortion through WoW reported experiencing obstacles to abortion care because of COVID-19. [40]

**Conclusion**

In summary, the COVID-19 pandemic had impact on access to abortion services, reducing request for elective abortion and post-abortion follow-up visits. Policies or protocols improving abortion access are urgently required.

**Funding:** This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Compliance with Ethical Standards:** The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

**References**


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**Table 1. Details of the abortions.**

<table>
<thead>
<tr>
<th></th>
<th>Before COVID-19 (n=1637)</th>
<th>During COVID-19 (n=941)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester I-TOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic abortion</td>
<td>88/1637 (5.4%)</td>
<td>53/941 (5.6%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>1248/1637 (76.2%)</td>
<td>637/941 (67.7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Second trimester I-TOP (therapeutic abortion)</td>
<td>301/1637 (18.4%)</td>
<td>251/941 (26.7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall elective abortion</td>
<td>1248/1637 (76.2%)</td>
<td>637/941 (67.7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall therapeutic I-TOP</td>
<td>389/1637 (23.8%)</td>
<td>304/941 (32.3%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Therapeutic I-TOP for fetal indications</td>
<td>338/389 (86.9%)</td>
<td>264/304 (86.8%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Therapeutic I-TOP for maternal indications</td>
<td>51/389 (13.1%)</td>
<td>40/304 (13.2%)</td>
<td>0.98</td>
</tr>
<tr>
<td>First trimester surgical abortion</td>
<td>418/1336 (31.3%)</td>
<td>301/940 (43.6%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>First trimester medical abortion</td>
<td>918/1336 (68.7%)</td>
<td>389/940 (56.4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Follow-up visit after abortion</td>
<td>1064/1637 (65.0%)</td>
<td>334/941 (35.5%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The data are presented as number (percentage). I-TOP: induced termination of pregnancy. Bold data: statistically significant.


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Fetal thymus reference range in healthy singleton pregnancies

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2Department of Obstetrics & Gynecology, Bağlent University Adana Hospital, Adana, Turkey

Abstract
Objective: To present the reference range of the fetal thymus gland according to gestational age groups.
Methods: In this prospective study, fetal thymus size was assessed in singleton, uncomplicated pregnancies between 19 and 38 weeks of gestation in our outpatient clinic between 2019 and 2020. Based on their monthly pregnancy follow-ups, fetal thymus measurement was divided into 5 gestational age groups (Group 1: 19–22 weeks, Group 2: 23–26 weeks, Group 3: 27–30 weeks, Group 4: 31–34 weeks, and Group 5: 35–38 weeks).
Results: Fetal thymus measurements of 210 patients were performed over one year, and as a result, 184 pregnant patients were included for assessment. Fetal thymus could be visualized at a rate of 93.5%. The 5th percentile of thymus transverse diameter, antero-posterior diameter, perimeter, thymus anterior-posterior diameter to thoracic diameter, and thymus perimeter to thoracic circumference were 11.03 mm, 5.60 mm, 32.52 mm, 0.33, and 0.32 in Group 1; 13.53 mm, 7.66 mm, 43.67 mm, 0.34, and 0.32 in Group 2; 20.43 mm, 11.22 mm, 47.72 mm, 0.33, and 0.32 in Group 3; 27 mm, 12.98 mm, 55.88 mm, 0.32, and 0.30 in Group 4; 28 mm, 13.59 mm, 63.4 mm, 0.32, and 0.30 in Group 5; respectively. Spearman’s rho correlation coefficients for the thymic measurements were 0.879, 0.869, 0.846, 0.236, and 0.267 respectively, and all p-values were less than 0.001. As a result of linear regression analysis between thymus measurements and BPD; the equations for the optimal models are as follows: thymus transverse diameter= -3.49+0.4×BPD (mm) (r=0.826, R²=0.682, p<0.001), thymus anterior-posterior diameter= -2.48+0.22×BPD (mm) (r=0.808, R²=0.653, p<0.001), thymus perimeter= -14.37+1.21×BPD (mm) (r=0.814, R²=0.663, p<0.001), thymus anterior-posterior diameter/thoracic diameter= 0.38+7.76E-4×BPD (r=0.213, R²=0.045, p=0.004) and thymus perimeter/thoracic circumference= 0.35+1.02E-3×BPD (r=0.263, R²=0.069, p<0.001). Thymus transverse diameter, anterior-posterior diameter, and perimeter increased linearly with increasing biparietal diameter (BPD).
Conclusion: We established the reference ranges of fetal thymus size. Thymus transverse diameter, antero-posterior diameter, and thymus perimeter have a strong relationship with gestational age and are easy and reproducible. Therefore, the knowledge of reference ranges of fetal thymus will enable the evaluation of thymic aplasia/hypoplasia.
Keywords: Fetal thymus, obstetric ultrasound, reference range.

Introduction
The thymus gland, which is a lymphoepithelial organ, plays a key role in the fetal immune system.[1,2] Evaluation of fetal thymus measurements in the neonatal period may allow the diagnosis of congenital absence or hypoplasia of the thymus.[3] It is known that 22q11.2 chromosome deletion syndromes including Di George syndrome, conotruncal facial anomalies and Shprintzen syndrome, chondroplasia punctata, Ellis-van Creveld syndrome, and ethanol exposure are often associated with thymus aplasia/hypoplasia.[1,4] Disorders in the immune system due to thymus hypoplasia will increase the susceptibility to
Thymic hypoplasia is also a common finding in preterm premature rupture of membranes (PPROM), chorioamnionitis, maternal preeclampsia, Down syndrome, and other aneuploidies. This finding can be considered as the cause of impaired immune functions in such pregnancy complications.

