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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	350 (Structured)	40	6	6
Review Article	5000	350	50	6	10
Case Report	1500	200	15	No tables	5
Letter to the Editor	1000	No abstract	10	No tables	No media
Image	200	No abstract	3	No table	3

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Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290–308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561–5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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CONTENTS

Zeynep Kamil Med J 2026;57(3):127–134
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ORIGINAL ARTICLE

Stillbirth and associated factors in a developing country

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ABSTRACT

Objective: Stillbirth is one of the most adverse outcomes for both families and obstetricians. In this study, we aimed to evaluate the incidence, causes, risk factors, delivery methods, and placental pathologies associated with stillbirth at our obstetric center.

Material and Methods: This retrospective descriptive study was conducted in the obstetrics clinic of a tertiary hospital. Stillbirths occurring between February 2018 and October 2023 were included in the study. A total of 109 stillbirths among 27,034 live births were included. The obstetric, perinatal, and neonatal outcomes of the women included in the study were examined.

Results: The stillbirth rate at our hospital was 4.03 per 1000 births. In this study, 49 (45%) women were admitted to the hospital with reduced fetal movement. Fetal growth restriction, observed in 21 (19.3%) cases, was determined to be the leading cause of stillbirth. The rate of unexplained/unclassifiable stillbirth was 18 (16.5%). Among the placentas of stillborn fetuses examined, the most frequently detected histopathological findings were perivillous/intervillous fibrin accumulation in 52 (74.3%) cases, calcification in 33 (47.1%), intraparenchymal hemorrhage/hematoma in 31 (44.3%), decidual inflammation in 31 (44.3%), increased syncytial knots in 26 (37.1%), and necrotic decidua in 23 (32.9%).

Conclusion: Stillbirth rates are among the main indicators of the quality of obstetric care. Stillbirth causes emotional devastation and grief among parents. To reduce stillbirth rates, specific risk factors in women should be identified, and strategies to prevent pregnancy complications should be established during antenatal visits. Pathological examination of the placenta should be performed as part of the evaluation of stillbirths.

Keywords: Etiology, fetal death, fetal demise, placental pathology, pregnancy.

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INTRODUCTION

Stillbirth is defined as the death of a fetus from the 20th week of gestation onward or of a fetus weighing 500 g or more when the gestational age is unknown. The fetal weight and gestational age limits used to define stillbirth differ among countries. Fetal death is characterized by the absence of signs of life, including heartbeat, respiration, umbilical cord pulsation, and extremity movement.[1] The global stillbirth rate is 13.9 per 1000 births. Stillbirth rates vary according to the level of development of countries. They are lower in high-income countries (3 per 1000 births) and higher in low-income countries (22.7 per 1000 births).[2] Stillbirth is divided into three categories according to the gestational week at which it occurs: early stillbirth between 20 and 27 weeks of gestation, late stillbirth between 28 and 36 weeks of gestation, and term stillbirth at 37 weeks of gestation or later.[3]

Risk factors for stillbirth include nulliparity, teenage and advanced maternal age, a previous history of stillbirth and adverse obstetric outcomes, Black race, maternal comorbidities such as diabetes and hypertension, acquired and hereditary thrombophilia, intrahepatic cholestasis of pregnancy, obesity, major life events involving traumatic, financial, emotional, or partner-related stress, substance use, uterine abnormalities, assisted reproductive technology, multiple pregnancy, postterm pregnancy, and a male fetus.[4] Identifying these risk factors in pregnant women and reassessing antenatal care in the presence of risk factors are essential. Unexplained stillbirth, congenital anomalies, fetal growth restriction, infection, genetic anomalies, hydrops fetalis, fetal cardiac channelopathy, placental abruption, umbilical cord and placental anomalies, and fetomaternal hemorrhage are possible etiologies of stillbirth. The leading causes of stillbirth in developed countries include genetic anomalies, placental disorders, and fetal growth restriction (FGR). In low-income countries, preeclampsia, prolonged labor, postterm pregnancy, and infection are common causes of stillbirth.[5]

In this study, we aimed to evaluate the incidence, causes, risk factors, delivery methods, and placental pathologies associated with stillbirth at our obstetric center.

MATERIAL AND METHODS

This retrospective descriptive study was conducted in the obstetrics clinic of a tertiary hospital. Stillbirths occurring between February 2018 and October 2023 were included in the study. Data on the pregnant women were obtained from the hospital's electronic database records. Fetuses confirmed to have no heartbeat on prenatal obstetric ultrasonography were included in the study. Fetuses weighing <500 g or at <20 weeks of gestation, live-born infants, and induced abortions were excluded. The obstetric, perinatal, and neonatal outcomes of the women included in the study were examined. The women's identification numbers were anonymized during the data collection phase.

