

e-ISSN: 2980-0579

Volume: 4

Issue: 4

Year: 2026

JCOGP

Journal of Controversies in
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ORIGINAL ARTICLES

- Growth and neurodevelopmental outcomes of infants born to mothers with COVID-19 during pregnancy 83-89
Eryılmaz Yıldır H, Saç R, Tapcı AE, Bayram Ö, Kahvecioğlu D, Taşar A.

- Evaluation of vaccination rates with influenza vaccines in pregnant females and their attitudes towards these vaccines..... 90-95
Aydoğmuş S, Ünsal Keser SN, Gözüküçük M, Cesur S, Üstün Y.

- Clinical and laboratory characteristics according to the onset of neonatal sepsis: a retrospective cohort study.....96-101
Sincar F, Kahvecioğlu D, Taş Güngör M, Geyik C.

- Acute abdomen in pregnancy in a tertiary referral center: diagnostic challenges and surgical outcomes.....102-107
Çayönü Kahraman N, Şeyhanlı Z, Özcan Ü, Duygulu Bulan D, Çağlar AT.

CASE REPORT

- A fetiform placental lesion in a monochorionic diamniotic placenta: a diagnostic challenge between teratoma and an acardiac co-twin—a case report 108-112
Yıldız AG, Haliloğlu S, Akın F, Üner H, Kahyaoğlu İ.

Growth and neurodevelopmental outcomes of infants born to mothers with COVID-19 during pregnancy^a

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Cite this article: Eryılmaz Yıldır H, Saç R, Tapcı AE, Bayram Ö, Kahvecioğlu D, Taşar A. Growth and neurodevelopmental outcomes of infants born to mothers with COVID-19 during pregnancy. *J Controv Obstetr Gynecol Ped.* 2026;4(4):83-89. doi:10.51271/JCOGP-0079

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Received: 28/06/2026

Accepted: 29/07/2026

Published: 28/10/2026

ABSTRACT

Aims: To evaluate the impact of intrauterine SARS-CoV-2 exposure on infant growth and neurodevelopment by comparing anthropometric measurements and Denver Developmental Screening Test II (DDST-II) results between infants born to mothers with COVID-19 during pregnancy and unexposed controls.

Methods: This retrospective case-control study included 40 term infants born to mothers with confirmed COVID-19 during pregnancy and 40 term infants born to mothers without COVID-19 infection. The well-child follow-up records from July 2020 to July 2022 were reviewed. Demographic characteristics, anthropometric measurements, and DDST-II results were analyzed.

Results: The groups were comparable in terms of demographic characteristics, birth weight, gestational age, and gender (all $p > 0.05$). In the study group, 45% of mothers had COVID-19 during their third trimester. At one month, head circumference (HC), length, and weight percentiles were similar between the groups. At six months, HC below the third percentile was more common in the exposed group (22.2% vs. 3.6%, $p = 0.045$), whereas length and weight percentiles did not differ. No significant differences were observed in anthropometric measurements at nine months. DDST-II showed age-appropriate neurodevelopment in 39 infants in each group; one infant in the exposed group had a suspicious result, and one control infant had an abnormal result.

Conclusion: Prenatal SARS-CoV-2 exposure was not associated with significant differences in infant growth or neurodevelopment during the first year of life. Larger prospective studies with longer follow-up periods are required to determine the long-term outcomes.

Keywords: Anthropometric measurements, COVID-19, development, growth

^aThis study was presented as a poster presentation at the Congress of Joint European Neonatal Societies, Rome, Italy, September 19, 2023.

INTRODUCTION

COVID-19 symptoms during pregnancy are the same as those observed in non-pregnant adults. Although more than 90% of patients with COVID-19 recover without hospitalization, the severity of the disease may escalate in the presence of risk factors. Older age, obesity, hypertension, and diabetes mellitus are risk factors for symptomatic COVID-19 during pregnancy. Furthermore, an increase in obstetric complications, such as preterm birth, premature rupture of membranes, fetal distress, and preeclampsia, has been reported in pregnant females with COVID-19.¹⁻⁴

Certain antenatally acquired viral infections can have permanent, potentially destructive effects on the developing fetal brain.^{5,6} Other viral infections that fail to cross the

placental barrier, including influenza, have also been consistently associated with adverse neurodevelopmental outcomes.⁷⁻¹¹ Infection and inflammation negatively affect motor development.¹²

It is generally accepted that respiratory viruses such as SARS-CoV-2 do not have intrauterine transmission. In a systematic review evaluating the effects of COVID-19 on maternal, perinatal, and neonatal outcomes, no conclusive evidence was identified regarding the maternal-fetal transmission of the virus.¹³ Moreover, no increase in the incidence of congenital anomalies has been reported.² However, it has been observed that the newborns of mothers who contracted COVID-19 during pregnancy were more likely to require admission



to the neonatal intensive care unit (NICU).¹⁴ There are also studies reporting an increase in intrauterine fetal and neonatal deaths in the presence of COVID-19 infection.^{4,15}

Although some studies have investigated the effects of intrauterine COVID-19 exposure on infant development, no consensus has yet been reached. While some studies indicate that infants exposed to COVID-19 are more neurodevelopmentally delayed,¹⁶ others have not found evidence of a neurodevelopmental delay but have shown that these infants have lower scores in areas such as fine motor skills and problem solving.¹⁷

The long-term effects of COVID during pregnancy on newborns remain uncertain. Several studies have reported negative neurodevelopmental outcomes.¹⁸⁻²⁰ However, there is insufficient information concerning the long-term effects of COVID-19 during pregnancy and its impact on physical growth and neurodevelopment in childhood. Some studies have reported an increase in the rates of neurodevelopmental diseases.^{17,18} In the current study, we retrospectively examined the well-child polyclinic follow-up data, demographic characteristics, anthropometric measurements, and Denver Developmental Screening Test II (DDST-II) results of healthy term infants under one year of age whose mothers had contracted SARS-CoV-2 during pregnancy. We aimed to evaluate the effect of COVID-19 infection during pregnancy on fetal growth and development by comparing the results with those of healthy controls.

METHODS

This study was approved by the Ethics Committee of Ankara Training and Researches Hospital of the University of Health Sciences (Date: 07.09.2022, Decision No: E-22-1072). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This was a retrospective, single-center study. Between July 2020 and July 2022, data obtained from the electronic medical records of term infants aged 0–12 months who were followed up at the Well-Child Polyclinic of the Department of Pediatric Health and Diseases at Health Sciences University Ankara Training and Research Hospital were examined in this study. The study group comprised infants born to mothers who had COVID-19 during pregnancy, and the control group comprised infants in the same age range who were followed up during the same period and whose mothers did not have a history of COVID-19 during pregnancy. Both groups included only infants with complete data from at least two of the first, sixth, and ninth month controls. Furthermore, all infants included in the sample had undergone anthropometric measurements at the well-child polyclinic and had completed well-child follow-up forms. They were all evaluated as “healthy” with a normal birth weight between the 10th and 90th percentiles according to their gestational age, and they also underwent DDST-II. Infants who were not followed up regularly or whose information could not be accessed, and those with complications at birth, hypoxia, or NICU admission were not included in the study. Infants with comorbidities, a history of premature birth (gestational age <37 weeks), low birth weight for gestational age, below the 10th percentile for intrauterine growth, who

had not undergone DDST-II, and who were older than 12 months were excluded.

General physical examination findings, percentile values of body weight (BW), body length (BL), and head circumference (HC) measurements, and DDST-II results were routinely recorded in the well-child polyclinic for infants aged 0–1 year of age. In addition, regular breast milk intake and vitamin D and iron supplementation were questioned and recorded during the follow-up period.

During all follow-up examinations, the BW of the infants was measured without clothing using a regularly calibrated Wunder BABY scale (barcode number: 1012616913) sensitive to 10 g. BL was measured in the supine position on a hard-floored bed, with the head fixed at a 90-degree angle to the bed, while the infant's whole body was stretched. In this position, the distance from the top of the head to the tip of the heel was measured by a physician using a non-flexible tape measure. HC was measured using a non-flexible tape measure from the most protruding point of the frontal bone at the front to the occipital protuberance at the back of the head.

All measurements were conducted according to the Neyzi percentile values for each month.²¹ The study and control groups were considered normal if their BW, BL, and HC values fell within the range of 3p-97p and non-normal if they were below 3p, and a statistical comparison was performed. As there were no infants with values above 97p in the study or control groups, this threshold was not included in the grouping.

During follow-up, breast milk intake was assessed every month. Infants who were constantly breastfed between 0 and 6 months were evaluated as having received breast milk regularly, whereas the remaining infants were considered to have received breast milk irregularly.

At our hospital, the DDST-II is performed by certified child development specialists who have successfully completed a comprehensive training program. In the current study, DDST-II was performed on infants aged six–nine months. The DDST-II was scored as “pass,” “fail,” “impossible,” and “untestable,” and the test result was interpreted as “normal,” “suspicious,” “abnormal,” and “untestable.”²² The DDST-II is a general developmental screening tool used in Türkiye and is applied twice to infants under follow-up in our clinic at ages 6-9 months and 18 months.

As this was a retrospective study based on available medical records, no a priori sample size or power calculations were performed. Instead, all eligible infants who met the inclusion criteria during the study period were included in the analysis.

Statistical Analysis

Data analysis was performed using SPSS v. 24.0, and the results were evaluated at a 95% confidence level. Kurtosis and Skewness coefficients were calculated to determine the suitability of quantitative variables for a normal distribution. It was concluded that the values were normally distributed since they were between -3 and +3. The relationship between normal and non-normal status according to percentile values

and other demographic data was analyzed using the Chi-square test. Statistical significance was set at $p < 0.05$.

RESULTS

The study included 80 infants, of whom 40 were in the study group and 40 were in the control group. The gender distribution was 55% ($n=22$) males and 45% ($n=18$) females in the study group and 57.5% ($n=23$) males and 42.5% ($n=17$) females in the control group. The mean age of the mothers was 28.48 ± 5.74 (min: 17-max: 40) years in the study group and 29.18 ± 6.02 (min: 17-max: 39) years in the control group ($p=0.596$). The median week of birth was 39 weeks in both groups (min: 37-max: 42+1 weeks in the study group, min: 37-max: 41+1 weeks in the control group) ($p=0.518$). The mean birth weight was $3,227.38 \pm 446.76$ g in the study group and $3,262.50 \pm 382.96$ g in the control group ($p=0.707$). In the study group, 25.0% of mothers contracted COVID-19 in the first trimester, 30.0% in the second trimester, and 45.0% in the third trimester. A comparison of the remaining demographic characteristics between the study and control groups is presented in **Table 1**.

Table 1. Comparison of the demographic characteristics of the study and control groups

		Study group		Control group		p*
		n	%	n	%	
Maternal comorbidity	Present	6	15.0	2	5.0	0.136
	Absent	34	85.0	38	95.0	
Follow-up during pregnancy	Present	37	92.5	36	90.0	0.692
	Absent	3	7.5	4	10.0	
Number of pregnancies	One	12	30.0	14	35.0	0.358
	Two	17	42.5	11	27.5	
	Three or more	11	27.5	15	37.5	
Number of living children	One	14	35.0	16	40.0	0.072
	Two	19	47.5	10	25.0	
	Three or more	7	17.5	14	35.0	
Miscarriage or stillbirth	None	31	77.5	34	85.0	0.541
	One	6	15.0	5	12.5	
	Two	3	7.5	1	2.5	
Mode of delivery	Cesarean section	18	45.0	18	45.0	1.000
	Normal vaginal	22	55.0	22	55.0	
Status of receiving breast milk	Regular	39	97.5	36	90.0	0.166
	Irregular	1	2.5	4	10.0	
Formula use	Present	8	20.0	16	40.0	0.051
	Absent	32	80.0	24	60.0	
Vitamin D supplementation	Regular	40	100.0	39	97.5	0.314
	Irregular	0	0.0	1	2.5	
Iron supplementation	Regular	33	82.5	34	85.0	0.762
	Irregular	7	17.5	6	15.0	

*Chi-square test

The first-month HC was determined to be at or below 3p in four (16.7%) and two (7.7 %) infants in the study and control groups, respectively ($p=0.295$). No significant differences

were detected in the first-month BW, BL, and HC percentile comparisons between the two groups ($p > 0.05$). At the sixth-month follow-up, 6 (22.2%) infants in the study group and one (3.6%) infant in the control group had an HC below 3p, indicating a statistically significant difference ($p < 0.045$). However, the length and weight percentiles of the two groups evaluated at the sixth month did not differ significantly ($p > 0.05$). At the ninth month, there were no significant differences between the two groups in terms of BW, BL, or HC percentiles ($p > 0.05$) (**Table 2 and Figure**).

Table 2. Comparison of the study and control groups according to whether their head circumference, length, and weight were within the normal percentile range at the first, sixth, and ninth-month follow-up visits

		Group				p*
		Study		Control		
		n	%	n	%	
First-month head circumference	Non-normal	4	16.7	2	7.7	0.295
	Normal	20	83.3	24	92.3	
First-month length	Non-normal	0	0.0	0	0.0	-
	Normal	19	100.0	18	100.0	
First-month weight	Non-normal	1	3.8	0	0.0	0.520
	Normal	25	96.2	24	100.0	
Sixth-month head circumference	Non-normal	6	22.2	1	3.6	0.045
	Normal	21	77.8	27	96.4	
Sixth-month length	Non-normal	4	14.8	4	14.3	0.626
	Normal	23	85.2	24	85.7	
Sixth-month weight	Non-normal	2	7.1	1	3.7	0.514
	Normal	26	92.9	26	96.3	
Ninth-month head circumference	Non-normal	3	14.3	2	6.3	0.304
	Normal	18	85.7	30	93.8	
Ninth-month length	Non-normal	3	14.3	4	12.5	0.580
	Normal	18	85.7	28	87.5	
Ninth-month weight	Non-normal	1	4.8	1	3.1	0.640
	Normal	20	95.2	31	96.9	
*Pearson's Chi-square test; Fisher's exact test was used where appropriate						

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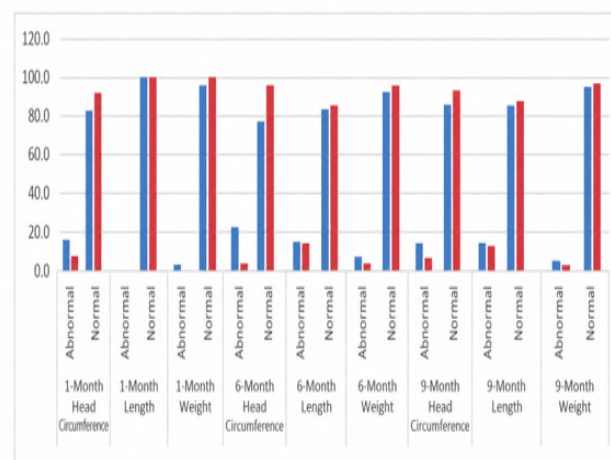


Figure. Distribution of the study and control groups according to whether their head circumference, length, and weight were within the normal percentile range at the first, sixth, and ninth months

Given that the physical examination and laboratory testing of infants with a low first-month percentile yielded normal results, only HC was checked and continued to be followed

up. At the sixth month, three of the six infants whose HC percentile was not normal had no other remarkable physical examination findings. Microcephaly screening and developmental tests of these infants were normal, and their HC values were within the normal range in subsequent measurements. The remaining three infants did not attend subsequent follow-up appointments. According to the sixth-month measurements, the BL percentile was 3p or below in four infants in each group. The BW assessment undertaken at the sixth month revealed that two infants in the study group and one infant in the control group had values outside the normal range. These infants were followed up in terms of both BL and BW.