Evaluation of the presence of thymus hypoplasia according to the week of gestation will be based on the knowledge of normal measurements of the fetal thymus gland. Owing to the developments in ultrasonographic imaging and the skills of clinicians, by the early second trimester, the thymus gland can be visualized and measurements can be taken in a short time provided the correct technique is used. In our study, it was aimed to determine the size of the fetal thymus gland according to weeks of gestation.

Methods
Fetal thymus measurements, which were performed only once for each patient with singleton pregnancies, for those who were routinely checked between 19–38 weeks of gestation in our outpatient clinic between November 2019 and November 2020 were included. If fetal thymus measurement was included once in the pregnancy follow-up, no re-measurement of the same patient in another week of gestation was included. Multiple pregnancies, pregnancies with fetuses with known chromosomal or major structural anomalies, preterm delivery (<37 weeks), intrauterine growth retardation, low birth weight (<2500 g), macrosomia (>4500 g), pregnancies with PPROM, chorioamnionitis, preeclampsia, and insulin-dependent gestational diabetes were excluded from the study. Also, the patients whose fetal thymus measurements could not be performed due to fetal position or maternal factors were not included. Fetal position was considered insufficient provided that the thymus could not be visualized due to shadowing of the surrounding bones.

Age, gravidity, parity, height, weight, body mass index, and weeks of gestation of the pregnant patients were recorded. The week of gestation was arranged according to the first day of the last menstrual period of the pregnant patient or due to the ultrasonography performed in the first three months of the pregnancy. The delivery process of the pregnant patients who had fetal thymus measurement was followed up. Birth week, birth weight and gender of the newborn, and any complications were recorded. Delivery information of the patients who delivered in other centers was obtained by phone calls.

The patients, whose fetal thymus measurements were performed starting from the 19 weeks of gestation, were divided into five groups as Group 1 (19+0 – 22+6 weeks), Group 2 (23+0 – 26+6 weeks), Group 3 (27+0 – 30+6 weeks), Group 4 (31+0 – 34+6 weeks), and Group 5 (35+0 – 38+6 weeks), based on their monthly pregnancy follow-ups.

All ultrasonographic examinations were performed transabdominally using Voluson E8 (5-8 MHz 3D transducer General Electric Healthcare; Little Chalfont, UK) device. Biometric measurements including biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC) were performed. As described by Yagel et al., after the four-chamber view was obtained in the upper abdomen transverse section and angled towards the cranial, 3-vessel view was obtained and fetal thymus measurements were performed by 2 experienced ultrasonographers. Maximum thymus diameter in the transverse section, the distance from the sternum to the end of the thymus in the anterior-posterior section, the distance between the sternum and the spine, thymus perimeter, and thoracic circumference were measured (Fig. 1). The ratio of thymic anteroposterior diameter to

![Ultrasonographic view of the fetal thymus at 27 weeks of gestation, showing the thymus (AO: ascending aorta; PA: main pulmonary artery; SVC: superior vena cava; →→: thymus).](image-url)
thoracal anteroposterior diameter (thymus-thoracic ratio) and the ratio of thymus perimeter to thoracic circumference (thymus perimeter/thoracic circumference) was calculated. To create a nomogram for thymus size, a linear regression relationship between fetal thymus diameter and gestational age was calculated. The 5th, 50th, and 95th percentiles of thymic diameter for each gestational age were calculated from the regression equation.

Our study was planned by the Declaration of Helsinki. This study was approved by Başkent University Review Board (project number= KA19/410, approval date= 09.01.2020). Informed consent was obtained from all patients participating in the study.

Statistical analyses
Assistance was received from Başkent University Statistics Unit to establish the sample size. “Sonographic Measurement of Fetal Thymus Size in Uncomplicated Singleton Pregnancies (2016 Wiley Periodicals, Inc; VOL. 00, NO. 00, Month 2016)” study is utilized.[9] Based on the sample calculation results of this study, in which predicted mean and SD of maximal diameter, perimeter, and thymus/thoracic ratio, based on weeks of gestation and BPD were calculated by the regression model, a total of 210 patients with 95% CI and 90% power were determined to be included in the study. G-Power 3.1 program was used for sample size calculation. Statistical Package for the Social Sciences (SPSS) 21.0 package program (IBM Corp., Armonk, NY, USA) was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, while continuous measurements were defined as mean and standard deviation (median and range where necessary). Descriptive statistics were performed. The strength of association between fetal thymus transverse diameter, thymus antero-posterior diameter, thymus perimeter and biparietal diameter of the fetus was calculated by using Spearman’s coefficient correlation. Linear regression analysis was performed by matching the gestational age with the fetal thymus measurements.

Results
In this study, in which fetal thymus measurements of 210 patients were performed over one year, delivery information of 16 patients could not be reached. Owing to newborn birth weight below 2500 g in five patients and above 4500 g in one patient, preterm delivery in two patients (24 and 26 weeks), preeclampsia (1 eclampsia) in two patients, and insulin-dependent diabetes mellitus in one patient, these patients were excluded from the study. Fetal thymus measurement could not be performed due to fetal position (n=7), maternal obesity (n=5), or oligohydramnios (n=2) in 14 patients who were in the last trimester and were initially planned to be included in the study (14/226, 6.25%). As a result, 184 pregnant patients, who had fetal thymus measurement after 19 weeks of gestation and who had a healthy delivery at term, were included in the study. There were 40 patients in the 19–22 weeks group, 56 patients in the 23–26 weeks group, 35 patients in the 27–30 weeks group, 26 patients in the 31–34 weeks group, and 27 patients in 35–38 weeks group. Obstetric histories of the study group were presented in Table 1.