The distribution of stillbirths by year, risk factors, etiology, number of antenatal care visits, maternal demographic characteristics, comorbidities, laboratory parameters, initial symptoms at admission, mode of delivery, and delivery time was evaluated at our obstetric center. Prenatal ultrasonographic findings, postnatal anthropometric measurements, and fetal sex were assessed. Placental pathology and fetal autopsy reports were reviewed. Maternal complications after delivery were also examined. Approval for the study was obtained from the Ethics Committee of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval number: 2023/209; date: October 11, 2023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1: The number of infants born and the profile of stillbirth rate

Years	Number of infants	Stillbirths	Stillbirth rate/1000 births
2018	4394	8	1.82
2019	5471	13	2.37
2020	4666	16	3.42
2021	4717	27	5.72
2022	4328	23	5.31
2023*	3458	22	6.36
Total	27034	109	4.03

*: Between January 2023 and October 2023.

Statistical Analysis

The data were statistically analyzed using the Statistical Package for the Social Sciences Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistical methods, including the mean, standard deviation, median, frequency, percentage, minimum, and maximum, were used to evaluate the study data.

RESULTS

Between February 2018 and October 2023, 27,034 births occurred at our clinic, including 109 stillbirths. The stillbirth rate at our clinic was 4.03 per 1000 births. Stillbirth rates by year are presented in Table 1.

Of the women who experienced stillbirth, 97 (89%) were Turkish and 12 (11%) were refugees. Seven (6.4%) women were younger than 20 years, and 20 (18.4%) were older than 35 years. Fifty-one (46.8%) women had a body mass index (BMI) of ≥30. The number of nulliparous women was 27 (24.8%). Six (5.5%) women had gestational diabetes mellitus (GDM), and 9 (8.3%) had severe coronavirus disease (COVID-19) (Table 2).

The most common blood group among the women was O, observed in 44 (40.4%), and 99 (90.8%) were Rh-positive. The platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, international normalized ratio (INR), D-dimer, and fibrinogen values were 231 (37–549), 11 (6–526), 21 (9–328), 0.56 (0.33–3.06), 0.99 (0.78–5.69), 2.92 (0.27–35.2), and 450 (41–1200), respectively (Table 3).

The number of fetuses with vertex presentation was 87 (79.8%). Oligohydramnios was observed in 15 (13.8%) cases. The time from hospital admission to delivery was 14.6±14.42 hours. Among the women who experienced stillbirth, 84 (77.1%)

Table 2: Maternal demographic and clinical characteristics

	n=109
Ethnicity	
Turk	97 (89)
Refugee	12 (11)
Maternal Age (years)	
20 or less	7 (6.4)
21–34	82 (75.2)
35 or more	20 (18.4)
Body mass index (kg/m^2)	
18–24	11 (10.1)
25–29	47 (43.1)
30 or more	51 (46.8)
Gestational age (weeks)	
20–27	28 (25.7)
28–36	45 (41.3)
37 or more	36 (33)
Gravida	2.82±1.79 2 (1–10)
Parity	27 (24.8)
Nulliparous	82 (75.2)
Multiparous	0.34±0.748
Abortions	0 (0–4)
Maternal chronic diseases	
Gestational diabetes mellitus	6 (5.5)
Migraine	2 (1.8)
Thyroid disorders	2 (1.8)
Panic attack	1 (0.9)
Asthma	1 (0.9)
Mitral valve regurgitation	1 (0.9)
Hypertensive disease in pregnancy	1 (0.9)
Allergic rhinitis	1 (0.9)
Epilepsy	1 (0.9)
Carrier of glutaric acidemia type 1	1 (0.9)
Antenatal care visits	
0	45 (41.3)
1–3	39 (35.8)
4 or more	25 (22.9)
Maternal anemia	28 (25.7)
Uterine anomalies	2 (1.8)
Assisted reproductive technology	2 (1.8)
SARS-CoV-2 RT-PCR test positivity	9 (8.3)
Initial symptoms of admitted	
Decreased fetal movement	49 (45)
Labor pain	25 (22.9)
Routine antenatal care	24 (22)
Hemorrhage	10 (9.2)
Premature rupture of membranes	1 (0.9)

Values are presented mean±SD, median (minimum–maximum) and n (%), SARS-CoV-2 RT-PCR: Severe acute respiratory syndrome coronavirus 2 Reverse transcription polymerase chain reaction.