At the ninth-month follow-up, values in or below 3p were detected in the HC measurements of three infants in the study group and two infants in the control group, in the BL measurements of three infants in the study group and four infants in the control group, and in the BW measurements of one infant in each group. One infant in the study group had both HC and BL values at or below 3p. The patient was followed up, and her progress was within normal limits. Her laboratory and developmental test results were normal. It was observed that one of the other two infants with a low HC showed normal values during the follow-up, whereas the remaining infant did not attend the subsequent follow-up appointments. Of the other two babies in the study group whose BL values were at or below 3p, one was observed to have a normal length during the follow-up, while the other did not attend the subsequent follow-up appointments. It was observed that the infants in the study group who had a low BW achieved a normal weight by the 18th month after following dietary recommendations. In the control group, one infant had both HC and BL values at the 3p limit, but these values increased to normal levels in subsequent follow-up visits. One infant with BW and BL values $\leq 3p$ was referred to an endocrinologist, but did not attend follow-up visits. The other patient with a low HC had normal HC measurements during subsequent follow-ups. The remaining two infants with a low BL in the control group achieved BL values within normal limits by the 15th-month of follow-up.

Upon comparison of the first-, sixth-, and ninth-month HC, BL, and BW percentiles according to gender, we determined that the HC of 96.4% of the male and 77.3% of the female infants were within normal limits at the first month ($p=0.051$). No statistically significant gender-related differences were found in the BL and BW percentiles evaluated at the first month or the HC, BL, and BW percentiles evaluated at the sixth and ninth months ($p>0.05$ for all). The comparison of the HC, BL, and BW percentiles of the infants in the study group according to the trimester of maternal COVID-19 revealed that the infants born to mothers who contracted COVID-19 during the second trimester had higher rates of HC measurements below 3p at all three follow-up evaluations; however, a statistical comparison could not be made (Table 3).

To observe the effect of SARS-CoV-2 infection during pregnancy on the neurodevelopment of infants, we used the results of the DDST-II, a test routinely performed at the well-child polyclinic of our hospital. DDST-II revealed that the neurodevelopment of 39 infants in each group was consistent

Table 3. Evaluation of whether the percentiles of the study group were within the normal range according to the trimester during which mothers had COVID-19

		Trimester of maternal COVID-19					
		First		Second		Third	
		n	%	n	%	n	%
First-month head circumference	Non-normal	1	16.7	2	22.2	1	11.1
	Normal	5	83.3	7	77.8	8	88.9
First-month length	Non-normal	0	0.0	0	0.0	0	0.0
	Normal	5	100.0	7	100.0	7	100.0
First-month weight	Non-normal	0	0.0	0	0.0	1	10.0
	Normal	6	100.0	10	100.0	9	90.0
Sixth-month head circumference	Non-normal	1	20.0	3	30.0	2	16.7
	Normal	4	80.0	7	70.0	10	83.3
Sixth-month length	Non-normal	2	40.0	1	9.1	1	9.1
	Normal	3	60.0	10	90.9	10	90.9
Sixth-month weight	Non-normal	1	20.0	1	9.1	0	0.0
	Normal	4	80.0	10	90.9	12	100.0
Ninth-month head circumference	Non-normal	0	0.0	2	28.6	1	14.3
	Normal	7	100.0	5	71.4	6	85.7
Ninth-month length	Non-normal	0	0.0	1	14.3	2	28.6
	Normal	7	100.0	6	85.7	5	71.4
Ninth-month weight	Non-normal	1	14.3	0	0.0	0	0.0
	Normal	6	85.7	7	100.0	7	100.0

COVID-19: Coronavirus disease 2019

with their age, while the results were suspicious in one infant in the study group and abnormal in one infant in the control group. The infant with a suspicious result in the study group had problems with gross motor skills, and his mother contracted COVID-19 during the second trimester (sixth month) of pregnancy. The infant with abnormal results in the control group had issues with language development.

DISCUSSION

In this study, we aimed to evaluate the effect of SARS-CoV-2 during pregnancy on the growth and development of infants in the first year after birth using anthropometric measurements and the DDST-II. At the sixth month, the HC values of six babies (22.2%) in the study group and one infant (3.6%) in the control group were found to be at or below 3p ($p<0.045$). The neurodevelopment of 39 infants in each group was consistent with their age according to the DDST-II, while one infant in the study group had a suspicious result and one infant in the control group had an abnormal result.

It has been reported that SARS-CoV-2 infection during pregnancy is associated with increased maternal death, maternal and neonatal morbidity, preterm birth, and an increased rate of cesarean deliveries.¹⁸ SARS-CoV-2 infection during pregnancy increases the risk of preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.²³ During the study period, 140 infants born to mothers who contracted SARS-CoV-2 during pregnancy were followed up. None of the mothers had a history of severe COVID-19 infection or related hospitalization. The final study group consisted of 40 infants

after excluding nine premature births, three low-birth-weight infants, five NICU admissions, and other cases that were lost to follow-up.

In two separate studies examining the pregnancy outcomes of females with and without a history of SARS-CoV-2 infection during pregnancy, the BW values of the infants were compared between the two groups, and no significant difference was detected.^{24,25} Similarly, in our study, there was no significant difference between the infants in the study and control groups in terms of their BW.

In a cohort study investigating the clinical course of SARS-CoV-2 infection and its impact on pregnant females, Şahin et al.²⁶ found that 44.7% of 533 pregnant females were infected in the third trimester, 30.9% in the second trimester, and 24.4% in the first trimester. In another study evaluating the effects of SARS-CoV-2 during and after pregnancy, Lokken et al.²⁷ reported that the majority of females contracted SARS-CoV-2 in the third trimester of pregnancy (56.3%), followed by the second trimester (27.9%) and the first trimester (15.8%). Similarly, in our study, 25.0% of mothers with a history of COVID-19 during pregnancy contracted the disease in the first trimester, 30% in the second trimester, and 45% in the third trimester.

There is no evidence supporting the idea that cesarean delivery prevents vertical transmission of COVID-19.²⁸ Mirbeyk et al.²⁹ conducted a systematic review of pregnant females with COVID-19 and their newborns and found a high rate of cesarean delivery (86%). A medical specialty thesis conducted in Türkiye to compare COVID-19-positive pregnant females at birth with non-COVID pregnant females in terms of maternal, neonatal, and perinatal outcomes showed a high rate of cesarean delivery (46 of 50 births) but noted no significant difference when compared with the control group.³⁰ Similarly, upon examining the modes of delivery among the pregnant females in our study and control groups, we observed that 45% of the females underwent cesarean sections, while 55% underwent normal vaginal delivery. There was no significant difference between the study and control groups in terms of the mode of delivery. However, as our study did not investigate whether COVID-19 was present at the time of birth, we were unable to determine the impact of this factor on the mode of delivery.

The optimal course of action for maintaining the health of a newborn is for a mother with suspected or diagnosed COVID-19 to breastfeed her infant and continue the normal process.³¹ A multicenter study conducted by the Turkish Neonatology Association on 125 newborns born to females infected with COVID-19 revealed that the rates of formula use (56.8%) and expressed breast milk use (36%) were higher than the rate of breast milk feeding.³² In our cohort, 97.5% of the infants in the study group and 90% of those in the control group received breast milk regularly for six months. The absence of a significant difference between the two groups and the high rate of infants regularly fed breast milk can be attributed to mothers being informed about the benefits of breastfeeding.

In a study conducted in South India on postpartum breastfeeding, the Breastfeeding Self-Efficacy Scale Short

Form (BSEF-SF) was administered to 63 COVID-19-positive and 63 COVID-19-negative mothers, and the scores were significantly lower in the former. In addition, the rate of mothers with above-average BSES-SF scores was significantly higher among those who received postpartum breastfeeding recommendations.³³

TORCH (intrauterine) infections are a risk factor for hearing impairment in newborns. At our hospital, auditory brainstem response (ABR) screening is performed on all healthy term babies who have not been admitted to the NICU. In our cohort, no infant from either group failed the hearing test. In a retrospective cohort study, Oskovi-Kaplan et al.³⁴ examined the hearing screening results of infants born to mothers who contracted COVID-19 during pregnancy and found no statistically significant difference between the COVID-19 and control groups in the risk of hearing loss. In another study, Alan et al.³⁵ compared the hearing screening results of infants born to pregnant females who tested positive and negative for SARS-CoV-2 during pregnancy. According to the ABR test results, the newborns in the COVID-19 group were more likely to have a “refer” result bilaterally than those in the control group. These discrepancies in the findings of previous studies concerning the effect of COVID-19 on hearing underscore the need for further research.

According to the first-month HC measurements, four infants (16.7%) in our study group and two (7.7%) in our control group had values outside the normal range ($p>0.05$). In addition, one infant in the study group had a BW in the low percentile group. At the sixth month, the HC percentile was evaluated to be within the normal range in six infants (22.2%) in the study group and one infant (3.6%) in the control group, indicating a statistically significant difference ($p=0.045$). Three infants with low HC measurements achieved normal HC values during follow-up, while the remaining three infants did not attend subsequent follow-up appointments. At the ninth-month follow-up of the infants, no significant difference was observed between the two groups in relation to the HC, BL, or BW measurements.

Zeng et al.³⁶ conducted a study in China and found that all physical growth parameters, including BW, BL, and HC, were above 3p in 72 newborns exposed to SARS-CoV-2. In a study from the USA, Schuh et al. included 33 infants born to mothers with SARS-CoV-2 infection and reported BW, BL, and WC measurements taken at the first postnatal visit, as well as at two, four, and six months. The authors stated that the infants had a normal distribution in terms of the Z-scores and growth rates of these measurements.³⁷ A common result obtained from these studies is the absence of short-term negative effects of intrauterine COVID-19 exposure on infants' physical growth. In addition, in the above-mentioned study, Schuh et al.³⁷ evaluated 15 newborns neurodevelopmentally using the Ages & Stages Questionnaires®, Third Edition (ASQ-3) and found the development of the infants to be appropriate for their age. According to the results of the DDST-II, which was conducted to observe the effect of SARS-CoV-2 infection during pregnancy on the neurodevelopment of the infants in our cohort, neurodevelopment was consistent with chronological age in 39 infants in each group. However, one infant in the study group had a suspicious result and one infant in the control group had an abnormal result.

A study comparing infants born to 222 mothers infected with SARS-CoV-2 and 7,550 mothers in the control (uninfected) group during the same period revealed a higher rate of neurodevelopmental diseases among infants born to infected mothers. The authors also noted a higher risk among those exposed to maternal infection in the third trimester.¹⁸ In another study, Pinheiro et al.¹⁷ did not find evidence of a higher neurodevelopmental delay in infants exposed to intrauterine SARS-CoV-2 compared to unexposed infants, but did show that the fine motor and problem-solving skills of infants with SARS-CoV-2 exposure were negatively affected, and they had lower scores in fine motor skills. In the current study, infants with suspicious DDST-II results in the study group had problems related to gross motor skills, while infants with abnormal DDST-II results in the control group had problems with language development. We also determined that the mother of the infant with a neurodevelopmentally suspicious result contracted COVID-19 in the second trimester (sixth month) of pregnancy.

Shah et al.¹⁶ administered the ASQ-3 to term infants born to pregnant females with SARS-CoV-2 to screen for neurodevelopmental delays. The ASQ-3 is a screening tool used to assess neurodevelopment in five specific domains: communication, fine motor, gross motor, problem solving, and personal-social skills. In the literature on the ASQ-3 developmental screening of healthy term infants without intrauterine COVID-19 exposure, 12.6-13.6% of infants have been reported to have delays in at least one developmental domain.³⁸ In contrast, Shah et al.¹⁶ determined that 24% of the infants were below the cut-off value, and 29% were near the cut-off value in at least one developmental domain, indicating a percentage increase in neurodevelopmental delay in infants with intrauterine COVID-19 exposure.

Limitations

This study had several limitations. First, its retrospective, single-center design limits the generalizability of the findings and may have introduced selection bias, as infants with incomplete medical records or loss to follow-up were excluded from the study. In addition, because this was a retrospective study based on available medical records, no a priori sample size calculations were performed. Second, the relatively small sample size, particularly after stratification according to the trimester of maternal infection, may have reduced the statistical power to detect subtle differences between groups and precluded multivariable analyses to adjust for potential confounders. Third, important confounding variables, including socioeconomic status, parental education, postnatal home environment, early developmental stimulation, nutritional factors, and maternal comorbidities, were not systematically available and, therefore, could not be accounted for in the analyses. These factors may independently influence infant growth and neurodevelopment and should be considered when interpreting our findings. Fourth, neurodevelopment was assessed using the DDST-II, which is a developmental screening tool rather than a diagnostic assessment, and may be less sensitive than comprehensive instruments such as the Ages and Stages Questionnaire, Third Edition (ASQ-3), or the Bayley Scales of Infant and Toddler Development, for detecting subtle developmental deficits, particularly in fine motor and problem-solving domains. Fifth, the follow-up period was limited to the first year of life and may not have been

sufficient to identify neurodevelopmental or growth abnormalities that emerge later in the childhood. Finally, detailed information regarding the severity of maternal COVID-19, viral load, and treatment during pregnancy was not systematically available, preventing the evaluation of possible dose-response or severity-related associations with infant outcomes.

CONCLUSION

In this retrospective case-control study, maternal COVID-19 infection during pregnancy was not associated with significant differences in birth weight, gestational age, or overall neurodevelopment during the first year of life compared to unexposed infants. A significantly higher rate of HC below the third percentile was observed in the study group at six months, although this difference was not sustained at nine months and did not correspond to abnormal neurodevelopmental screening results in the affected infants. These findings are reassuring but should be interpreted with caution, given the limited sample size and short follow-up duration. Larger prospective multicenter studies with extended follow-up and more comprehensive neurodevelopmental assessment tools are needed to clarify the long-term impact of prenatal SARS-CoV-2 exposure on childhood growth and development and to determine whether the transient HC findings observed here reflect a true biological effect or a chance finding.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Ankara Training and Research Hospital, University of Health Sciences (Date: 07.09.2022, Decision No: E-22-1072).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: AET, HEY, DK; Design: RS, DK, ÖB; Data Collection: HEY, AT, DK; Data Analysis: AET, AT, RS; Interpretation of Data: HEY, ÖB, AT; Drafting of the Manuscript: AET, DK; Critical Revision: AT, RS.