In Table 2, 5–95th percentile values of thymus measurements according to weeks of gestation are demonstrated. The 5th percentile of thymus transverse diameter, antero-posterior diameter, perimeter, thymus anterior-posterior diameter to thoracic diameter, and thymus perimeter to thoracic circumference were 11.03 mm, 5.60 mm, 32.52 mm, 0.33, and 0.32 in Group 1; 13.53 mm, 7.66 mm, 43.67 mm, 0.34, and 0.32 in Group 2; 20.43 mm, 11.22 mm, 47.72 mm, 0.33, and 0.32 in Group 3; 27 mm, 12.98 mm, 55.88 mm, 0.32, and 0.30 in Group 4, 28 mm, 13.59 mm, 63.4 mm, 0.32, and 0.30 in Group 5, respectively. Spearman’s rho correlation coefficient were 0.879, 0.869, and 0.846 for thymus transverse diameter, thymus anterior-posterior diameter, and thymus perimeter, respectively (all p-values <0.001) (Fig. 2). Thymus anterior-posterior diameter/thoracic anterior-posterior diameter was 0.43±0.06 and mean thymus perimeter/thoracic circumference was 0.42±0.06

Table 1. Obstetric and perinatal outcomes of the study group.

<table>
<thead>
<tr>
<th>Description</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median maternal age, years (range)</td>
<td>31 (19–43)</td>
</tr>
<tr>
<td>Median gravidity, range</td>
<td>2 (1–8)</td>
</tr>
<tr>
<td>Median parity, range</td>
<td>1 (1–4)</td>
</tr>
<tr>
<td>Median BMI, kg/m² (range)</td>
<td>26.2 (16.8–50.4)</td>
</tr>
<tr>
<td>Median gestational age at admission, weeks (range)</td>
<td>26±3 (19±0–38±2)</td>
</tr>
<tr>
<td>Median gestational age at delivery, weeks (range)</td>
<td>38±5 (37±1–40±6)</td>
</tr>
<tr>
<td>Median birth weight, g (range)</td>
<td>3305 (2500–4260)</td>
</tr>
<tr>
<td>Fetal gender (female/male), n</td>
<td>91/93</td>
</tr>
</tbody>
</table>
Fetal thymus reference range in healthy singleton pregnancies

During all weeks of gestation. As the week of gestation progressed, a poor correlation of the thymus anterior-posterior/thoracic diameter and thymus perimeter/thoracic circumference with BPD was observed. Spearman’s rho correlation coefficients were 0.236 and 0.267, respectively (all p-values <0.001) (Fig. 2). As a result of linear regression analysis between thymus measurements and BPD, the equations for the optimal models are as follows: thymus transverse diameter = -3.49 + 0.4 × BPD (mm) (r=0.826, R²=0.682, p<0.001), thymus anterior-posterior diameter = -2.48 + 0.22 × BPD (mm) (r=0.808, R²=0.653, p<0.001), thymus perimeter = -14.37 + 1.21 × BPD (mm) (r=0.814, R²=0.663, p<0.001), thymus anterior-posterior diameter / thoracic diameter = 0.38 + 7.76E-4 × BPD (r=0.213, R²=0.045, p=0.004) and thymus perimeter / thoracic circumference = 0.35 + 1.02E-3 × BPD (r=0.263, R²=0.069, p<0.001) (Fig. 3). Thymus transverse diameter, anterior-posterior diameter, and perimeter increased linearly with increasing biparietal diameter (BPD).

**Discussion**

Thymus measurement is not routinely performed in the fetal ultrasonographic examination. However, knowledge of normal thymus size according to weeks of gestation will enable the evaluation of thymic aplasia/hypoplasia. Therefore, we presented the normal range for fetal thymus measurements according to the weeks of gestation in healthy singleton pregnancies in this study.

Fetal thymic function and volume depend on genetic, nutritional, neural, endocrine, and immune factors. Factors that cause placental implantation changes such as...
Fig. 2. Thymus measurements according to gestational age groups.
Fetal thymus reference range in healthy singleton pregnancies

Fig. 3. Linear regression analyses of fetal thymus measurements and biparietal diameter.
as hypoxia, maternal diabetes, preeclampsia, and intrauterine growth retardation may induce fetal stress, leading to thymocyte depletion, and consequently, reduction in thymus size.\textsuperscript{[12]} Since the detection of a small thymus in pregnancies with growth retardation may be an early indicator of adverse perinatal outcomes, it will enable clinicians to manage these pregnant patients more carefully, with necessary preventive measurements.\textsuperscript{[13]}

Therefore, to detect abnormal fetal thymus measurements in pregnancy follow-ups in this study, we determined the reference ranges of thymus size starting from the 5th month in fetal ultrasonographic evaluation in healthy pregnancies. This can be easily used in daily practice and is suitable for monthly follow-ups.