Table 3: Maternal hematological parameters and biochemical tests values

	n=109 (%)
Blood type	
A	34 (31.2)
B	23 (21.1)
AB	8 (7.3)
0	44 (40.4)
Rhesus	
Positive	99 (90.8)
Negative	10 (9.2)
White blood cells ($10^3/\mu$L)	12.52±4.71
Neutrophil ($10^3/\mu$L)	9.79±4.45
Lymphocyte ($10^3/\mu$L)	1.95±0.61
Platelet (f)	232.43±81.60
Prenatal hemoglobin (g/dl)	11.75±1.46
Postnatal hemoglobin (g/dl)	10.52±1.72
Subtraction of hemoglobin (g/dl)	1.22±1.04
Alanine aminotransferase (u/l)	23.95±56.03
Aspartate aminotransferase (u/l)	32.32±42.78
Creatinine (mg/dl)	0.61±0.28
Blood urea nitrogen (mg/dl)	14.9±8.35
Blood uric acid (mg/dl)	4.68±1.8
Lactate dehydrogenase (u/l)	329±182.79
C-reactive protein (mg/dl)	2.4±3.03
International normalized ratio	1.04±0.46
D-dimer (mg/L)	6.02±8.89
Fibrinogen (mg/dl)	451.06±172.4
Hepatitis B positivity	1 (0.9)
Hepatitis C positivity	0 (0)
HIV positivity	0 (0)
Urine protein dipstick test	
Negative	86 (78.9)
1+	13 (11.9)
2+	6 (5.6)
3+	4 (3.7)

Values are presented mean±SD and n (%). SD: Standard deviation.

underwent spontaneous vaginal delivery, and 25 (22.9%) underwent cesarean delivery. Dinoprostone was used for labor induction in 25 (29.8%) women. Disseminated intravascular coagulation (DIC) developed in 5 (4.6%) women, and postpartum uterine atony developed in 2 (1.8%). Placental examinations were performed in 70 (64.2%) cases, and fetal autopsies were performed in 7 (6.4%) cases (Table 4).

Table 4: Evaluation of perinatal outcomes

	n=109
Fetal presentation	
Vertex	87 (79.8)
Breech	21 (19.3)
Transverse	1 (0.9)
Amniotic fluid	
Normal	92 (84.4)
Oligohydramnios	15 (13.8)
Polyhydramnios	2 (1.8)
Ultrasound evaluation of the placenta	
Normal	101 (92.7)
Abruption	7 (6.4)
Lacunae	1 (0.9)
Macrosomia (>95th percentile)	9 (8.3)
Time from hospital admission to delivery (h)	14.6±14.42
Type of delivery	
Spontaneous vaginal delivery	84 (77.1)
Cesarean delivery	25 (22.9)
Induction of labor methods*	
No	16 (19)
Misoprostol	13 (15.5)
Dinoprostone	25 (29.8)
Oxytocin	15 (17.9)
Misoprostol+cervical balloon (Foley's)	8 (9.5)
Dinoprostone+cervical balloon (Foley's)	5 (6)
Oxytocin+cervical balloon (Foley's)	2 (2.4)
Fetal gender	
Male	54 (49.5)
Female	55 (50.5)
Birth weight (g)	1893.53±1073.83
Birth length (cm)	42.29±8.15
Disseminated intravascular coagulation	5 (4.6)
Hemolysis, elevated liver enzyme, low platelet syndrome	1 (0.9)
Uterine atony	2 (1.8)
Postpartum intravenous iron treatment	11 (10.1)
Postpartum blood transfusion	12 (11)
Perineal wound*	
No	50 (59.5)
Episiotomy	11 (13.1)
Perineal tears	23 (27.4)
Rhesus isoimmunisation	8 (7.3)
Length of hospital stay (h)	55.17±28.70
Pathological examination of placenta	70 (64.2)
Fetus autopsy	7 (6.4)
Maternal death	0 (0)

Values are presented mean±SD and n (%). *: In women who had vaginal delivery.

Table 5: Pathological findings of the placentas that were sent for pathological examination (n=70)

	n (%)
Perivillous/intervillous fibrin	52 (74.3)
Calcification	33 (47.1)
Intraparenchymal hemorrhage/hematoma	31 (44.3)
Decidual inflammation	31 (44.3)
Syncytial knot increase	26 (37.1)
Necrotic decidua	23 (32,9)
Hydropic chorionic villi	16 (22.9)
Congestion dilation around vessels within the cord	13 (18.6)
Preplacental bleeding	11 (15.7)
Infarction	9 (12.9)
Fibrotic chorion villi	9 (12.9)
Ischemia in chorion villi	8 (11.4)
Chorion inflammation	5 (7.1)
Villous chorangioma	4 (5.7)
Immature chorionic villi	4 (5.7)
Villitis	3 (4.3)
Necrosis of chorionic villi	3 (4.3)
Retroplacental hematoma	2 (2.9)
Subchorionic cyst	1 (1.4)
Increased coiling index in the umbilical cord	1 (1.4)
Concentric umbilical vessel inflammation	1 (1.4)
Chorioamnionitis (Cytomegalovirus infection)	1 (1.4)
Accumulation of yellow-brown pigment in villi	1 (1.4)