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Evaluation of vaccination rates with influenza vaccines in pregnant females and their attitudes towards these vaccines

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Cite this article: Aydoğmuş S, Ünsal Keser SN, Gözüküçük M, Cesur S, Üstün Y. Evaluation of vaccination rates with influenza vaccines in pregnant females and their attitudes towards these vaccines. *J Controv Obstetr Gynecol Ped.* 2026;4(4):90-95. doi:10.51271/JCOGP-0080

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Received: 22/05/2026

Accepted: 23/09/2026

Published: 28/10/2026

ABSTRACT

Aims: The primary aim of this study was to determine the seasonal influenza vaccination rate among pregnant females and to identify the main reasons for non-vaccination. The secondary aim was to describe pregnant females' perceptions regarding the protective effect of influenza vaccination and the sources of vaccine recommendation.

Methods: The study was conducted as a cross-sectional survey study on pregnant females aged 18-45 in the first, second, and third trimesters who applied to the Health Sciences University Ankara Training and Research Hospital Gynecology and Obstetrics Clinic between November 2023 and April 2024. The researchers reviewed the relevant literature and prepared a survey consisting of 19 questions to be administered to the participants.

Results: The mean age of the pregnant females included in the study was 25.66 ± 5.2 (18-42) years, and the mean gestational age was 26.02 ± 5.8 weeks (2-40 weeks). The influenza vaccination rate during the current pregnancy was 16.5% (66/400). Of the participants, 334 (83.5%) did not believe that the influenza vaccine was protective, whereas 66 (16.5%) believed that it was protective. The influenza vaccine had been recommended by a physician to 229 (57.3%) participants. Concern that the influenza vaccine might harm the baby was the most commonly reported reason for not receiving the vaccine.

Conclusion: The influenza vaccination rate among pregnant females in this study was low. A large proportion of participants did not believe that the influenza vaccine was protective, and concern that the vaccine might harm the baby was the most commonly reported reason for not being vaccinated. These findings highlight the need for healthcare professionals, particularly physicians providing antenatal care, to provide pregnant females with clear and evidence-based information regarding the benefits and safety of influenza vaccination.

Keywords: Influenza vaccines, pregnancy, surveys and questionnaires, health knowledge, attitudes, practice

INTRODUCTION

Influenza causes seasonal epidemics every year, and these epidemics have economic consequences and are responsible for deaths in risk groups. Influenza continues to be a current issue because pandemics and, occasionally, more severe seasonal epidemics caused by new mutations can result in mass deaths.¹ The best and most important way to protect against influenza is to receive an influenza vaccine every year. The World Health Organization (WHO) recommends that vulnerable populations, those who are at higher risk of serious health consequences of influenza than others; pregnant females, healthcare workers, people with chronic health problems (diabetes, human immunodeficiency virus (HIV), asthma, heart or lung disease, etc.), people over the age of 65, and children between the ages of 6 months and 5 years old, receive an influenza vaccine every year.²⁻⁵ Patients may refuse influenza vaccines and other vaccines for reasons such as not believing in the safety of the influenza vaccine, concerns about its effectiveness, personal beliefs, fear of

injections, and the possibility of getting sick due to the vaccine.⁶⁻⁸ Pregnant females represent an important target group for seasonal influenza vaccination because pregnancy is associated with an increased risk of severe influenza-related complications. Current recommendations from the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) recommend influenza vaccination for females who are or will be pregnant during the influenza season. An age-appropriate inactivated or recombinant influenza vaccine can be administered during any trimester of pregnancy. Despite these recommendations and the established maternal and neonatal benefits of vaccination, influenza vaccination coverage during pregnancy remains suboptimal worldwide. A recent systematic review including 78 studies on influenza vaccination during pregnancy reported that most studies (55/78) had vaccination coverage rates below 50%, with healthcare professional recommendation, maternal attitudes,



parity, and previous influenza vaccination among the important determinants of vaccine uptake.⁹

Vaccination coverage during pregnancy also remains an important concern in Türkiye. Recent data from Türkiye have demonstrated low influenza vaccination uptake among pregnant females, although reported rates vary considerably across study populations and settings. These findings indicate that maternal perceptions of vaccine safety and effectiveness and recommendations from healthcare professionals may play important roles in vaccine acceptance. However, local data regarding influenza vaccination uptake and the specific reasons underlying non-vaccination among pregnant females remain limited. Therefore, evaluating vaccination rates together with pregnant females's perceptions and reasons for vaccine refusal may help identify context-specific barriers to maternal influenza vaccination.

Many studies have shown that influenza vaccines are safe during pregnancy and have shown that the vaccine does not cause adverse outcomes such as spontaneous abortion, stillbirth or congenital anomalies.¹⁰ Many pregnant females refuse to be vaccinated against influenza, thinking that it may harm the fetus.

The primary aim of this study was to determine the seasonal influenza vaccination rate among pregnant females attending an obstetrics outpatient clinic and to identify the main reasons for non-vaccination. The secondary aim was to describe pregnant females's perceptions regarding the protective effect of influenza vaccination and the sources of vaccine recommendation. We hypothesized that influenza vaccination uptake among pregnant females would be low and that concerns regarding vaccine safety, particularly potential harm to the baby, would represent an important barrier to vaccination.

METHODS

This study was approved by the Ethics Committee for Clinical Research at the Ankara Training and Research Hospital of the University of Health Sciences (Date: 20.12.2023, Decision No: 1502/2023). All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

The study was conducted as a cross-sectional survey study between November 2023 and April 2024 on pregnant females aged 18-45 in the first, second and third trimester who applied to the Health Sciences University Education and Research Hospital Gynecology and Obstetrics Polyclinic.

A total of 463 pregnant females were assessed for participation during the study period. Of these, 62 declined to participate. One additional participant was excluded because she did not meet the eligibility criteria and did not complete the questionnaire. Consequently, 400 pregnant females were included in the final analysis, corresponding to a participation rate of 86.4%. All questionnaires included in the final analysis were complete, and there were no missing data for the variables analyzed.

Pregnant females aged 18–45 years who were in any trimester of pregnancy, attended the obstetrics outpatient clinic during the study period, were able to communicate effectively and understand the questionnaire, and voluntarily agreed to participate in the study were eligible for inclusion. Pregnant females with multiple pregnancies or high-risk pregnancies were excluded from the study. Females who were not pregnant, those who were unable to communicate effectively or complete the questionnaire, and those who declined to participate were also excluded. The original questionnaire included items on educational level, income level, employment status, gravidity, parity, and previous pregnancy history; however, individual-level records for educational level, income level, gravidity, and parity were not retained in the final analysis dataset and were therefore unavailable for comparative analyses. The variables available for the present analysis included age, gestational week, smoking status, and the presence of additional medical conditions. Influenza vaccination history, including previous influenza vaccination, was also assessed. In addition, participants were asked about their perceptions regarding the protective effect of the influenza vaccine, the source of vaccine recommendation, influenza vaccination during the current pregnancy, and reasons for non-vaccination.

The survey asked about the pregnant females's ages, gestational weeks, smoking status –if any–, and additional diseases (diabetes, hypertension, heart failure, chronic kidney disease, immunosuppression, chronic bronchitis or emphysema, chronic liver disease, other diseases, etc.). In addition, participants were asked whether they believed the influenza vaccine was protective, who recommended the influenza vaccine (family doctor, nurse, pharmacist, other), whether they had received the influenza vaccine during the current pregnancy, and, if not, the reason for non-vaccination (not knowing that they should receive the vaccine, thinking it would harm the baby, not being recommended by their doctor, not thinking it would be beneficial, thinking the appropriate time had passed, fear of side effects, being unable to obtain it, not knowing that it was free, negative news about the vaccine in the press, fear of needles). It was stated that more than one response option could be selected.

Statistical Analysis

An a priori power analysis was performed using G*Power software to determine the required sample size before participant recruitment. The sample size calculation was based on the anticipated effect size, with a statistical power of 90% and a type I error (α) of 0.005. The minimum required sample size was calculated as 400 participants. Accordingly, 400 pregnant females were included in the study.

Statistical analyses were performed using SPSS version 24.0. Descriptive data were presented as mean $\pm$ standard deviation, median (interquartile range), or number and percentage, as appropriate. The distribution of continuous variables was assessed before comparative analyses. Because age and gestational week were not normally distributed between vaccination groups, comparisons were performed using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. A p value < 0.05 was considered statistically significant.

RESULTS

Of the 463 pregnant females assessed for participation, 400 were included in the final analysis, corresponding to a participation rate of 86.4%.

Four hundred pregnant females aged 18-45 years in the first, second and third trimesters who applied to the Health Sciences University Ankara Education and Research Hospital Gynecology and Obstetrics Polyclinic between November 2023 and April 2024 were included in the study. Data are shown in **Table 1**.

Table 1. Demographic data and obstetric characteristics of the participants

Demographic data	Mean±SD (min-max) or n (%)
Age	25.66±5.2 (18-42)
Pregnancy week	26.02±5.8 (2-40)
Smoking	
No	300 (75)
Yes	100 (25)
Duration of smoking (years)	4.75±3 (1-10)
Additional disease	
No	393 (98.3)
Yes	7 (1.8)
Diabetes	7 (1.8)
Hypertension	0 (0)
Heart failure	0 (0)
Chronic renal failure	0 (0)
Immunosuppression	0 (0)
COPD	0 (0)
Chronic liver diseases	0 (0)
Other	0 (0)

SD: Standard deviation, min: Minimum, max: Maximum, COPD: Chronic obstructive pulmonary disease

The mean age of the participants was 25.66±5.2 years, and the mean gestational age was 26.02±5.8 weeks. While 300 (75%) of the participants were non-smokers, 100 (25%) were smokers. 393 (98.3%) of the participants did not have any chronic disease. 7 (1.8%) of the participants had diabetes mellitus as an additional chronic disease. The participants did not have chronic diseases such as hypertension, heart failure, chronic renal failure, immunosuppressive disease, and chronic obstructive pulmonary disease.

The study sample, which consisted mostly of pregnant females under the age of 30, was questioned about their views on the effectiveness of the influenza vaccine, who recommended the influenza vaccine during pregnancy, and the reasons for not getting the influenza vaccine during pregnancy. The data obtained are shown in **Table 2**. Of the participants, 334 (83.5%) did not believe that the influenza vaccine was protective, whereas 66 (16.5%) believed that it was protective.

Among these participants, those who did not believe that the influenza vaccine was protective had not been vaccinated. A doctor had recommended the influenza vaccine to 229 (57.3%) of the participants. The reasons for not receiving the influenza vaccine were 29 (7.3%) not knowing that the

Table 2. Participants' responses to questions about influenza vaccination

Do you believe that the influenza vaccine protects against influenza?	
No	334 (83.5)
Yes	66 (16.5)
Who recommended the influenza vaccine?	
Doctor	229 (57.3)
Other (friends, socialmedia, etc.)	171 (42.8)
Have you had an influenza vaccination this year?	
No	334 (83.5)
Yes	66 (16.5)
Did you receive an influenza vaccination last year?	
No	334 (83.5)
Yes	66 (16.5)
What is your reason for not receiving an influenza vaccination?	
I didn't know I needed to be vaccinated.	29 (7.3)
Because I think it will harm the baby.	121 (30.3)
Because I think the appropriate time has passed.	62 (15.5)
Because I'm afraid of the side effects.	81 (20.3)
Because I cannot obtain it.	11 (2.8)
Because I didn't know it was free.	66 (16.5)
Duetonegative news about the vaccine in the press	30 (7.5)

vaccine should be administered, 121 (30.3) thinking that it would be harmful to the baby, 62 (15.5) thinking that the appropriate time had passed, 81 (20.3) fearing its side effects, 11 (2.8) being unable to obtain it, 66 (16.5) not knowing that it was free, and 30 (7.5%) not getting it due to negative news about the vaccine in the press.

Comparative analyses were performed according to influenza vaccination status. There were no statistically significant differences between vaccinated and unvaccinated participants in terms of age, gestational week, trimester, smoking status, presence of additional disease, or whether the vaccine was recommended by a physician (all $p>0.05$). In contrast, belief that the influenza vaccine was protective and influenza vaccination in the previous year were significantly associated with current influenza vaccination status (both $p<0.001$) (**Table 3**).

DISCUSSION

It is very important to be vaccinated against influenza, which can cause serious disease during pregnancy, before, during, or after pregnancy. Pregnant females are more prone to influenza infection and influenza-related morbidity. Influenza infection may require hospitalization and admission to the intensive care unit.¹¹ For this reason, the WHO and the American College of Obstetricians and Gynecologists (ACOG) recommend that all pregnant females and those planning a pregnancy be vaccinated during the influenza season.¹² Licensed inactivated influenza vaccines can be used safely during pregnancy.

Influenza vaccination is recommended for pregnant females, regardless of trimester.¹³ Maternal influenza vaccination is an essential part of antenatal care for both the mother and the newborn. Pregnant females are at increased risk of

Table 3. Comparison of demographic and clinical characteristics according to influenza vaccination status

Variable	Vaccinated (n=66)	Unvaccinated (n=334)	p value
Age, years, median (Q1–Q3)	25.0 (22.25–29.75)	25.0 (21.0–30.0)	0.263
Gestational week, median (Q1–Q3)	27.0 (22.0–28.0)	27.0 (22.0–29.75)	0.796
Trimester, n (%)			0.887
First trimester	1 (1.5)	8 (2.4)	
Second trimester	39 (59.1)	191 (57.2)	
Third trimester	26 (39.4)	135 (40.4)	
Smoking, n (%)	17 (25.8)	83 (24.9)	0.877
Presence of additional disease, n (%)	0 (0.0)	7 (2.1)	0.606*
Belief that influenza vaccine is protective, n (%)	66 (100.0)	0 (0.0)	<0.001*
Vaccine recommended by a physician, n (%)	36 (54.5)	193 (57.8)	0.683
Influenza vaccination in the previous year, n (%)	66 (100.0)	0 (0.0)	<0.001*

Data are presented as median (Q1–Q3) or n (%), as appropriate. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. *Fisher's exact test.

admission to intensive care units, preterm labor and maternal death, which are serious complications of influenza.¹¹ Therefore, all obstetricians and gynecologists should inform and raise awareness of the pregnant females they follow about the benefits and safety of influenza vaccination. Both the pregnant female and the fetus benefit from influenza vaccination through maternal passive immunization.¹²

The influenza vaccine is safe during pregnancy and has a well-established safety profile for both the mother and the fetus. Pregnant females are at a higher risk of influenza-related hospitalization, especially during the second and third trimesters. Influenza-related hospitalization rates are also high in newborns, especially those under 6 months of age, and children aged 0–4. The primary reason for administering the influenza vaccine to pregnant females is to protect them from influenza. Vaccination also protects infants under 6 months of age against influenza and influenza-related complications throughout the influenza season.¹³

In the present study, the influenza vaccination rate among pregnant females was only 16.5%, indicating that vaccine uptake remained low despite the established recommendations for influenza vaccination during pregnancy. This finding is consistent with previous studies from Türkiye reporting low levels of influenza vaccination among pregnant females. The low vaccination rate observed in our study is likely to reflect multiple interacting factors rather than a single barrier. In particular, limited confidence in vaccine effectiveness, concerns regarding vaccine safety, insufficient knowledge about the benefits of vaccination during pregnancy, and the influence of healthcare professional recommendations have previously been identified as important determinants of maternal influenza vaccine acceptance. Our findings further support the importance of maternal perceptions, as belief in the protective effect of the influenza vaccine was significantly associated with current vaccination status ($p < 0.001$).