Many authors present different ultrasonographic parameters in fetal thymus development. Thymus measurement parameters can be 2 or 3 dimensional (volume data set).\textsuperscript{[7–9,14]} In Tai’s study, it was stated that measurement of transverse diameter is more advantageous than thymus perimeter and thymus/thoracic ratio in thymus evaluation due to less interobserver variability.\textsuperscript{[14]} On the other hand, it has also been reported that the thymic/thoracic ratio is a good predictor in the assessment of thymus in diabetic pregnant patients.\textsuperscript{[7,15]} Chaoui et al. reported that the mean thymic/thoracic ratio in healthy fetuses was 0.44, independent of gestational age.\textsuperscript{[16]} Also, in our study, the mean thymic/thoracic ratio was 0.43; however, no stability was found during pregnancy similar to the Iran study.\textsuperscript{[7]} Therefore, in our study, we determined the reference range of 5 parameters owing to short measurement time and practicality in many cases in three-vessel cross-sections, with a non-invasive cost-free method. On the other hand, measuring only three parameters (thymus transverse diameter, anterior-posterior diameter, and perimeter) that are strongly correlated with gestational age may also be a better choice to assess thymus size.

Fetal thymus localization may always not be possible in the early and last weeks of pregnancy depending on fetal mobility, technique, and the characteristics of the ultrasound device.\textsuperscript{[17]} It was stated in 1989 that the thymus gland could be seen from the 14th week of pregnancy at a rate of 74%.\textsuperscript{[18]}

Despite important factors such as variability of thymic contours, the isoechoic structure of thymus and fetal position, current developments in ultrasound imaging have increased the visibility of the fetal thymus and allowed it to be visualized at earlier weeks.\textsuperscript{[18–20]} It has been possible to visualize thymus 100% with the utilization of methods such as high-resolution transvaginal scan, thy-box (Doppler use), and 3D.\textsuperscript{[5,12]} In the study of Tangshewinsirikul et al., thymus measurements were formulated according to weeks in healthy fetuses between 17 and 38 weeks of gestation, and an estimated reference range was determined. In this study, it was reported that 1% of the measurement could not be performed due to fetal position; however, the trimester in which the measurements could not be taken was not specified.\textsuperscript{[9]} However, in our study, fetal thymus could be visualized at a rate of 93.5%, similar to the study of Cho et al.\textsuperscript{[9]} All of the cases, whose measurements could not be performed, were in the last trimester and they were planned to be included in the study in terms of fetal thymus evaluation only at a glance.

As a result of our study, we observed that all thymic measurements (transverse diameter, anterior-posterior diameter, perimeter) increase linearly as the week of gestation progresses. In the study of Cho et al., the authors determined that the transverse diameter of the thymus at 33 weeks of gestation was similar in millimeters, while it was lower in earlier weeks, and it was slightly higher than the week of gestation after 33 weeks.\textsuperscript{[9]} In our study, while we observed the thymus transverse diameter to be lower in millimeters compared to the week of gestation before 27 weeks, it was similar to the week of gestation after 27 weeks. It can be considered that these differences may occur due to ethnic or environmental changes as well as differences in measurement methods.

In our study, in which the reference range of all measurement parameters of the thymus was determined, we observed that thymic transverse diameter, thymus anterior-posterior diameter, and thymus perimeter nomograms were in high correlation (0.85–0.87) as the week of gestation progressed, while did not find ratio of thymic to thoracic anterior-posterior diameter and ratio of thymus perimeter to thoracic circumference nomograms useful. This ratio instability might be related to the thymus measurement skills. Research with larger series may bring about a more stable ratio of thymic to thoracic diameter and thymic.
to the thoracic circumference. In some studies, thymus transverse diameter is often used as the only parameter due to its practicality and ease of measurement.\textsuperscript{[1,13,22,23]} However, studies are evaluating 2 or more thymus parameters.\textsuperscript{[5,6,9,14,17]} As a result, it is not evident which measurement methods are more sensitive and valuable in the evaluation of thymus aplasia.

Including the small number of patients for each week of gestation, being performed in a single-center, and excluding 6.5% of the patients due to lack of measurements are the main limitations of the study. Multicentric studies involving large populations from different regions and ethnic groups are needed on this subject. On the other hand, measurement of the fetal thymus by experienced specialists with standard measurement techniques in selected healthy singleton pregnancies is the strength of the study.

**Conclusion**

There are a limited number of studies on this subject, and the reference range for fetal thymus gland measurements in our country has not been determined yet. We consider that this study will contribute to the evaluation of abnormal thymus by determining the normal range for fetal thymus measurements according to the weeks of gestation.

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**Compliance with Ethical Standards:** The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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First trimester diagnosis of an unusual case of double aneuploidy with karyotype 48,XXY,+18 (Klinefelter-Edwards syndromes)

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1Department of Perinatology, Tepecik Training & Research Hospital, University of Health Sciences, İzmir, Turkey
2Department of Medical Genetics, Tepecik Training & Research Hospital, University of Health Sciences, İzmir, Turkey
3Department of Obstetrics & Gynecology, School of Medicine, İzmir Tınaztepe University, İzmir, Turkey

Abstract

Objective: Double aneuploidy cases involving autosomal and sex chromosomes are very rare. Therefore, it is difficult to determine the clinical features and prognosis of these cases. In this case, a fetus with 48,XXY,+18 karyotype is presented.