In our study, 288 abnormal pathological findings were identified during the pathological examination of 70 placentas. The most common finding was perivillous/intervillous fibrin accumulation, observed in 52 (74.3%) placentas. This was followed by calcification in 33 (47.1%), intraparenchymal hemorrhage/hematoma in 31 (44.3%), decidual inflammation in 31 (44.3%), increased syncytial knots in 26 (37.1%), and necrotic decidua in 23 (32.9%) placentas (Table 5).

When stillbirths were classified according to their causes using the ReCoDe (relevant condition at death) system, 40 (36.7%) were classified under fetal causes, 20 (18.4%) under placental causes, 18 (16.5%) under amniotic fluid-related causes, and 18 (16.5%) remained unclassified (Table 6).

DISCUSSION

Our study determined that stillbirth rates increased between 2018 and 2023. The stillbirth rate was 1.82 per 1000 births in 2018 and 6.36 per 1000 births in 2023. The stillbirth rate among Syrian refugees living in our country was 2.95 per 1000 births. According to World Health Organization (WHO) data, the stillbirth rate in our country is 4.22 per

Table 6: Classification of stillbirths in our clinic, 2018–2023 using the ReCoDe (relevant condition at death) system

Classification	n=109	Code	Subgroup Classification	n=109
A. Fetus	40 (36.7)	1	Lethal congenital anomaly	6 (5.5)
		2	Infection	10 (9.2)
		3	Non-immune hydrops	3 (2.8)
		4	Isoimmunisation	–
		5	Fetomaternal hemorrhage	–
		6	Twin-twin transfusion	–
		7	Featl growth restriction	21 (19.3)
B. Umbilical cord	2 (1.8)	1	Prolapse	–
		2	Constricting loop or knot	2 (1.8)
		3	Velamentous insertion	
		4	Umblical cord - other	–
C. Placenta	20 (18.4)	1	Placental abruptio	10 (9.2)
		2	Placenta praevia	1 (0.9)
		3	Vasa Praevia	–
		4	Placental insufficiency /infarction	9 (8.3)
		5	Other	
D. Amniotic fluid	18 (16.5)	1	Chorioamnionitis	1 (0.9)
		2	Oligohydramnios	15 (13.8)
		3	Polyhydramnios	2 (1.8)
E. Uterus	2 (1.8)	1	Rupture	–
		2	Anomalies	2 (1.8)
		3	Others	–
F. Mother	9 (8.3)	1	Diabetes	6 (5.5)
		2	Thyroid diseases	2 (1.8)
		3	Essential Hypertension	–
		4	Hypertensive diseases in pregnancy	1 (0.9)
		5	Lupus or antiphospholipid Syndrome	–
		6	Cholestasis	–
		7	Drug abuse	–
		8	Other	–
G. Intrapartum	–	1	Asphyxia	–
		2	Birth Trauma	–
H. Trauma	–	1	External	–
		2	Iatrogenic	–
I. Unclassified	18 (16.5)	1	No relevant condition identified	18 (16.5)
		2	No information available	–

Values are presented n (%).

1000 births. In the Syrian Arab Republic, the rate is 10.7 per 1000 births. In Europe, the WHO region in which our country is located, the stillbirth rate is 3.97 per 1000 births.[6] When we compared the stillbirth rates among Syrian refugees who immigrated to our country because of the civil war in their country, we found that the stillbirth rate decreased by approximately 70%, from 10.7 to 2.95 per 1000 births. Although the stillbirth rate at our clinic is below the national average, it is slightly higher than the European average.

During the COVID-19 outbreak, our clinic was designated as a pandemic obstetric center in our region. During this period, pregnant women with severe COVID-19 infection and poor general condition were admitted to and treated at our obstetric center. Nine pregnant women with severe COVID-19 infection experienced stillbirth. These cases increased the stillbirth rate at our clinic. However, we believe that the quarantine measures implemented during the COVID-19 pandemic may have limited pregnant women's access to antenatal care and consequently increased stillbirth rates. In the study conducted by Kc et al.,[7] the stillbirth rate increased from 14 per 1000 births before the first quarantine to 21 per 1000 births during the quarantine. DeSisto et al.[8] reported that the risk of stillbirth increased in women with severe COVID-19 infection. Severe COVID-19 infection is thought to increase the risk of stillbirth because of placental inflammation and hypoperfusion. We believe that the increasing stillbirth rates at our clinic may be attributed to the adverse effects of severe COVID-19 infection on pregnancy outcomes, difficulties experienced by pregnant women in accessing obstetric care during the pandemic quarantine period, and the lack of early treatment for pregnancy-related complications.