Another important finding of the present study was that 30.3% of participants reported concern that influenza vaccination might harm the baby, making this the most frequently reported reason for non-vaccination. Similar concerns have been reported among pregnant females in Türkiye and internationally, suggesting that perceived fetal risk remains an important barrier to maternal influenza vaccination. This concern appears to contrast with the available evidence regarding vaccine safety during pregnancy, as systematic evaluations have not demonstrated an increased risk of major adverse pregnancy or birth outcomes following seasonal influenza vaccination. Therefore, the low vaccination rate observed in our population may partly reflect a discrepancy between the available scientific evidence regarding vaccine safety and pregnant females's perceptions of fetal risk. Addressing this discrepancy through clear and consistent risk-benefit communication during routine antenatal care may be important for improving informed vaccine decision-making.

Clinical and observational studies, have consistently demonstrated the safety of influenza vaccination. Seasonal influenza vaccination of pregnant females and adults is similar in terms of effectiveness.¹² Although the effectiveness of influenza vaccination may be lower than that of some other adult vaccines, vaccination provides significant protection against influenza. The newborns of vaccinated pregnant females also benefit from this vaccine. Four large-scale randomized controlled trials and numerous observational studies, have shown that maternal influenza vaccination provides protection in newborns.

Influenza vaccination during pregnancy provides two benefits, protecting both the mother and the baby from influenza. However, vaccination rates during pregnancy are low in many countries, including Türkiye. Vaccine hesitancy, as defined by the WHO, has been identified as a threat to global health. Studies on tetanus, influenza, and pertussis vaccines in pregnant females in high-income countries have identified low vaccination rates as a result of a lack of healthcare personnel's recommendation of the vaccine, concerns about pregnant females' safety, and access restrictions.^{14–16} In our study, the most common reason for pregnant females not receiving the influenza vaccine was safety concerns, followed by fear of side effects and lack of knowledge that it was free.

The biggest reason why pregnant females or females planning to get pregnant do not accept vaccination is the lack of information about the benefits of influenza vaccination. Therefore, the adverse effects of influenza and the benefits of vaccination should be clearly explained to patients.

A retrospective analysis conducted in the United States, it was reported that 14,168 (40.6%) of 4,919 pregnant females received an influenza vaccination during pregnancy. This study reported a positive and statistically significant association between receiving an influenza vaccination during pregnancy and infant influenza vaccination when the infants became eligible.¹⁷

It has been reported that, in a patient cohort of 4 million, influenza vaccination could save \$3.7 billion annually, is cost-

effective, and can reduce morbidity and mortality in mothers and babies. Therefore, healthcare professionals are advised to strongly recommend influenza vaccinations to pregnant females every year.¹⁸

A study conducted in South Korea conducted a survey examining pregnant females' influenza vaccination history, general attitudes toward the influenza vaccine, and factors influencing their decisions about influenza vaccination. The study found a 37.3% rate of influenza vaccination during pregnancy. Factors positively associated with influenza vaccination were reported as perceived risk of influenza infection, recommendations from healthcare professionals, and confidence in the effectiveness of the vaccine. The most common reasons for not being vaccinated were reported as concerns about harmful effects and lack of recommendations from healthcare professionals. The study reported that the rate of influenza vaccination among pregnant females was much lower than the general population.¹⁹

Consequently, providing accurate information about the influenza vaccine, recommending the influenza vaccine to pregnant females, and encouraging pregnant females to get vaccinated as part of a health policy were reported as important.^{20,21}

In a study conducted in Türkiye among 353 pregnant females, 191 (54.1%) reported accepting the influenza vaccine. No statistically significant differences were found between the groups in terms of maternal age, body mass index, gravida, number of children, socioeconomic status, smoking status, or occupation. Vaccination rates for females in their third trimester were lower than those in their first and second trimesters (35.7% and 67.7% vs. 64.2%, respectively). Vaccination rates were also lower among females with at least a university degree. While 82.2% of females who accepted the vaccine stated that the vaccine was beneficial to their baby, this rate was reported as 55% in the unvaccinated group. The most common reason for refusal was the belief that influenza is not a serious illness. Vaccination rates were particularly high among pregnant females who believed the influenza vaccine was beneficial to their baby. In this study, females who had sufficient knowledge, had a low level of education, had a previous influenza infection, and decided to vaccinate their babies were reported to be more likely to receive the influenza vaccine.^{22,23}

Limitations

The present study has several limitations. First, this was a single-center study conducted among pregnant females attending one obstetrics outpatient clinic; therefore, the findings may not be generalizable to all pregnant females in Türkiye or to populations with different sociodemographic and healthcare characteristics. Second, the cross-sectional design allows the identification of associations but does not permit conclusions regarding causal relationships between participants' perceptions and influenza vaccination behavior. Third, because the questionnaire was administered face-to-face, responses concerning vaccination attitudes and behaviors may have been influenced by social desirability or recall bias. Finally, although the questionnaire underwent content evaluation, pilot testing, and reliability assessment before its use, it was specifically developed for the present

study, which should be considered when comparing our findings with studies using different or standardized instruments. Multicenter studies involving larger and more diverse populations may provide further evidence regarding the determinants of influenza vaccination during pregnancy.

Another limitation of the present study is that, although educational level, income level, gravidity, and parity were included as items in the original questionnaire, the corresponding individual-level records were not retained in the final analysis dataset. Consequently, these variables were unavailable for additional comparative analyses between vaccinated and unvaccinated participants, and their potential associations with influenza vaccine uptake could not be evaluated.

CONCLUSION

As a result, the influenza vaccination rate among pregnant females in our study was low, with only 16.5% of participants reporting vaccination. Most participants did not believe that the influenza vaccine was protective, and concern about potential harm to the baby was the most frequently reported reason for not being vaccinated. These findings suggest that misconceptions regarding the safety and effectiveness of influenza vaccination remain important barriers to vaccination during pregnancy. Healthcare professionals involved in antenatal care should provide clear, evidence-based information about influenza vaccination and actively address pregnant females' concerns regarding vaccine safety.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee for Clinical Research at the Ankara Training and Research Hospital of the University of Health Sciences (Date: 20.12.2023, Decision No: 1502/2023).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: SA; Design: SA; Data Collection and/or Processing: SNÜK; Analysis and/or Interpretation: SC; Literature Review: MG; Writing the Article: YÜ, SC; Critical Review: SA, SNÜK.

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Clinical and laboratory characteristics according to the onset of neonatal sepsis: a retrospective cohort study

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Cite this article: Sincar F, Kahvecioğlu D, Taş Güngör M, Geyik C. Clinical and laboratory characteristics according to the onset of neonatal sepsis: a retrospective cohort study. *J Controv Obstetr Gynecol Ped.* 2026;4(4):96-101. doi:10.51271/JCOGP-0081

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Received: 28/06/2026

Accepted: 12/10/2026

Published: 28/10/2026

ABSTRACT

Aims: Neonatal sepsis remains a major cause of neonatal morbidity and mortality despite advances in neonatal intensive care. Although early-onset sepsis (EOS) and late-onset sepsis (LOS) differ in their pathophysiology and clinical presentation, comparative data including neonates who experience both EOS and LOS remain limited. This study aimed to compare the clinical and laboratory characteristics of neonates with EOS, LOS, and combined EOS+LOS.

Methods: This retrospective cohort study included 289 neonates with sepsis admitted to a tertiary neonatal intensive care unit between January 2020 and January 2022. Patients were classified into three groups: EOS (n=207), LOS (n=32), and EOS+LOS (n=50). Demographic characteristics, clinical findings, microbiological results, and laboratory parameters were compared among the groups.

Results: Neonates with EOS+LOS had lower gestational age, birth weight, and Apgar scores and longer hospitalization than neonates with EOS or LOS alone. Platelet count and plateletcrit (P-LCT) were lowest in the EOS+LOS group, while mean platelet volume was higher in EOS+LOS than in EOS. Neonates with EOS had higher white blood cell count, hemoglobin, absolute neutrophil count, and neutrophil-to-lymphocyte ratio (NLR) than both the LOS and EOS+LOS groups; red cell distribution width and C-reactive protein were higher in EOS than in LOS. Hematocrit was lower in EOS+LOS than in both EOS and LOS, and absolute lymphocyte count was higher in LOS than in both EOS and EOS+LOS.

Conclusion: Clinical and laboratory characteristics differ according to the onset of neonatal sepsis. Routinely available hematological parameters may complement clinical assessment and support the early evaluation of neonatal sepsis. Larger prospective multicenter studies are needed to validate these findings.

Keywords: Early-onset sepsis, late-onset sepsis, newborn, biomarkers, hematological parameters

INTRODUCTION

Neonatal sepsis remains a major cause of neonatal morbidity and mortality worldwide despite advances in neonatal intensive care and antimicrobial therapy. The burden of disease is greatest among preterm and low-birth-weight infants because of their immature immune system and increased exposure to invasive procedures. Although improvements in perinatal care have reduced its incidence in developed countries, neonatal sepsis continues to be associated with substantial mortality and prolonged hospitalization.¹⁻⁴

Neonatal sepsis is classified as early-onset sepsis (EOS) or late-onset sepsis (LOS) according to the timing of disease onset. EOS is primarily associated with vertical maternal transmission, whereas LOS is commonly related to nosocomial or community-acquired infections. Because these conditions differ in microbiological etiology, risk

factors, and host immune response, differences in their clinical presentation and laboratory findings are expected.^{3,4}

Early diagnosis remains challenging because the clinical manifestations of neonatal sepsis are nonspecific and often overlap with those of noninfectious neonatal disorders. Although blood culture is considered the diagnostic gold standard, its sensitivity is limited and results require 48–72 hours, making early clinical decision-making difficult. Consequently, readily available laboratory markers, including white blood cell count, platelet indices, C-reactive protein, neutrophil-to-lymphocyte ratio, and nucleated red blood cell count, have been increasingly investigated as adjunctive diagnostic tools.⁵⁻⁷

Most previous studies have evaluated EOS and LOS separately, whereas comparative data including neonates

who experienced both EOS and LOS are scarce. Therefore, this study aimed to compare the clinical characteristics and routinely available hematological and biochemical parameters among neonates with EOS, LOS, and combined EOS+LOS to identify potential diagnostic differences according to the timing of sepsis onset.

METHODS

Ethics

This study was approved by the Ethics Committee of Ankara Training and Research Hospital, University of Health Sciences (Date: 05.10.2022, Decision No: E-22-1099). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because of the retrospective study design, the requirement for informed consent was waived.

Study Design and Participants

This retrospective single-center cohort study was conducted in the tertiary Neonatal Intensive Care Unit of Ankara Training and Research Hospital, Türkiye, between January 2020 and January 2022. Medical records of neonates aged ≤ 30 days who were diagnosed with neonatal sepsis were retrospectively reviewed. Demographic characteristics, maternal and perinatal data, clinical findings, microbiological results, treatment information, and laboratory parameters were extracted from the hospital's electronic medical record system.

Neonates with culture-proven sepsis or clinically diagnosed sepsis requiring antibiotic treatment were eligible for inclusion. Patients with incomplete medical records, isolated urinary tract infection without systemic involvement, or noninfectious conditions that could mimic neonatal sepsis, including perinatal asphyxia, transient tachypnea of the newborn, respiratory distress syndrome, pulmonary hypoplasia, congenital diaphragmatic hernia, congenital or acquired heart disease, adrenal disorders, intraventricular hemorrhage, hypoxic-ischemic encephalopathy, inherited metabolic diseases, and neonatal abstinence syndrome, were excluded. Transient tachypnea of the newborn and respiratory distress syndrome were considered exclusionary only when they provided a noninfectious explanation for the clinical presentation; respiratory failure itself was not used as an exclusion criterion in neonates who otherwise fulfilled the study definition of sepsis.

A total of 289 neonates met the eligibility criteria and were classified into three groups according to the onset of sepsis: EOS; $n=207$, LOS; $n=32$, and combined EOS+LOS ($n=50$). The EOS+LOS group comprised neonates who experienced two distinct sepsis episodes during the same hospitalization, with an initial EOS episode followed by a subsequent LOS episode. For the EOS+LOS group, the laboratory values used in the between-group analyses were those obtained during the initial EOS episode; laboratory data from the subsequent LOS episode were not consistently available and were therefore not included in these comparisons.

Data Collection

The collected variables included gestational age, birth weight, gender, mode of delivery, Apgar scores, maternal

infection history, premature rupture of membranes, duration of hospitalization, timing of antibiotic initiation, clinical manifestations of sepsis, complete blood count parameters including plateletcrit (P-LCT), C-reactive protein, procalcitonin (PCT), interleukin-6, blood gas analysis, lactate level, and blood, urine, and cerebrospinal fluid culture results. To avoid abbreviation ambiguity, PCT is used exclusively for procalcitonin in the text, whereas plateletcrit is abbreviated as P-LCT. Patients with positive blood cultures were classified as having culture-proven sepsis, whereas those with negative blood cultures but compatible clinical and laboratory findings were classified as having clinical sepsis. Blood cultures were obtained before initiation of empirical antibiotic therapy in all patients.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (minimum–maximum), according to data distribution, whereas categorical variables were presented as numbers and percentages. Comparisons among the three groups were performed using one-way ANOVA or the Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables. When an overall group comparison was statistically significant, pairwise post-hoc comparisons were evaluated with Bonferroni adjustment. In **Tables 1** and **2**, superscript letters identify the significant pairwise contrasts (a: EOS vs LOS; b: EOS vs EOS+LOS; c: LOS vs EOS+LOS). Statistical significance was defined as $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 289 neonates with sepsis were included in the study. Of these, 207 (71.6%) were classified as having EOS, 32 (11.1%) as LOS, and 50 (17.3%) experienced two distinct episodes, with EOS followed by LOS during the same hospitalization (EOS+LOS).

The baseline demographic and perinatal characteristics of the study population are summarized in **Table 1**. Significant differences were observed among the three groups with respect to gestational age, birth weight, Apgar scores, hospitalization duration, timing of antibiotic initiation, sex distribution, small-for-gestational-age status, and prematurity (all $p<0.05$). Infants in the EOS+LOS group were generally more premature, had lower birth weights and Apgar scores, and required longer hospitalization than those in the other groups.

The clinical manifestations observed at the time of diagnosis are presented in **Table 3**. Respiratory manifestations were the most frequent presenting feature, followed by metabolic and gastrointestinal manifestations.

Blood cultures were positive in 17 neonates (5.9%), yielding 20 bacterial isolates. The most frequently isolated organism was *Staphylococcus epidermidis*, followed by *Staphylococcus haemolyticus* and *Escherichia coli*. Only one patient had a positive cerebrospinal fluid culture, which yielded *Listeria monocytogenes*. The most commonly prescribed empirical antibiotic regimen was ampicillin plus gentamicin.