Case: Cystic hygroma, cleft lip and palate, and clubbed foot were detected in the prenatal ultrasonographic evaluation of a 31-year-old pregnant woman at 13 weeks of gestation. Chorionic villus sampling revealed double aneuploidy including Klinefelter and Edwards syndromes. The molecular result was consistent with the occurrence of nondisjunction error involving chromosome 18 in maternal meiosis I (mat MI) but the finding of the extra X chromosome could not be fully explained. Post-abortion fetal pathology specimen confirmed prenatal diagnosis.

Conclusion: Double aneuploidy cases may rarely present with structural anomalies due to maternal meiosis error, without advanced maternal age, as in this case.

Keywords: Klinefelter, Edwards, trisomy 18, 48XXY, double aneuploidy, structural anomaly, meiosis nondisjunction, case report.

Introduction

Autosomal trisomy is a genetic disorder that occurs as a result of nondisjunction in the maternal meiotic phase. Trisomy 13, 18 and 21 are the most commonly diagnosed types of autosomal trisomy. Sex chromosome trisomies such as XXX (triple X syndrome), XXY (Klinefelter syndrome) and XYY (XYY syndrome) are caused by parental meiotic nondisjunction or postzygotic nondisjunction. These chromosomal aberrations are seen very rarely as double aneuploidy with an incidence of less than 1 in 30,000 births. Clinical features and prognosis are not well known in such cases, due to the scarce availability of follow-up data and the limited number of cases reported in the literature. In this case report, a prenatally diagnosed fetus with 48,XXY,+18 karyotype is presented.

Case Report

A 31-year-old, gravida 2, abort 1 woman was referred to the Perinatology Outpatient Clinic of Tepecik Training and Research Hospital due to fetal cystic hygroma at 13 weeks gestation. Prenatal ultrasonographic examination revealed cystic hygroma, cleft lip and palate, and clubfoot (Fig. 1). QF-PCR examination of chorionic villus sampling material detected the chromosome 18 markers as 1:1:1 and 2:1. This result was compatible with Trisomy 18. QF-PCR result of the patient's sex chromosomes was also found to be consistent with XXY. Afterward, FISH analysis was performed on the chorionic villus sampling material, and probes related to chromosome 18 had 3 detected signals, probes related to...
chromosome X had 2 detected signals, and probes related to chromosome Y had 1 detected signal. These studies showed that the prenatal result is consistent with 48, XXY,+18 (Figs. 2 and 3). Chromosome analysis was performed from the mother and father’s peripheral blood. Both of mother and father’s peripheral blood chromosomal analyses showed a normal karyotype. The molecular results, along with the 48, XXY,+18 karyotype, were compatible with the occurrence of nondisjunction error involving chromosome 18 in maternal meiosis I (mat MI) but the finding of the extra X chromosome could not be fully explained. Nondisjunction of XXY chromosome might be related to maternal meiosis 1 or maternal meiosis 2 (mat MI or MII) (Table 1). The parents opted for termination of pregnancy at 14 weeks of gestation. Images of the anatomic specimen were not available as termination was performed elsewhere. Post-abortive fetal pathology specimen evaluation confirmed prenatal diagnosis.

Discussion
The present case was prenatally identified with two aneuploidies involving Klinefelter syndrome and trisomy 18 and ultrasound findings with cleft lip and palate, clubbed foot, and cystic hygroma. The occurrence of double aneuploidy in the same fetus is known to be an uncommon phenomenon. The first case with autosomal and sex chromosomal anomalies (48, XXY,+21) was presented by Ford et al. in 1959. Since double aneuploidy cases usually result in abortion, there are few cases reported in the literature. Diego-Alvarez et al. reported the rate of double aneuploidy 2.18% among 321 karyotyped spontaneous abortions between 4 and 24 weeks of gestation. However, the expected frequency of double aneuploidy among very early spontaneous abortions is thought to be higher than the observed one. Therefore, the occurrence of clinically undetected pregnancy losses might be the main reason of the scarcity of data on such rare aneuploidies. Furthermore, advances in ultrasonographic devices and screening for aneuploidy over the years provide improvements in the prenatal diagnosis of these cases.

The most frequently reported double aneuploidies in live births involve sex chromosomes combined with either trisomy, 13, 18, or 21. Thus far, a total of 16 case reports in the literature described the combination of trisomy 18 and Klinefelter syndrome. The diagnosis

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**Table 1.** Molecular analysis of 18 and X chromosomes with polymorphic markers. mat MI, maternal meiosis I nondisjunction error; mat MII, maternal meiosis II nondisjunction error.

<table>
<thead>
<tr>
<th>Locus</th>
<th>18C</th>
<th>18D</th>
<th>18B</th>
<th>18M</th>
<th>18J</th>
<th>XY2</th>
<th>X3</th>
<th>X9</th>
<th>Xq26.2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Maternal</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paternal</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>mat MI</td>
<td>mat MI or MII</td>
<td></td>
<td></td>
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</tbody>
</table>
First trimester diagnosis of an unusual case of double aneuploidy with karyotype 48,XXY,+18