Table 1. Demographic and perinatal characteristics according to the onset of neonatal sepsis

	EOS (n=207)	LOS (n=32)	EOS+LOS (n=50)	p value
Maternal age*	27.38±6.56	27.56±6.96	27.34±6.62	0.66
Gravidity**	2 (1–9)	3 (1–8)	3 (1–12)	0.28
Parity**	2 (1–9)	2 (1–6)	3 (1–9)	0.55
Gestational age (weeks)**	39 (28.4–41.5)	38.5 (34–41)	35.6 (28–41)	<0.001 ^{bc}
Birth weight (g)*	3179.65±573.79	3003±548.14	2379.2±962.72	<0.001 ^{bc}
Apgar score at 1 min**	8 (2–9)	8 (5–9)	7 (1–9)	<0.001 ^{bc}
Apgar score at 5 min**	9 (5–10)	9 (7–10)	8 (3–10)	<0.001 ^{bc}
Day of hospital admission**	1 (1–3)	3 (1–29)	1 (1–1)	<0.001 ^{abc}
Day of antibiotic initiation**	2 (1–4)	7 (4–29)	1 (1–3)	<0.001 ^{abc}
Length of hospital stay (days)**	9 (2–27)	12 (7–31)	25 (7–250)	<0.001 ^{abc}
Mode of delivery, n (%)				
Vaginal	117 (57.9%)	18 (60.0%)	22 (44.0%)	0.18
Cesarean delivery	85 (42.1%)	12 (40.0%)	28 (56.0%)	
Male gender, n (%)	126 (60.9%)	11 (34.4%)	27 (54.0%)	0.02 ^a
SGA, n (%)	2 (1.0%)	3 (9.4%)	1 (2.0%)	0.01 ^a
Preterm birth, n (%)	34 (16.4%)	4 (12.5%)	28 (56.0%)	<0.001 ^{bc}
Maternal infection/risk factor, n (%)				
None	119 (58.9%)	24 (80%)	31 (62%)	0.08
Maternal infection	35 (17.3%)	2 (6.7%)	4 (8%)	
PROM/PPROM	19 (9.4%)	0 (0.0%)	3 (6%)	
Other maternal diseases, n (%)	29 (14.4%)	4 (13.3%)	12 (24.0%)	0.19

*Mean (±SD); **Median (minimum–maximum). SGA: Small for gestational age. PROM: Premature rupture of membranes. PPROM: Preterm premature rupture of membranes. For mode of delivery, percentages correspond to the records included in the original subgroup extraction (EOS, n=202; LOS, n=30; EOS+LOS, n=50), while the overall study-group sizes remained EOS n=207, LOS n=32, and EOS+LOS n=50. Superscripts denote significant Bonferroni-adjusted pairwise comparisons: a, EOS vs LOS; b, EOS vs EOS+LOS; c, LOS vs EOS+LOS. Significant pairwise p values: Gestational age b<0.001, c=0.002; birth weight b<0.001, c<0.001; Apgar 1 min b<0.001, c=0.002; Apgar 5 min b<0.001, c<0.001; day of admission a<0.001, b=0.011, c<0.001; antibiotic initiation day a<0.001, b=0.047, c<0.001; hospitalization duration a=0.004, b<0.001, c<0.001; male gender a=0.023; SGA a=0.005; prematurity b<0.001, c<0.001. EOS: Early-onset sepsis, LOS: Late-onset sepsis

Table 2. Comparison of laboratory parameters according to the onset of neonatal sepsis

Laboratory	EOS (n=207)	LOS (n=32)	EOS+LOS (n=50)	p value
WBC (/mm ³)**	19010 (3800–127960)	13095 (2370–45260)	12480 (4820–37340)	<0.001 ^{ab}
Platelet count (/mm ³)**	285500 (75000–734000)	292000 (59000–680000)	240000 (21000–510000)	0.04 ^c
Hemoglobin (g/dl)*	17.82±2.59	15.85±3.35	15.53±4.21	<0.001 ^{ab}
Hematocrit (%)*	52.51±7.94	52.51±9.89	45.79±12.15	<0.001 ^{bc}
RDW (%)**	17.5 (14.4–51.5)	16.65 (14.1–21.2)	16.95 (14.1–24.3)	0.004 ^a
Neutrophil (%)**	65.75 (22.9–89)	40.25 (8.3–77.5)	51.05 (11–85)	<0.001 ^{ab}
Lymphocyte (%)**	23.8 (2.6–50)	41.8 (14–75)	31 (8.4–64)	<0.001 ^{ab}
NRBC (%)**	1.3 (0–91.1)	0.2 (0–32.3)	2.1 (0–167.9)	0.006 ^{ac}
NRBC (10 ³ /mm ³)**	0.26 (0–13.69)	0.04 (0–15.2)	0.19 (0–14.8)	0.01 ^a
ANC (/mm ³)**	11750 (1540–102750)	4925 (820–32070)	5690 (940–28120)	<0.001 ^{ab}
ALC (/mm ³)**	4435 (1190–18600)	5100 (710–9000)	4100 (970–12260)	0.01 ^{ac}
MPV (fL)*	9.77±0.84	9.90±1	10.2±1.1	0.01 ^b
Plateletcrit (P-LCT, %)**	0.28 (0.08–3)	0.30 (0.06–0.69)	0.25 (0.06–0.60)	0.04 ^c
NLR**	2.6 (0.4–19.2)	0.9 (0.1–5.46)	1.41 (0.31–9.85)	<0.001 ^{ab}
CRP (mg/dl)**	10.9 (0.1–143)	3.89 (0.3–44)	8.15 (0.2–165)	0.002 ^a
pH**	7.33 (6.98–7.49)	7.36 (7.26–7.42)	7.34 (7.11–7.47)	0.12
HCO ₃ ⁻ (mmol/L)**	19.4 (8.2–26)	20.2 (14.6–25.6)	19.8 (9.7–24.2)	0.2
Lactate (mmol/L)**	3.6 (1.1–19.0)	3 (1.7–5)	3.2 (1.03–14.7)	0.08

*Mean (±SD); **Median (minimum–maximum). WBC: White blood cell count, RDW: Red cell distribution width, NRBC: Nucleated red blood cells, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, MPV: Mean platelet volume, P-LCT: Plateletcrit, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, HCO₃⁻: Bicarbonate. Superscripts denote significant Bonferroni-adjusted pairwise comparisons: a, EOS vs LOS; b, EOS vs EOS+LOS; c, LOS vs EOS+LOS. Significant pairwise p values: WBC a=0.002, b<0.001; platelet count c=0.042; hemoglobin a=0.003, b<0.001; hematocrit b<0.001, c=0.014; RDW a=0.014; neutrophil percentage a<0.001, b<0.001; lymphocyte percentage a<0.001, b=0.003; NRBC percentage a=0.005, c=0.012; absolute NRBC a=0.009; ANC a<0.001, b<0.001; ALC a=0.027, c=0.013; MPV b=0.008; P-LCT c=0.037; NLR a<0.001, b=0.001; CRP a=0.001. The extreme WBC and NRBC values were rechecked against the original patient-level dataset and confirmed as recorded values rather than transcription or data-entry errors. EOS: Early-onset sepsis, LOS: Late-onset sepsis

Laboratory findings according to the onset of sepsis are presented in **Table 3**. Bonferroni-adjusted pairwise comparisons showed that white blood cell count, hemoglobin, absolute neutrophil count, and neutrophil-to-lymphocyte ratio (NLR) were higher in EOS than in both LOS and

EOS+LOS, whereas red cell distribution width and C-reactive protein were higher in EOS than in LOS. Hematocrit was lower in EOS+LOS than in both EOS and LOS. Platelet count and P-LCT were lower in EOS+LOS than in LOS, while mean platelet volume was higher in EOS+LOS than in EOS.

Absolute lymphocyte count was higher in LOS than in both EOS and EOS+LOS. NRBC percentage was higher in EOS than in LOS and in EOS+LOS than in LOS, while absolute NRBC count was higher in EOS than in LOS. No significant differences were observed among the groups in blood pH, bicarbonate, or lactate levels.

Table 3. Clinical manifestations observed at presentation

Clinical manifestation	EOS (n=207), n (%)	LOS (n=32), n (%)	EOS+LOS (n=50), n (%)	Overall (n=289), n (%)
Respiratory manifestations	183 (88.4%)	23 (71.9%)	43 (86.0%)	249 (86.2%)
Metabolic disturbances	56 (27.1%)	7 (21.9%)	18 (36.0%)	81 (28.0%)
Gastrointestinal manifestations	25 (12.1%)	12 (37.5%)	2 (4.0%)	39 (13.5%)
Circulatory manifestations	19 (9.2%)	7 (21.9%)	7 (14.0%)	33 (11.4%)
Neuromotor manifestations	14 (6.8%)	1 (3.1%)	9 (18.0%)	24 (8.3%)
Skin manifestations	3 (1.4%)	3 (9.4%)	0 (0.0%)	6 (2.1%)
Genitourinary manifestations	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
Hematological manifestations	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (0.3%)

Values are presented as n (%). More than one clinical manifestation could be present in the same patient; therefore, the cumulative number of manifestations may exceed the total number of patients. EOS: Early-onset sepsis, LOS: Late-onset sepsis

DISCUSSION

In this retrospective cohort study, we compared the clinical and laboratory characteristics of neonates with EOS, LOS, and combined EOS+LOS. The principal findings were that neonates with combined EOS+LOS had lower gestational age, lower birth weight, lower platelet indices, and longer hospitalization, whereas EOS was associated with higher inflammatory and hematological parameters, including white blood cell count, absolute neutrophil count, nucleated red blood cell count, red cell distribution width, and neutrophil-to-lymphocyte ratio. These findings suggest that the onset of neonatal sepsis is associated with distinct clinical and hematological profiles.

Prematurity and low birth weight are well-established risk factors for neonatal sepsis because of immune immaturity, impaired epithelial barriers, and the frequent need for invasive procedures. Consistent with previous reports, infants in the EOS+LOS group had significantly lower gestational age and birth weight and experienced longer hospitalization than those with EOS or LOS alone. Lower Apgar scores observed in this group may also reflect greater perinatal vulnerability. Collectively, these findings suggest that infants who develop both EOS and LOS represent a particularly high-risk subgroup requiring prolonged hospitalization and closer clinical surveillance.^{3,8}

Among the laboratory findings, inflammatory markers were more pronounced in the EOS group. White blood cell count, absolute neutrophil count, and (NLR) were significantly higher in EOS than in both LOS and EOS+LOS, whereas C-reactive protein was significantly higher in EOS than in

LOS. These observations are consistent with previous studies demonstrating that routinely available hematological and inflammatory markers may differ according to the timing and phase of neonatal infection. Although none of these biomarkers alone has sufficient diagnostic accuracy, their combined interpretation together with clinical findings may improve the early recognition of neonatal sepsis.⁹⁻¹¹

Platelet and erythrocyte indices also differed according to the timing of sepsis onset. The EOS+LOS group showed the lowest platelet count and P-LCT, whereas mean platelet volume differed significantly among the groups. Thrombocytopenia is a well-recognized hematological manifestation of neonatal sepsis and may reflect platelet consumption during systemic inflammation.⁸ Mean platelet volume has also been investigated as an adjunctive marker in neonatal sepsis.¹² Red cell distribution width and nucleated red blood cell measures also differed by sepsis-onset group.^{13,14} These changes may reflect platelet consumption, systemic inflammation, tissue hypoxia, and bone marrow activation during sepsis. Because these indices are inexpensive and routinely available as part of a complete blood count, they may provide additional diagnostic information when interpreted alongside conventional inflammatory markers rather than being used individually.

Blood culture positivity was relatively low in our cohort, with only 17 of 289 neonates (5.9%) having culture-confirmed infection. Importantly, blood cultures were obtained before the initiation of empirical antibiotic therapy in all patients; therefore, prior neonatal antimicrobial exposure does not explain the low culture positivity rate observed in our cohort. The low rate should primarily be interpreted in the context of our inclusion criteria, which permitted enrollment of neonates with clinically diagnosed sepsis despite negative blood cultures. In addition, the limited sensitivity of blood culture in neonates, particularly when small blood volumes are inoculated, may have contributed to the low microbiological yield. Because the exact blood volume inoculated into culture bottles was not consistently documented in this retrospective dataset, its potential effect could not be quantified. Accordingly, the low proportion of culture-confirmed cases should be considered when interpreting our findings. Gram-positive organisms predominated among culture-positive cases, with *Staphylococcus epidermidis* being the most frequently isolated pathogen.^{15,16}

The mortality rate in our cohort was relatively low compared with previous reports. Although the retrospective nature of the study precludes identification of the underlying reasons, early diagnosis, prompt initiation of empirical antimicrobial therapy, and management in a tertiary neonatal intensive care unit may have contributed to this favorable outcome.

Limitations

This study has several limitations. First, its retrospective single-center design may limit the generalizability of the findings. Second, in the EOS+LOS group, the laboratory values used for the between-group analyses were obtained during the initial EOS episode. Laboratory data from the subsequent LOS episode were not consistently available; therefore, within-patient longitudinal comparison

between the EOS and subsequent LOS episodes could not be performed. Finally, some biomarkers, including interleukin-6, procalcitonin, and the immature-to-total neutrophil ratio, were not available for all patients. In addition, the low blood culture positivity rate and the inclusion of a substantial proportion of clinically diagnosed, culture-negative sepsis cases may have introduced diagnostic heterogeneity. Although blood cultures were obtained before empirical antibiotic treatment in all patients, the exact blood volume inoculated for culture was not consistently available in the retrospective records. In addition, although clinical manifestations were retrospectively collected from medical records, group-specific distributions were successfully extracted and evaluated for all cohorts. For all patients from the archived retrospective dataset, and only verified overall frequencies are therefore reported.

Despite these limitations, our study has several strengths. To our knowledge, relatively few studies have simultaneously compared demographic characteristics, clinical findings, and routinely available hematological parameters among neonates with EOS, LOS, and combined EOS+LOS within the same cohort. The inclusion of the EOS+LOS group provides additional insight into a subgroup of neonates who may represent a more vulnerable population and who are infrequently evaluated separately in the existing literature. Our findings suggest that simple hematological indices derived from routine complete blood counts may complement clinical assessment but should not replace microbiological confirmation.

CONCLUSION

The present study demonstrated that the clinical presentation and routinely available laboratory parameters differ according to the onset of neonatal sepsis. Neonates with combined EOS+LOS were characterized by greater prematurity, lower birth weight, longer hospitalization, and more pronounced platelet abnormalities, whereas EOS was associated with a stronger inflammatory and hematological response, including higher white blood cell count, absolute neutrophil count, neutrophil-to-lymphocyte ratio, nucleated red blood cell count, and C-reactive protein levels.

These findings suggest that readily available hematological indices obtained from routine complete blood counts may complement clinical assessment and assist in the early evaluation of neonatal sepsis according to disease onset. Although none of these biomarkers should be interpreted in isolation, their combined use may improve diagnostic accuracy and support timely clinical decision-making.

Further prospective, multicenter studies with larger cohorts are warranted to validate these findings and determine the clinical utility of these hematological parameters in the diagnosis and risk stratification of neonatal sepsis.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Ankara Training and Research Hospital, University of Health Sciences (Date: 05.10.2022, Decision No: E-22-1099).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: FS, DK; Design: FS, DK; Control: DK, MTG; Data Collection and/or Processing: FS; Analysis and/or Interpretation: FS, DK, CG; Literature Review: FS, CG, MTG; Writing the Article: FS, DK; Critical Review: FS, DK, CG, MTG.

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Acute abdomen in pregnancy in a tertiary referral center: diagnostic challenges and surgical outcomes

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Cite this article: Çayönü Kahraman N, Şeyhanlı Z, Özcan Ü, Duygulu Bulan D, Çağlar AT. Acute abdomen in pregnancy in a tertiary referral center: diagnostic challenges and surgical outcomes. *J Controv Obstetr Gynecol Ped.* 2026;4(4):102-107. doi:10.51271/JCOGP-0082

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Received: 26/07/2026

Accepted: 20/10/2026

Published: 28/10/2026

ABSTRACT

Aims: Acute abdomen during pregnancy is a challenging clinical condition requiring prompt diagnosis and management to prevent adverse maternal and fetal outcomes. This study aimed to evaluate the clinical characteristics, diagnostic approaches, and surgical outcomes of pregnant patients presenting with acute abdomen.

Methods: This single-center retrospective study included 13 pregnant patients diagnosed with acute abdomen who underwent surgical intervention (laparotomy or laparoscopy) between October 2025 and January 2026. Demographic, clinical, laboratory, imaging, surgical, and obstetric outcomes were analyzed. Statistical analyses were performed using non-parametric tests, and correlations were assessed using Spearman's method.

Results: The median maternal age was 29 years, and the median gestational age at admission was 24 weeks. The most common diagnosis was ovarian torsion (53.8%), followed by less frequent conditions including appendicitis and other etiologies. Ultrasound was used in all patients, while magnetic resonance imaging (MRI) was performed in selected cases (15.4%). Laparotomy was the predominant surgical approach (92.3%). Maternal and neonatal outcomes were generally favorable, with a median delivery at 37 weeks and a low rate of neonatal intensive care unit (NICU) admission (15.4%). A significant association was observed between trimester and pain duration ($p=0.027$). Additionally, a strong negative correlation was found between gestational age at admission and the interval from diagnosis to delivery ($\rho=-0.97$, $p<0.001$).

Conclusion: Acute abdomen in pregnancy requires timely diagnosis and a multidisciplinary approach. Gynecological causes, particularly ovarian torsion, may predominate in surgically managed cases. Generally favorable maternal and neonatal outcomes were observed following surgical management in this small retrospective case series.

Keywords: Acute abdomen, pregnancy, adnexal torsion, ultrasonography, magnetic resonance imaging

INTRODUCTION

Acute abdomen in pregnancy constitutes a complex clinical scenario necessitating immediate diagnosis and intervention due to the potential for considerable maternal and fetal morbidity.¹ The differential diagnosis is extensive and encompasses both obstetric and non-obstetric etiologies, many of which may require immediate surgical intervention.² The assessment of abdominal pain in pregnant individuals is frequently complicated by the physiological and anatomical alterations that occur during pregnancy.^{3,4}

Pregnancy-induced changes, including the displacement of abdominal organs by the expanding uterus, physiological leukocytosis, and nonspecific gastrointestinal symptoms, may conceal traditional clinical findings and postpone diagnosis.⁵ Moreover, symptoms including nausea, vomiting, and abdominal discomfort often coincide with typical pregnancy-related illnesses, so complicating clinical evaluation.⁶

Acute appendicitis is the predominant non-obstetric surgical emergency in pregnancy, representing a substantial fraction of cases. A delayed diagnosis of appendicitis may lead to perforation, resulting in heightened maternal morbidity and negative fetal outcomes, such as preterm labor and fetal demise.^{7,8} Consequently, timely and precise diagnosis is crucial for enhancing outcomes.⁸ Beyond appendicitis, a variety of obstetric and non-obstetric causes can result in acute abdomen during pregnancy, a clinical disease that can be difficult to diagnose. Biliary tract disorders, acute pancreatitis, intestinal blockage, urinary tract pathologies (such as urolithiasis and pyelonephritis), and gynecologic illnesses including adnexal torsion and rupture are some of the most significant non-obstetric causes. Optimizing maternal and fetal outcomes requires a multidisciplinary approach, early and thorough differential diagnosis, and the use of safe and appropriate imaging modalities.



Despite technological advances in imaging and clinical care, the diagnosis and treatment of acute abdomen in pregnancy remain challenging, and there is still a need for better characterization of clinical presentation, diagnostic techniques, and surgical results. In this context, the present study aims to analyze the clinical characteristics, diagnostic procedures, and surgical results of pregnant women presenting with acute abdomen at a tertiary care hospital.

METHODS

The study was approved by the Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 17.02.2026, Decision No: AEŞH-BADEK2-2026-160). The ethics committee approval explicitly covered the retrospective use of medical records from the study period, preceding the approval date. All study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee, as documented in the approval.

This single-center, retrospective, descriptive-analytical study was conducted at the Perinatology Clinic of Ankara Etlik City Hospital, a tertiary referral center for advanced maternal-fetal medicine care in Türkiye. Medical records of pregnant women evaluated for acute abdomen between October 1, 2025, and January 1, 2026, were retrospectively reviewed. Acute abdomen was defined as acute abdominal pain requiring immediate diagnostic evaluation and/or surgical intervention.⁹

The study population consisted of all 13 consecutive pregnant patients who underwent emergency surgical intervention for acute abdomen during the study period. Patients with abdominal pain who were managed conservatively were not included, as the study specifically focused on surgically managed acute abdominal emergencies. Exclusions were made for patients not pregnant, those lacking complete or accessible critical clinical data (such as gestational age, surgical indication, or operative findings), and those who underwent surgery for obstetric reasons (e.g., uterine rupture or placenta accreta spectrum).

The subsequent variables were documented, demographic and obstetric information, maternal age, gravida, parity, gestational week at admission and delivery, trimester at admission, gestational duration from diagnosis to delivery, and presence of comorbidities. Clinical data, duration of symptoms, pain localization, body temperature, and laboratory findings including hemoglobin (HGB), white blood cell (WBC) count, C-reactive protein (CRP), platelet count (PLT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Imaging and diagnostic data included the imaging modalities used, such as ultrasound and/or magnetic resonance imaging (MRI), as well as the associated radiological findings (Figure 1). Surgical data comprised the surgical approach (laparotomy or laparoscopy), operation duration, intraoperative findings, and the final diagnosis confirmed by intraoperative and/or histopathological evaluation (Figure 2).

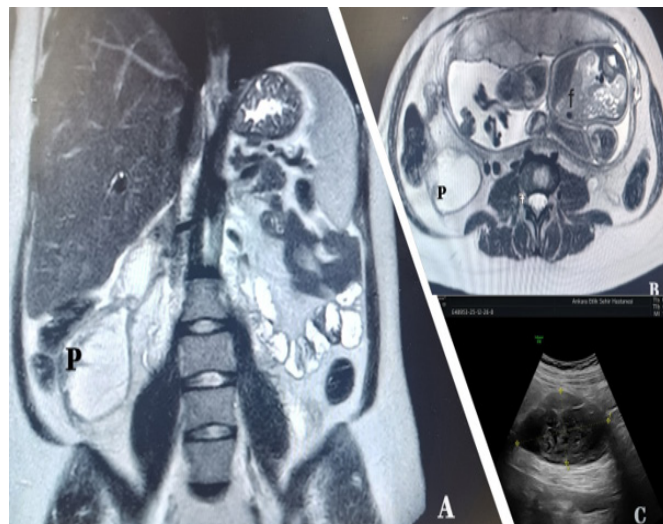


Figure 1. Magnetic resonance imaging and ultrasonographic findings of a pancreatic pseudocyst during pregnancy (A) Magnetic resonance imaging (MRI) demonstrating a bilobulated pancreatic pseudocyst extending from the pancreatic head to the right adnexal region. (B) MRI showing the pancreatic pseudocyst (P) and its anatomical relationship with the fetus (F) (C) Transabdominal ultrasonography demonstrating the extension of the pancreatic pseudocyst into the right adnexal region

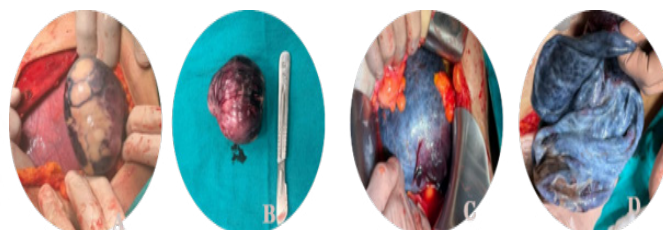


Figure 2. Intraoperative findings of pedunculated uterine myoma torsion and ovarian torsion during pregnancy (A) Intraoperative view demonstrating torsion of a pedunculated uterine myoma at 30 weeks of gestation. (B) Gross appearance of the torsioned pedunculated uterine myoma. (C) Intraoperative view showing torsion of a large left ovarian cyst at 12 weeks of gestation. (D) Gross appearance of the excised torsioned ovary

Maternal and neonatal outcomes included length of hospital stay, mode of delivery, gestational age at delivery, birth weight, Apgar scores, and admission to the neonatal intensive care unit (NICU). Diagnoses were classified based on system involvement as either pertaining to the female reproductive system or the gastrointestinal system (GIS). Trimesters were delineated as first (≤ 13 weeks), second (14–27 weeks), and third (≥ 28 weeks).

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (minimum–maximum), whereas categorical variables were represented as count (n) and percentage (%). The normality of the distribution was assessed, and due to the non-normal distribution of variables, non-parametric tests were utilized. Comparisons between groups were performed using the Kruskal–Wallis test for continuous variables. Given the small sample size and low expected cell frequencies, the Fisher–Freeman–Halton exact test was used for categorical comparisons across trimesters.

Following the identification of a statistically significant difference, post hoc pairwise comparisons were performed using the Bonferroni-adjusted Mann–Whitney U test.

Spearman correlation analysis was employed to evaluate the relationships between gestational week of admission and specific clinical indicators, as well as between pain duration and laboratory data. A p-value below 0.05 was considered statistically significant.

RESULTS

Thirteen pregnant individuals with acute abdomen were included in the study. The median maternal age was 29 (26–39) years, and the median gestational age at admission was 24 (6–34) weeks. In the population, most patients were in the third trimester (n=6, 46.2%), followed by the first trimester (n=5, 38.5%) and the second trimester (n=2, 15.4%). Comorbid conditions were present in six patients (46.2%) (Table 1).

Table 1. Demographic, obstetric, and neonatal outcome characteristics of pregnant patients presenting with acute abdomen (n=13)

Maternal age (years)	29 (26-39)
Gravida	4 (1-6)
Parity	1 (0-4)
Presence of comorbidity, n (%)	6 (46.2)
Gestational age at admission (weeks)	24 (6-34)
Gestational age at delivery (weeks)	37 (33-40)
Diagnosis-to-delivery interval (weeks)	10 (1-34)
Birth weight (g)	2980 (2030-3400)
Mode of delivery, n (%)	
Vaginal delivery	6 (46.2)
Cesarean section	7 (53.8)
Apgar score at 1 minute	9 (7-10)
Apgar score at 5 minutes	10 (7-10)
NICU admission, n (%)	2 (15.4)
Values are presented as median (minimum–maximum) or n (%), as appropriate. Apgar: Appearance, Pulse, Grimace, Activity, Respiration, NICU: Neonatal intensive care unit	

The median gestational week at delivery was 37 (33–40) weeks, and the median interval from diagnosis to delivery was 10 (1–34) weeks. The median birth weight was 2980 (2030–3400) grams. Cesarean delivery occurred in 53.8% of patients, whilst 46.2% underwent vaginal delivery. The median Apgar values at 1 minute and 5 minutes were 9 (7–10) and 10 (7–10), respectively. Two neonates (15.4%) required admission to the NICU due to respiratory distress associated with preterm birth. One neonate was delivered at 33 weeks of gestation following maternal laparotomy and detorsion for ovarian torsion at 24 weeks, with Apgar scores of 7 at both 1 and 5 minutes. The other neonate was delivered approximately one week after maternal surgery for a pancreatic pseudocyst at 34 weeks of gestation. No surgery-related postoperative maternal complications were observed among the 13 patients (Table 1).

The median duration of pain was 12 (2–96) hours, with the right lower quadrant being the most common site of pain localization (69.2%). The median body temperature was 36.2 °C, with a range of 36 to 36.9 °C. Laboratory results indicated a median WBC count of 14.5 (7.7–23.0) $\times 10^9/L$ and a CRP level of 11 (1–46) mg/L (Table 2).

The most frequent diagnosis was ovarian torsion (53.8%), followed by ovarian cyst rupture (7.7%), acute appendicitis (7.7%), pedunculated fibroid torsion (7.7%), heterotopic

Table 2. Clinical presentation and laboratory findings of pregnant patients diagnosed with acute abdomen (n=13)

Pain duration (hours)	12 (2-96)
Pain localization, n (%)	
Right lower quadrant	9 (69.2)
Left lower quadrant	4 (30.8)
Body temperature (°C)	36.2 (36-36.9)
Hemoglobin (g/dl)	10.8 (9.1-13)
White blood cell count ($\times 10^9/L$)	14.5 (7.7-23.0)
C-reactive protein (mg/L)	11 (1-46)
Platelet count ($\times 10^3/\mu L$)	221 (143-570)
Aspartate Aminotransferase (U/L)	14 (9-38)
Alanine Aminotransferase (U/L)	10 (7-48)
Values are presented as median (minimum–maximum) or n (%), as appropriate.	

pregnancy (7.7%), acute cholecystitis (7.7%), and pancreatic pseudocyst (7.7%). Ultrasound was utilized in all patients, whereas MRI was conducted in 15.4% of cases. MRI was performed in two clinically stable patients with suspected non-gynecological causes of acute abdomen, namely acute appendicitis and pancreatic pseudocyst, because of diagnostic uncertainty following ultrasonographic evaluation. Both examinations were performed during daytime hours when MRI was available. In both cases, MRI provided additional diagnostic information, and the MRI findings were confirmed by intraoperative findings.

Laparotomy was the primary surgical method (92.3%). The median time of the procedure was 70 (30–140) minutes, and the median hospital stay was 3 (2–12) days (Table 3, Figure 3).

Table 3. Final diagnoses, imaging modalities, and surgical characteristics of pregnant patients with acute abdomen (n=13)

Final diagnosis, n (%)	
Acute appendicitis	1 (7.7)
Ovarian torsion	7 (53.8)
Ovarian cyst rupture	1 (7.7)
Pedunculated fibroid torsion	1 (7.7)
Heterotopic pregnancy	1 (7.7)
Acute cholecystitis	1 (7.7)
Pancreatic pseudocyst	1 (7.7)
Female reproductive system disorders, n (%)	10 (76.9)
Gastrointestinal system disorders, n (%)	3 (23.1)
Imaging modality used, n (%)	
Ultrasound	13 (100)
Magnetic Resonance Imaging	2 (15.4)
Surgical approach, n (%)	
Laparotomy	12 (92.3)
Laparoscopy	1 (7.7)
Operation duration (minutes)	70 (30-140)
Length of hospital stay (days)	3 (2-12)
Values are presented as median (minimum–maximum) or n (%), as appropriate. Imaging modalities are not mutually exclusive.	