Fig. 2. Positive quantitative fluorescent polymerase chain reaction results with extra short tandem repeat markers in 48,XXY,+18: Trisomy 18 is identified by a trisomic diallelic pattern for D18S978, D18S535, GATA178F11, and D18S976 (≥1.8) and a trisomic triallelic pattern for D18S386 (1:1:1). XXY is identified by a trisomic diallelic pattern for Amelogenin, T3:3X,XY2,ZFYX,T1:7X and XY3.
was made postnatally in most of the cases. Only four (%25) of these fetuses were diagnosed during the pre-natal period (Table 2). Van Ravenswaaij-Arts et al. performed amniocentesis at 31 weeks of gestation, due to polyhydramnios and fetal growth retardation, bilateral cleft lip on ultrasound. The sample analyzed revealed a 48,XXY,+18 karyotype that was initially misinterpreted as pseudomosaicism. Komwilaisak et al. reported a 33-week fetus with ultrasound findings of large for the date, single umbilical artery with the absence of the left umbilical artery, polyhydramnios, and fetal growth restriction. Karyotyping from the cordocentesis led to the diagnosis of 48,XXY/+18, which was confirmed after delivery of the fetus. Begam et al. presented a case of 34 weeks with several markers of chromosomal anomalies including choroid plexus cyst, severe asymmetrical intrauterine growth restriction, strawberry-shaped head, micrognathia, cerebellar hypoplasia, membranous ventricular septal defect, bilateral clubfeet, clinodactyly, and pectus excavatum. Amniocentesis and cytogenetic analysis of their case revealed double aneuploidy of both trisomy 18 and Klinefelter syndrome, 48,XXY+18. Chen et al. delivered a fetus at 22 weeks of gestation with clenched hands, arthrogryposis of the left wrist, aplasia of the left thumb, micrognathia, low-set ears, hypertelorism, rocker-bottom feet, and a normal penis. Cytogenetic analysis of cultured amniocytes revealed a karyotype of 48,XXY,+18.

Taken together, infants or fetuses with a karyotype of 48,XXY,+18 may present typical abnormalities of trisomy 18 and Klinefelter syndrome. The most common findings were growth restriction, heart defects, micrognathia, suggesting the clinical picture is dominated by the symptoms associated with trisomy 18. Among all prenatally detected cases, the diagnoses were possible in the second or third trimester of pregnancy. In literature, however, this is the first reported case of 48,XXY,+18 syndrome detected in the first trimester of pregnancy by chorion villus sampling. Most of the mentioned findings in previous cases were not present in our case due to the diagnosis in the early weeks of gestation. But it should also be kept in mind that some associated structural anomalies of 48,XXY,+18 syndrome could be demonstrated before routine mid-trimester anomaly scan.

It has been found that the extra chromosomes in double aneuploidy are almost always of maternal origin. Similarly, extra chromosomes in our case were originated from meiosis 1 for chromosome 18 and meiosis 1 and 2 for chromosome X. The most proposed explanation for the cause of nondisjunction was advanced maternal age. It has been demonstrated that maternal age in double trisomy cases is significantly higher than that for single trisomy cases. In contrast to the literature, we did not find maternal age as a contributing factor for the development of nondisjunction.

There was great variation in neonatal survival of fetuses with a double aneuploidy. Hou reported a case with the longest survival. In his report, a male fetus was delivered at 39 weeks of gestation with growth restriction, heart defects, micrognathia, congenital diaphragmatic hernia, single umbilical artery, congenital diaphragmatic hernia, left renal hypoplasia, right hydronephrosis, clenched hands, clinodactyly, inguinal hernia, high-arched palate, and cryptorchidism. Cytogenetic analysis of that case revealed double aneuploidy of both trisomy 18 and Klinefelter syndrome, 48,XXY+18, and remained alive up to 21 months. All other antenatally reported cases were terminated or resulted in neonatal death.
First trimester diagnosis of an unusual case of double aneuploidy with karyotype 48,XXY,+18.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Karyotype</th>
<th>Maternal age (y)</th>
<th>Paternal age (y)</th>
<th>Major abnormalities and outcome</th>
<th>Parental origin of aneuploidy</th>
<th>Cell stage of nondisjunction Chr. 18</th>
<th>Cell stage of nondisjunction Chr. X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Ravenswaaij-Arts et al.[5]</td>
<td>47,XY,+3/48, XXY,+18/46,XY</td>
<td>26</td>
<td>NA</td>
<td>Prenatal ultrasound at 31 weeks: • IUGR, polyhydramnios, and bilateral cleft lip. Amniocentesis: • Delivery at 38 weeks, 1746 g, bilateral cleft lip and palate, microenopsis, cryptorchidism, ventriculomegaly, camptodactyly, an atrioventricular septal defect, hypoplasia of cerebellar vermis, facial dysmorphism, clenched hands, and neonatal death (10 days).</td>
<td>NA</td>
<td>PZM (suspected)</td>
<td>PZM (suspected)</td>
</tr>
<tr>
<td>Komwilaisak et al.[6]</td>
<td>48,XXY,+18</td>
<td>21</td>
<td>NA</td>
<td>Prenatal ultrasound at 33 weeks: • IUGR, polyhydramnios, single umbilical artery, micrognaithia, bilateral club hands, clenched hands, and rocker-bottom feet. Cordosentesis: • Delivery at 38 weeks, 2200 g, microcephaly, bilateral cataract, microtia, microenopsis, undescended testicles, two-vessel cord, facial dysmorphism, and neonatal death (18 days).</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Begam et al.[7]</td>
<td>48,XXY,+18</td>
<td>NA</td>
<td>NA</td>
<td>Prenatal ultrasound at 34 weeks: • IUGR, choroid plexus cysts, cerebellar hypoplasia, ventricular septal defect, club feet, clinodactyly, and pectus excavatum. Amniocentesis: • Facial dysmorphism, clenched hands, and neonatal death (2 days).</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chen et al.[8]</td>
<td>48,XXY,+18</td>
<td>42</td>
<td>43</td>
<td>Prenatal ultrasound at 18 weeks: • Choroid plexus cysts. Prenatal ultrasound at 22 weeks: • A flexion contracture, • Deformity of left wrist, and absence of left thumb. Amniocentesis: • Termination at 22 weeks, 332 g, facial dysmorphism, micrognaithia, arthrogryposis of left wrist, aplasia of left thumb, clenched hands, and a normal penis.</td>
<td>Maternal MI</td>
<td>MII</td>
<td>MII or PZM</td>
</tr>
<tr>
<td>Present case</td>
<td>48,XXY,+18</td>
<td>31</td>
<td>NA</td>
<td>Prenatal ultrasound at 14 weeks: • Cleft lip and palate, pes equinovarus and cystic hygroma. • Termination at 14 weeks, NA.</td>
<td>Maternal MI</td>
<td>MII</td>
<td>MII or MII</td>
</tr>
</tbody>
</table>