A statistically significant variation in pain duration was seen among trimesters (p=0.027). The post hoc analysis revealed that the difference occurred between the first and third trimesters (p=0.017). The duration of gestation from diagnosis to delivery varied considerably across trimesters (p=0.011), with post hoc analysis revealing a significant

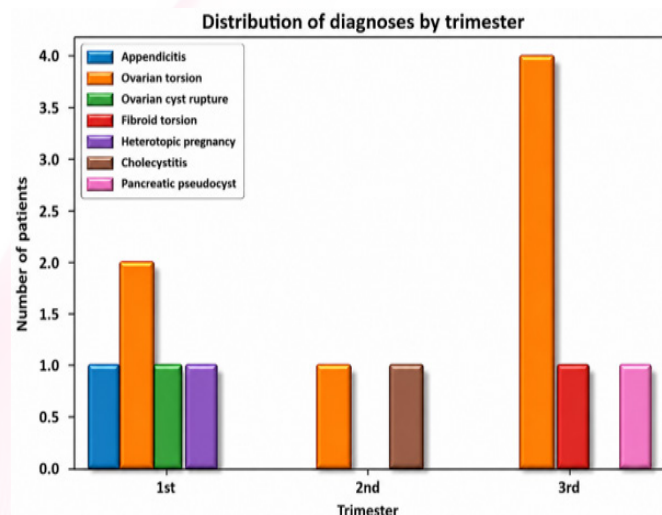


Figure 3. Distribution of surgically confirmed diagnoses according to trimester of pregnancy at admission. The figure illustrates the distribution of surgical diagnoses among pregnant patients presenting with acute abdomen during the first (n=5), second (n=2), and third (n=6) trimesters. Diagnoses were established based on intraoperative findings and/or histopathological evaluation

difference between the first and third trimesters ($p=0.006$). No notable variations were detected in maternal age, duration of operation, rates of preterm birth, mode of delivery, length of hospital stay, or system involvement throughout trimesters ($p>0.05$, **Table 4**).

Table 4. Comparison of demographic, clinical, and obstetric outcomes according to trimester of admission

	1 st trimester n=5	2 nd trimester n=2	3 rd trimester n=6	p value
Maternal Age (years)	29 (27-36)	33.5 (28-39)	28.5 (26-34)	0.481 ^a
Pain duration (hours)	4 (1-9)	35 (24-46)	24.5 (4-96)	0.027 ^{a,c}
Operation duration, (minutes)	60 (50-140)	100 (80-120)	70 (30-90)	0.424 ^a
Preterm birth n (%)				
<37 weeks	1 (20)	1 (50)	3 (50)	0.767 ^b
≥37 weeks	4 (80)	1 (50)	3 (50)	
Mode of delivery, n (%)				
Vaginal delivery	4 (80)	1 (50)	1 (16.7)	0.111 ^b
Cesarean section	1 (20)	1 (50)	5 (83.3)	
Length of hospital stay (days)	4 (2-6)	2 (2-2)	3 (2-12)	0.256 ^a
Diagnosis-to-delivery interval (weeks)	29 (23-34)	17 (9-25)	4.5(1-10)	0.011 ^{a,d}
Female reproductive system disorders, n (%)	4 (80)	1 (50)	5 (83.3)	0.738 ^b
Gastrointestinal system disorders, n (%)	1 (20)	1 (50)	1 (16.7)	

Values are presented as median (minimum–maximum) or n (%), as appropriate. a: Kruskal Wallis test, b: Fisher–Freeman–Halton exact test, c: Post hoc Bonferroni-corrected Mann–Whitney U test showed a significant difference between G1 and G3 ($p=0.017$). No statistically significant difference was found between G1 and G2 ($p=0.051$). d: Post hoc Bonferroni-corrected Mann–Whitney U test showed a significant difference between G1 and G3 ($p=0.006$). G1: First trimester, G2: Second trimester, G3: Third trimester

Spearman correlation analysis demonstrated a robust negative association between the gestational week at admission and the interval from diagnosis to birth ($\rho=-0.97$, $p<0.001$). A moderate positive connection was identified between gestational week and pain duration ($\rho=0.59$, $p=0.034$). No statistically significant relationships were seen between pain duration and CRP ($\rho=-0.36$, $p=0.224$) or WBC levels ($\rho=-0.41$, $p=0.161$, **Table 5**).

DISCUSSION

Acute abdomen during pregnancy remains a significant diagnostic and therapeutic challenge due to physiological, anatomical, and biochemical changes that may obscure classical clinical findings.³ In the present study, we evaluated

Table 5. Spearman correlation analysis of gestational age at admission, diagnosis-to-delivery interval, and selected clinical variables (n = 13)

	Spearman's ρ	p-value
Gestational age at admission vs. diagnosis-to-delivery interval	-0.97	<0.001
Gestational age at admission vs. pain duration	0.59	0.034
Pain duration vs. C-reactive protein	-0.36	0.224
Pain duration vs. white blood cell count	-0.41	0.161

Spearman's rank correlation coefficient (ρ) was used to assess associations between continuous variables. A p value less than 0.05 was considered statistically significant

the clinical characteristics, diagnostic approaches, and surgical outcomes of pregnant patients presenting with acute abdomen, and our findings are largely consistent with the existing literature.^{9,10}

One of the most notable findings of our study was that gynecological causes, particularly ovarian torsion, constituted the most common etiology (53.8%), whereas acute appendicitis accounted for a relatively small proportion of cases (7.7%). This differs from the majority of the literature, where acute appendicitis is reported as the most common non-obstetric surgical emergency in pregnancy.^{11,12} As our institution is a tertiary referral center specializing in maternal–fetal medicine, its referral patterns may have contributed to a higher representation of gynecological

emergencies, particularly ovarian torsion. Furthermore, the inclusion of only surgically managed patients, the small sample size, and the relatively short three-month study period may have influenced the distribution of diagnoses. Therefore, the predominance of ovarian torsion in our cohort should be interpreted within the context of these selection and institutional factors rather than as representative of the general pregnant population. Nevertheless, the predominance of adnexal pathologies in our cohort highlights the importance of considering gynecologic causes alongside gastrointestinal etiologies in pregnant patients presenting with acute abdomen.

Consistent with previous reports, clinical evaluation alone was insufficient for definitive diagnosis. Pregnancy-related physiological changes, including leukocytosis and displacement

of abdominal organs, may mask or mimic pathological findings.¹³⁻¹⁵ In our study, laboratory parameters such as WBC count and CRP levels demonstrated variability and were not significantly correlated with symptom duration, supporting the limited specificity of inflammatory markers in pregnancy.

With regard to imaging, ultrasonography was utilized in all patients, in line with current recommendations as the first-line modality due to its safety and accessibility.¹⁶ However, MRI was performed in a limited number of cases (15.4%). While this may reflect adequate diagnostic yield of ultrasonography in our cohort or limited availability of MRI, the literature supports MRI as a valuable problem-solving tool when ultrasound findings are inconclusive, given its superior soft-tissue resolution and lack of ionizing radiation.¹⁷ Increased use of MRI may further improve diagnostic accuracy and reduce unnecessary surgical interventions.¹⁸

In terms of surgical management, laparotomy was the predominant approach (92.3%) in our study. Although laparoscopy has been associated with shorter hospital stay and reduced blood loss in several studies, concerns regarding fetal safety and technical challenges persist.^{18,19} The choice of surgical approach was influenced by several factors, including advanced gestational age, large adnexal masses, and the need for emergency surgical intervention. In contrast, laparoscopy was performed in one patient at six weeks of gestation for ovarian torsion, and successful detorsion was achieved. These observations suggest that the surgical approach was individualized according to gestational age, underlying pathology, and clinical circumstances. Nevertheless, both approaches are considered safe when performed with appropriate indications and expertise.^{20,21}

Maternal and neonatal outcomes in our study were generally favorable. The median gestational age at delivery was 37 weeks, with low rates of NICU admission (15.4%) and high Apgar scores. However, given the small sample size, retrospective design, and absence of a comparison group, these observations cannot establish an association between the timing of surgical intervention and maternal or neonatal outcomes.

An additional noteworthy aspect of our study is the presence of rare causes of acute abdomen. Conditions such as pedunculated fibroid torsion and heterotopic pregnancy, although uncommon, may lead to significant maternal morbidity if not promptly recognized.^{22,23} Pedunculated fibroid torsion can occur due to uterine enlargement and anatomical displacement during pregnancy and often requires urgent surgical intervention.²² Similarly, heterotopic pregnancy poses a diagnostic challenge, particularly in early gestation, and delayed diagnosis may result in serious complications.²³ These rare entities emphasize the importance of maintaining a broad differential diagnosis and highlight the critical role of imaging and clinical suspicion. The imaging findings presented in this study may contribute to improved recognition and management of such uncommon conditions.

Furthermore, we observed a significant association between trimester and pain duration, with longer symptom duration

in later gestational weeks. A strong negative correlation was observed between gestational age at admission and the diagnosis-to-delivery interval ($\rho=-0.97$, $p<0.001$). However, this finding should be interpreted cautiously, as the interval from diagnosis to delivery is mathematically dependent on gestational age at admission and gestational age at delivery. Therefore, the observed correlation may primarily reflect this inherent mathematical relationship rather than an effect of the acute abdominal condition or surgical intervention on delivery timing. No causal inference can be drawn from this association.

Limitations

This study has several limitations. First, the small sample size, particularly the inclusion of only two patients in the second-trimester group, limits the statistical power and generalizability of our findings. Therefore, comparisons between trimester groups should be interpreted cautiously, as the small number of observations increases statistical uncertainty and limits the ability to detect potentially meaningful differences. Second, the retrospective and single-center design introduces potential selection and information biases. Third, the inclusion of only surgically managed patients may underestimate the full clinical spectrum of acute abdomen in pregnancy, particularly those managed conservatively.

In addition, the inclusion of rare and clinically challenging cases may contribute to the literature by highlighting uncommon etiologies and real-life decision-making processes in this complex patient population. Further multicenter studies with larger cohorts are needed to better define optimal diagnostic pathways and to clarify the role of advanced imaging and minimally invasive surgical techniques in this patient population.

CONCLUSION

Acute abdomen during pregnancy is a complex clinical condition that requires prompt diagnosis and a multidisciplinary approach. In surgically managed patients, gynecologic etiologies—particularly ovarian torsion—may be more common than expected. In this small retrospective case series, generally favorable maternal and neonatal outcomes were observed following surgical management; however, the study design does not allow conclusions regarding the effects of intervention timing on these outcomes. Increased clinical awareness and appropriate use of imaging are essential to improve diagnostic accuracy and patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Scientific Researches Evaluation and Ethics Committee of Ankara Etlik City Hospital (Date: 17.02.2026, Decision No: AEŞH-BADEK2-2026-160).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All

participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

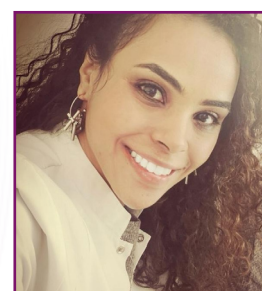
Concept: NÇK, ATÇ; Design: NÇK, ZŞ, ATÇ; Control: ATÇ; Data Collection and/or Processing: NÇK, ZŞ, ÜÖ, DDB; Analysis and/or Interpretation: NÇK, DDB, ATÇ; Literature Review: NÇK; Article Writing: NÇK; Critical Review: NÇK, ZŞ, ÜÖ, ATÇ.

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A fetiform placental lesion in a monochorionic diamniotic placenta: a diagnostic challenge between teratoma and an acardiac co-twin—a case report^a

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Cite this article: Yıldız AG, Haliloğlu S, Akın F, Üner H, Kahyaoğlu İ. A fetiform placental lesion in a monochorionic diamniotic placenta: a diagnostic challenge between teratoma and an acardiac co-twin—a case report. *J Controv Obstetr Gynecol Ped.* 2026;4(4):108-112. doi:10.51271/JCOGP-0083

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Received: 26/09/2026

Accepted: 26/10/2026

Published: 28/10/2026

ABSTRACT

Placental teratomas are extremely rare non-trophoblastic tumors of the placenta. A fetiform teratoma is a rare subtype of mature teratoma consisting of highly differentiated tissues that may resemble a malformed fetus but lack true organogenesis, axial skeletal organization and developed systemic anatomical structures. However, it can be difficult to distinguish fetiform-like lesions, particularly those with placental attachment, from a severely regressed or acardiac twin. This case report presents the clinical, macroscopic and histopathological findings of an unusual placental mass, resembling a fetus and containing hair-like structures, which was incidentally detected during a cesarean section in a 26-year-old patient who had had an uneventful antenatal course. Histopathological examination revealed a monochorionic diamniotic placenta containing two umbilical cords, one of which was markedly short, and a lesion measuring approximately 5×5×2.5 cm directly connected to the placenta by the short umbilical cord. Microscopic examination revealed mature tissues derived from multiple germ layers, including skin and skin appendages, adipose tissue, cartilage, striated muscle, ganglionic elements, central nervous system tissue and the choroid plexus. No vertebral axis, long appendicular bones, organized visceral structures or developed systemic anatomical structures were detected. However, the monochorionic diamniotic placental structure and the markedly short second umbilical cord raised the possibility of a severely regressed twin. While the morphological features of the lesion are consistent with a mature fetiform teratoma, a severely regressed or acardiac monozygotic twin could not be definitively ruled out on the basis of morphological findings alone. Without molecular comparative analysis, it is difficult to make a definitive diagnostic distinction between these two possibilities. This case highlights the importance of interpreting morphological findings in conjunction with placental anatomy and, where possible, molecular data when assessing fetiform placental lesions.

Keywords: Placenta, teratoma, fetus in fetu, pregnancy; twin, fetiform placental lesion, monochorionic diamniotic placenta

^aAn earlier version of this case was presented as an oral presentation under the title “Fetiform Teratoma: A Rare Incidental Intraoperative Finding” at the 3rd International Congress of the Gynecology and Obstetrics Association, held on 15–19 May 2026. The presentation was accepted as an oral presentation (Abstract No. 8041) and was included in the congress abstract book.

INTRODUCTION

Placental tumors are generally classified as trophoblastic and non-trophoblastic lesions.¹ Among non-trophoblastic placental lesions, placental teratomas are extremely rare germ cell tumors; very few cases have been reported in the English-language literature since they were first described by Morville in 1925.²⁻⁵ They are typically located on the fetal surface of the placenta, between the amnion and the chorion, and are usually detected incidentally after delivery.⁴

A fetiform-type teratoma is an extremely rare subtype of mature teratoma characterized by highly differentiated tissues that may resemble a malformed fetus but lack true organogenesis, a vertebral axis and organized anatomical

structures.⁶ This lesion has historically also been referred to as a ‘homunculus’; however, this terminology remains controversial in modern pathological literature⁷ and, for this reason, the term ‘fetiform-like teratoma’—which is currently accepted—is used throughout this report. Because of its distinctive characteristics, it must be distinguished from fetus in fetu and fetus acardius amorphus, which differ in terms of embryological origin, pathological features and clinical outcomes.^{8,9}

A placental fetiform teratoma is an extremely rare entity, and only a limited number of cases have been described in the literature. A recent systematic review reported 17



histopathologically confirmed fetiform teratomas; however, none of the confirmed cases involved a lesion located in the placenta.⁸ However, in some cases, it is debatable whether placental fetiform-like masses represent a germ cell neoplasm or a severely regressed or acardiac twin; in making this distinction, molecular genetic comparison and genotyping of the lesion against the placenta or the healthy twin, in addition to morphological assessment, may contribute to the diagnostic evaluation.¹⁰ It is therefore important to evaluate morphological findings in conjunction with placental anatomy, clinical features and, where possible, molecular comparative data.

This study presents an unusual fetiform-like placental lesion detected in a monochorionic diamniotic placenta, the morphological features of which are consistent with a fetiform-like teratoma, although the possibility of a severely regressed acardiac twin must also be considered. In addition to the clinical and histopathological characteristics of the case, the diagnostic distinction between a fetiform teratoma and a regressed/acardiac twin, as well as the limitations of this distinction, are discussed in the light of the current literature.

CASE REPORT

A 26-year-old patient, gravida 5, para 2, with a history of two previous abortions, was admitted to our clinic at 38 weeks and 5 days' gestation for an elective cesarean section following two previous cesarean deliveries. No abnormalities were detected during antenatal care, and the pregnancy had been monitored without complications at an external center. The patient first presented at our clinic at 12 weeks' gestation; at that time, the ultrasound scan revealed no findings suggestive of a twin pregnancy. The first-trimester combined screening was normal; the PAPP-A level was 2.63 mIU/ml (1.53 MoM), the free beta-hCG level was 64.4 ng/ml (1.7 MoM), nuchal translucency was measured at 0.9 mm and the crown-rump length at 57 mm, and the combined risk was calculated to be less than 1 in 10,000. The second-trimester detailed anomaly ultrasound scan was also normal. At her first appointment, the patient was 165 cm tall and weighed 80 kg (BMI 30 kg/m²); her total weight gain during pregnancy was 10 kg; she did not smoke and the pregnancy had occurred spontaneously. The placenta was anteriorly situated.

Although the pregnancy had been monitored at an external center as an apparently uncomplicated pregnancy, a pathological examination of the delivered placenta revealed a monochorionic diamniotic placental structure and two umbilical cords, one of which was markedly short.

During a cesarean section performed under spinal anesthesia, a live baby girl weighing 3150 g and measuring 50 cm in length was delivered, with Apgar scores of 9 and 10 at 1 and 5 minutes respectively. Following the removal of the placenta and membranes, macroscopic examination revealed an irregular-appearing mass containing hair-like structures adjacent to the placenta (Figure 1). The material was subsequently sent to the pathology laboratory for histopathological examination.

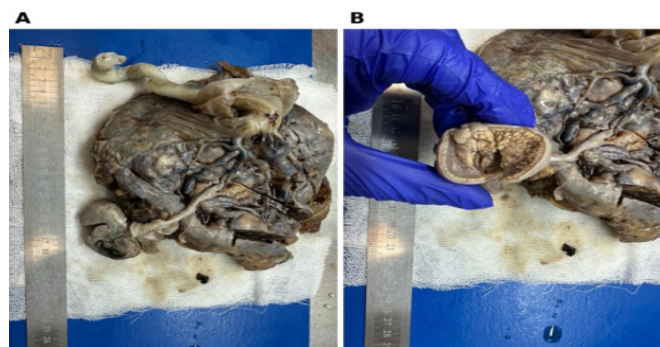


Figure 1. Gross and cut-surface appearance of the fetiform placental lesion. A. Gross appearance of the lesion, showing an irregular nodular mass adjacent to the fetal surface of the placenta with a fetal skin-like external appearance. B. Cut surface of the lesion, revealing a soft, heterogeneous, yellow-tan appearance without gross evidence of organogenesis or organized anatomical structures

Macroscopic pathological examination revealed that the placenta measured 19×15×6 cm and contained two umbilical cords, measuring 27 cm and 6.5 cm in length respectively. The monochorionic diamniotic configuration was confirmed by histological examination of the dividing membrane between the cords, which showed two apposed amniotic layers without intervening chorionic tissue (Figure 2B). In sections taken from the short umbilical cord, a single umbilical artery and a single umbilical vein were observed (Figure 2A). Continuity of the cord vessels into the lesion and placental vascular anastomoses were not specifically documented in the available pathology report. A nodular mass measuring approximately 5×5×2.5 cm and bearing hair follicles on its surface was directly connected to the placenta by the hypoplastic umbilical cord, which measured 6.5 cm in length and 0.5 cm in diameter. The lesion was soft in consistency, cream-pink in color and had a surface appearance resembling fetiform skin. No distinct organ development or organized anatomical structure was observed on macroscopic examination.

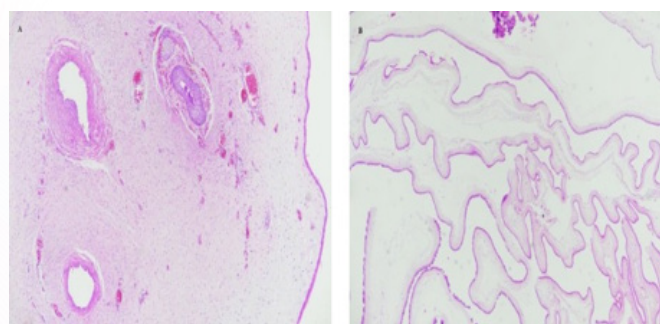


Figure 2. Histopathological findings of the umbilical cord and placental membranes. A. Cross-section of the short umbilical cord demonstrating a single umbilical artery and one umbilical vein (H&E×40). B. Monochorionic diamniotic dividing membrane showing two apposed amniotic layers without intervening chorionic tissue (H&E×40)

Microscopic examination revealed skin and skin appendages, subcutaneous adipose tissue and cartilage within the lesion (Figure 3). In addition, areas of skeletal muscle, ganglionic elements and central nervous system tissue, as well as choroid plexus-like structures, were identified (Figure 4). No vertebral axis, long appendicular bones, organized visceral structures or developed systemic anatomical organization were observed.

Areas of infarction, foci of dystrophic calcification, perivillous fibrin deposits and increased syncytial nodes were also

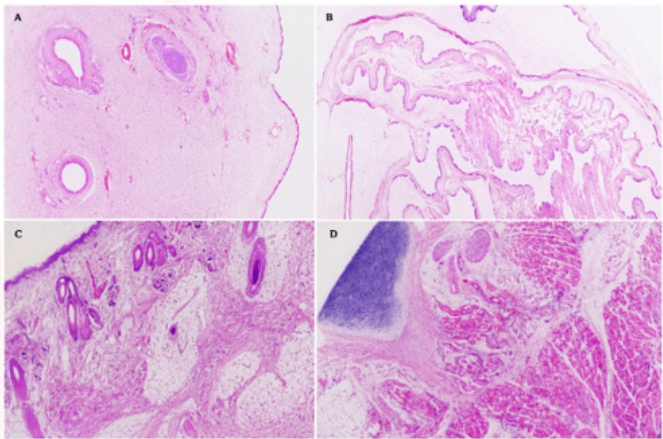


Figure 3. Histopathological features of the fetiform placental lesion. A. Mature skin with adnexal structures and underlying adipose tissue. B. Mature adipose tissue, brown adipose tissue, skeletal muscle, and scattered ganglionic elements within the lesion. C. Coexisting mature white adipose tissue and brown adipose tissue. D. Mature cartilage and skeletal muscle bundles (H&E×100 for all panels). H&E: Hematoxylin and eosin.

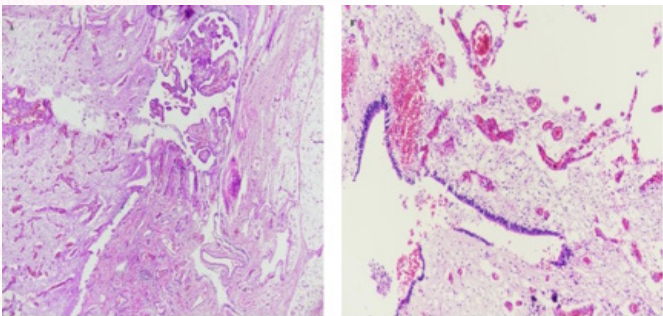


Figure 4. Neural components within the fetiform placental lesion. A. Mature neural tissue with choroid plexus-like structures and adjacent fibroadipose tissue. B. Central nervous system-type tissue showing cerebellar differentiation (H&E×100 for both panels). H&E: Hematoxylin and eosin.

observed in the placental tissue. The morphological findings were assessed as consistent with a fetiform-like placental lesion. However, a definitive distinction between a mature fetiform-like teratoma and a severely regressed or acardiac twin could not be made on the basis of clinical and histopathological findings alone. The timeline is shown in [Table](#).

DISCUSSION

Placental teratomas are extremely rare non-trophoblastic placental lesions; since Morville's initial description in 1925,

only a limited number of cases have been reported in the literature.^{1,2,4} The fetiform variant is even rarer. In a recent systematic review, only 17 fetiform-type teratomas meeting strict morphological criteria were identified.⁸ In this context, the present case represents an unusual fetiform-like placental lesion developing in a monochorionic diamniotic placenta and is of particular interest in terms of the diagnostic differentiation between a placental teratoma and a severely regressed or acardiac twin.

Fetiform teratomas are highly differentiated, mature teratomas that, macroscopically, may resemble a malformed fetus but lack true organogenesis and the regular anatomical organization characteristic of a fetus.^{3,6,9} Histopathological examination of our case revealed mature tissues derived from different germ layers, including skin and skin appendages, adipose tissue, cartilage, skeletal muscle, ganglionic elements, central nervous system tissue and the choroid plexus. No vertebral axis, long appendicular bones, organized visceral structures or immature neuroepithelial elements were observed. These features are consistent with a mature fetiform teratoma in terms of traditional morphological criteria. However, particularly in fetiform lesions with placental involvement, these morphological features alone may not definitively indicate a neoplastic origin.

The etiology of placental teratoma remains unclear. Proposed mechanisms include the aberrant migration of primordial germ cells, abnormal differentiation of germ cells, and developmental processes associated with abnormal twinning.^{1,4,9} The aberrant migration of primordial germ cells is one of the main hypotheses explaining why placental teratomas are classified as germ cell neoplasms. However, the presence of a markedly short second umbilical cord in the present case suggests that the possibility of a severely regressed twin or an acardiac twin in a monochorionic diamniotic placental environment should also be considered.

The main diagnostic challenge in this case is determining whether the lesion represents a true germ cell neoplasm or a monozygotic twin that has regressed to a significant extent. The absence of a vertebral axis, long appendicular bones and organized visceral structures is interpreted in favor of a fetiform teratoma according to traditional morphological

Table. Timeline of the clinical course and diagnostic evaluation		
Timepoint	Clinical event	Findings
12 weeks of gestation	First evaluation at our institution	Ultrasonography showed a singleton pregnancy with no evidence of a second gestational sac or embryo. First-trimester combined screening was low risk.
Second trimester	Detailed fetal anomaly examination	No fetal structural abnormalities were detected.
38 weeks+5 days	Admission for elective cesarean delivery because of previous cesarean sections	Pregnancy had remained clinically uncomplicated.
At delivery	Cesarean section under spinal anesthesia	A live female infant weighing 3150 g was delivered, with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively.
Immediately after delivery	Gross examination of the placenta	An irregular, hair-bearing nodular mass adjacent to the fetal surface of the placenta was identified. The placenta contained two umbilical cords, one of which was markedly short.
Histopathological examination	Evaluation of the placenta, membranes, umbilical cords, and fetiform lesion	Monochorionic diamniotic placental membranes were confirmed. The short cord contained a single umbilical artery and one umbilical vein. The lesion contained mature tissues from multiple germ layers, without a vertebral axis, appendicular long bones, organized viscera, or developed systemic anatomical structures.
Postoperative period	Maternal and neonatal follow-up	The postoperative course of both the mother and the newborn was uneventful, with no maternal or neonatal complications observed.

criteria, while the presence of a monochorionic diamniotic placental structure and a separate, markedly short second umbilical cord supports the possibility of a twin-origin developmental process. The fact that a second gestational sac or embryo was not visualized on the ultrasound scan at 12 weeks' gestation does not definitively rule out the possibility of a monozygotic twin that was lost at an earlier stage or has regressed significantly. Therefore, in the present case, it is difficult to make a definitive distinction between these two entities based solely on the absence of fetiform organization or axial skeletal elements.

Limitations

The limitations of this distinction have also been demonstrated at the molecular level by McHenry et al.¹⁰ The authors carried out DNA genotyping on a lesion that could be assessed as consistent with a placental teratoma according to traditional morphological criteria, and demonstrated that the lesion and normal placental tissue shared largely the same genetic profile at the microsatellite loci examined. In light of these findings, the lesion was re-evaluated as a monozygotic acardiac/amorphous twin, and the importance of ruling out a monozygotic twin origin at the molecular level in the diagnosis of placental teratoma was emphasized. The fact that no molecular comparative analysis was performed in the present case limits the ability to definitively distinguish between a teratomatous origin and the possibility of a severely regressed monozygotic twin.

Short tandem repeat (STR) analysis, or other informative molecular genetic methods, carried out on the lesion, normal placental tissue and, where possible, the healthy twin, may provide further evidence regarding the origin of the lesion. Such investigations can also be carried out on tissue that has been properly fixed in formalin and embedded in paraffin. However, molecular results must also be interpreted with caution; the genetic composition of germ cell teratomas is not homogeneous, and heterozygous genetic features may be preserved in some mature teratomas. It is therefore more appropriate to evaluate molecular findings in conjunction with morphological, clinical and placental findings.

The fundamental significance of this finding lies not so much in its clinical outcomes as in the fact that it highlights the diagnostic difficulties encountered in the classification of placental fetiform-like lesions. Particularly in cases where a second umbilical cord is present in a monochorionic placenta, the diagnosis of a fetiform teratoma should not be based solely on morphological features; the possibility of severe regression or an acardiac monozygotic twin should also be considered. The evaluation of morphological, clinical and placental findings, together with molecular genetic data where possible, may contribute to a more accurate classification of the etiology of these rare lesions.

CONCLUSION

This case presents an unusual fetiform-like placental lesion detected in a monochorionic diamniotic placenta. The absence of a vertebral axis, long appendicular bones and organized visceral structures, coupled with the presence of mature but disorganized tissues originating from different germ layers, is

consistent with a mature fetiform-like teratoma according to traditional morphological criteria. However, the presence of a markedly short second umbilical cord and a monochorionic diamniotic placental structure necessitates consideration of the possibility of severely regressed or acardiac monozygotic twins. The lack of molecular comparative data limits the ability to definitively distinguish between these two possibilities. It is therefore important, when assessing fetiform-like placental lesions, to interpret morphological findings in conjunction with placental anatomy, clinical features and, where possible, molecular genetic data.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient for publication of the clinical details and accompanying images.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Concept: AGY, SH; Design: AGY; Control: İK; Resources: SH, HÜ; Materials: HÜ; Data Collection and/or Processing: SH; Analysis and/or Interpretation: AGY; Literature Review: FA; Writing The Article: AGY; Critical Review: İK.

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