Chr: chromosome; IUGR: intrauterine growth restriction; MI: meiosis I nondisjunction error; MII: meiosis II nondisjunction error; NA: not available; PZM: postzygotic mitotic error.
Conclusion
In conclusion, we presented a rare case of double aneuploidy (48,XXY,+18) with cystic hygroma, cleft lip and palate, and clubfoot diagnosed at early weeks of gestation. In this case, extra chromosomes were of maternal origin but not associated with advanced maternal age. Therefore, the possibility of this rare chromosomal abnormality should be considered in the differential diagnosis of structural malformations in the first trimester of pregnancy even in the absence of advanced maternal age.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

References
Prenatal diagnosis of Galen vein aneurysm: when to deliver?

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Abstract

Objective: Prenatal diagnosis of Galen vein aneurysm using color Doppler has become relatively easy. Management and timing of delivery is however challenging because of cardiac function deterioration. Ultrasound follow-up is essential to detect signs of fetal cardiac failure which must be weighed against risks of prematurity. Postnatal deterioration of the vital signs can follow a short period of improvement after birth. This report illustrates the many pitfalls that could affect the final outcome, raising the issue of the proper timing for delivery.

Case: A 23-year-old G1P0 spontaneous pregnancy was referred at 28 WA for a Galen vein aneurysm. The ultrasound finding included a 35 by 14 mm vascular structure with a turbulent flow, occupying the central part of the head. After 48 hours in-hospital surveillance through non-stress tests twice daily, she had a cesarean section due to a persistent non-reactive fetal heart rate, with absent variability. Unfortunately, despite a stable state for the first ten days, the baby’s cardiac function deteriorated abruptly on day 11, and the baby died of heart failure despite medical management.

Conclusion: The timing of delivery in cases with Galen vein aneurysm is challenging mainly in the case of premature babies, as the prognosis is globally bad. Postnatal deterioration of the vital signs can follow a short period of improvement after delivery.

Keywords: Fetal, Galen vein aneurysm, malformation, prematurity, ultrasound.

Introduction

Galen vein aneurysm is a rare occurrence involving cerebral vessels and leading to a high output cardiac failure, potentially leading to fetal demise. We report a case that highlights the difficulty in the clinical management of this entity.

Case Report

A 23-year-old G1P0 spontaneous pregnancy was referred at 28 WA for a Galen vein aneurysm. The ultrasound finding included a tubular irregular vascular structure (35x14 mm in diameter) with a turbulent flow, occupying the central part of the head (Fig. 1). Biometry was around the 20th percentile. Cardiac overload was evident, with a spherical shape heart, dilated neck vessels, and tricuspid regurgitation. At 33 weeks, IUGR was more obvious, reaching the 10th percentile for all the biometric parameters. Umbilical artery Doppler then displayed an absent diastolic flow; and ductus venosus revealed an abnormal a wave. Mid-cerebral artery Doppler was measurable despite the aneurysm and remained in the normal range. After 48 hours in-hospital surveillance by non-stress tests twice daily, she had a cesarean section due to a persistent non-reactive fetal heart rate, with a pathologically reduced variability. The baby weighed 1800 g and was doing relatively well, with a 5-minute Apgar score of 9.

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As the baby was stable for the first 48 hours, occlusion of the aneurysm by interventional radiology was postponed until reaching a weight of 2500 g. This decision was based on literature review—expert opinions from centers having a relatively extensive experience in cases of Galen vein aneurysm—and furtherly based on the preference of our radiology team. Unfortunately, despite a stable neonatal condition for the first ten days, the baby’s cardiac function deteriorated abruptly on day 11, and the baby died of heart failure despite medical support. This case raises the question regarding the timing of delivery and scheduling the interventional radiology procedure, with both prenatal and postnatal outcomes being at risk for these babies. This case report has been approved and registered by our institution’s review board under the number CEHDF-899.

Discussion

Despite its rarity, Galen vein aneurysm represents the most frequent cerebral arteriovenous malformation detected prenatally, and approximately 30% of all pediatric vascular malformations. The prognosis depends on gestational age at diagnosis and aneurysm size.\(^1\) Tricuspid regurgitation, major brain lesion and volume of the lesion on MRI are also associated with a poor outcome.\(^2\) Prognosis also depends upon prematurity as most babies are delivered because of the risk of heart failure.

Some cases present regression following delivery, suggesting a more conservative approach after delivery.\(^3\) In our case, despite a relatively favorable postnatal outcome, a rapid deterioration of the cardiac status occurred after 11 days. A similar case has been reported by Cherif et al., who evidenced that after an initial period of improvement, the cardiac status deteriorated suddenly on day 14, which led to fetal death on day 36 despite medical treatment; the authors concluded that heart failure can occur much after the first days of life.\(^4\) Embolization is a therapy of choice; the results are variable as a few authors report high failure rate and neonatal death.\(^1,5\)

Prognostic features on ultrasound have been reported, and include mapping of intracranial feeding arteries, assessment and measurement of flow in the straight sinus, existence of ‘steal’ retrograde aortic flow, and the appearance of high-output cardiac state.\(^6\) The related outcome appears poor, with only about 30–50% of patients diagnosed with the condition being alive without mental impairment.\(^1,2\) Deciding for delivery to allow radiology intervention appears to have a limited impact due to the existing serious prognosis involved, and the timing of this decision can be challenging.

Conclusion

The timing of delivery in cases with Galen vein aneurysm is challenging mainly in the case of premature babies, as the prognosis is globally bad. Postnatal deterioration of the vital signs can follow a short period of improvement after delivery.

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Bladder dissection for cesarean hysterectomy in case of severe placenta percreta: tips and tricks

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Abstract
Objective: In this article, we report a severe case of placenta percreta in order to present our surgical approach for bladder dissection in a pregnancy with placenta accreta spectrum (PAS).

Case: Bladder dissection was performed using bipolar forceps and bipolar scissors and with a meticulous lateral-to-medial dissection on each side.

Conclusion: We recommend electrodissection of the bladder using bipolar forceps. Bipolar device may indeed help in the hemostasis of the placenta vessels while performing the bladder dissection.

Keywords: Placenta previa, accreta, hysterectomy, postpartum hemorrhage.

Introduction
Placenta accreta spectrum (PAS) is a complication of pregnancy characterized by an abnormal adherence of the placenta to the uterine wall. Recently, Einerson et al. argued that PAS exists as a disorder of defective decidua and uterine scar dehiscence, not as disorder of destructive trophoblast invasion. PAS can be classified clinically and radiologically by its histopathologic grade, in placenta accreta, increta and percreta.

PAS is associated with high risk of maternal morbidity, and the severity of the complications varies according to the depth of villous invasion. The gold standard approach for PAS is cesarean hysterectomy performed at around 32–34 weeks according to the severity of the condition. Different surgical techniques have been suggested in order to improve maternal outcome and reduce blood loss. Bladder dissection is often the most prolonged surgical time, may be associated with protracted venous bleeding, and therefore requires meticulous dissection.

Here, we report a severe case of placenta percreta in order to present our surgical approach for bladder dissection.

Case Report
A 35-year-old woman was referred to our institution at 29 weeks of gestation for suspected placenta accreta and frank hematuria. She had two prior cesarean deliveries at term, and one prior abortion with surgical evacuation in her history. Ultrasound examination showed placenta previa with presence of placenta lacunae, loss of the clear space, increased vascularity and disruption of the bladder-myometrial interface with suspicious of bladder and cervical invasion (Fig. 1). MRI showed uterine bulging,
focal interruption to myometrial wall and bladder invasion of the placental tissue.

A cesarean hysterectomy at 32 weeks was planned. At the time of intervention, a cystoscopy was performed and ureteral stents were placed. The cystoscopy showed placental vessels on the posterior wall of the bladder with no trigone involvement.

Midline access was performed and showed placenta accreta with lateral and anterior invasion. Hysterotomy was made vertically toward the fundus to deliver the fetus avoiding the placenta. Then, the bladder flap was ligated to the skin.

Superior devascularization was then performed with ligation of the round ligaments and utero-ovarian pedicles bilaterally. The uterus was then skeletonized down to the cardinal ligaments and retroperitoneal dissection was performed. We also performed peritoneal dissection to locate the bifurcation of the common iliac arteries and the ureters. The internal iliac artery was then ligated bilaterally. Bladder dissection was performed using bipolar forceps and bipolar scissors. Meticulous lateral-to-medial dissection on each side was performed (Supplementary material: S-Video 1). Then, an adequate exposure for vault entry was created and the main uterine artery pedicles were ligated. The colpotomy was performed with circumferential incision around the cervicovaginal margin, the vaginal angles were ligated and vaginal vault closed after removal of the uterus (Fig. 2).

Discussion
Bladder dissection is the most high-risk step at the time of cesarean hysterectomy for placenta accreta. The risk of massive bleeding is high and any inadvertent injury to the blood vessels may lead to a massive life-threatening hemorrhage. In this video article, we recommend electrodissection of the bladder using bipolar forceps. Bipolar device may indeed help in the hemostasis of the placenta vessels while performing the bladder dissection, and should be used as gold standard technique over monopolar cautery that can lead to vessel injury. Notably, placenta previa and accreta are also characterized by newly formed blood vessels. The newly formed feeding blood vessels as a result of ‘neovascularization’ lack the tunica media (i.e. the muscle layer) and, therefore, may not be amenable for traditional hemostatic measures such as sutures or diathermy, which are dependent on the tunica media. This can result in torrential bleeding during a hysterectomy, and higher risk of damage to adjacent organs such as the bladder or ureters.\[8\]
Conclusion
In summary, we provided surgical technique details regarding hemostasis of the placenta vessel at level of bladder at the time of cesarean hysterectomy for placenta accreta using bipolar device.

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References

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