In this study, we found that approximately one-fifth of all stillbirths occurred in mothers of advanced age (>35 years). Dongarwar et al.[9] showed that women of advanced age had a 40%–50% higher risk of stillbirth than women aged 20–29 years. Advanced maternal age increases the risk of stillbirth because of the higher prevalence of comorbidities such as diabetes and hypertension and complications such as preterm birth. Additionally, older mothers are more likely to have fetuses with abnormalities, including congenital anomalies and chromosomal disorders.[10] Approximately half (46.8%) of the women who experienced stillbirth had a BMI >30 kg/m². Akselson et al.[11] determined that the risk of stillbirth was four times higher in women with obesity than in women of normal weight and that maternal disease and tobacco use were more common among women with obesity. Twenty-seven (24.8%) women who experienced stillbirth were nulliparous. Devabhaktuni et al.[12] found that the risk of stillbirth was three times higher in nulliparous women than in multiparous women.

Maternal parity is an indicator of birth weight. Low birth weight has been found to be more common among nulliparous women. Birth weight is one of the indicators of fetal health, and low birth weight has been shown to increase the risk of stillbirth.[13] In our study, the mean weight of stillborn infants was 1893.53±1073.83 g. In nulliparous women, the risk of low birth weight is higher because of adverse intrauterine environmental conditions; accordingly, the rates of stillbirth and perinatal death are also higher. In this study, 45 (41.3%) women who experienced stillbirth did not receive antenatal care during pregnancy. This rate is exceptionally high. The WHO recommends at least eight routine examinations during pregnancy as part of obstetric care. These examinations allow risks to be detected earlier through the assessment of both the fetus and the mother.[14]

Twenty-eight (25.7%) women included in our study were anemic. Fetal tissues, which divide rapidly and have high metabolic activity, have a considerable need for oxygen. Maternal anemia negatively affects oxygen transport to the fetus, thereby restricting organogenesis and tissue growth. Consequently, the risk of stillbirth increases significantly. A systematic review by Young et al.[15] found that mothers with low hemoglobin levels were 1.43 times more likely to experience stillbirth. A unicornuate uterus was detected in 2 (1.8%) women in this study. Congenital uterine anomalies may prevent the establishment of the necessary intrauterine conditions for fetal development. Tellum et al.[16] reported that among 326 women with a unicornuate uterus, live birth rates were lower than those among women without congenital uterine anomalies.

In our study, 2 (1.8%) women became pregnant using assisted reproductive technologies. In the meta-analysis conducted by Wong et al.,[17] the risk of stillbirth was 1.41 times higher among women who conceived using *in vitro* methods. It remains unclear whether this increased risk of stillbirth is attributable to the assisted reproductive technology itself or to the underlying etiology of infertility. In this study, 49 (45%) women were admitted to the hospital with reduced fetal movement. Warland et al.[18] determined that the risk of stillbirth increased by 30%–55% among women who noticed a decrease in fetal movement during the preceding week. Pregnant women who report reduced fetal movement should be carefully evaluated by their obstetricians.

In this study, the women's hemoglobin level was 11.9 (7.7–15.2) g/dL, platelet count was 231 (37–549)×10^9/L, and fibrinogen level was 450 (41–1200) mg/dL at the time of hospital admission. In their study of placental abruption cases resulting in fetal death, Atallah et al.[19] found that the hemoglobin level was 10.6 (9.2–11.5) g/dL, platelet count was 204 (138–242)×10^9/L, and fibrinogen level was 190 (140–290) mg/dL. They found that hemoglobin and platelet levels were not significantly associated with severe maternal complications in cases of fetal death due to placental abruption. They also found that fibrinogen levels <190 mg/dL were predictive of the risk of severe maternal complications, with a sensitivity of 83%, specificity of 83%, positive predictive value of 83%, and negative predictive value of 83%.

Our study detected oligohydramnios in 15 (13.8%) and polyhydramnios in 2 (1.8%) stillbirth cases. Figueroa et al.[20] reported that the risk of stillbirth increased fivefold in pregnant women with oligohydramnios. Amniotic fluid at normal levels provides a physical barrier for the fetus and supports fetal lung maturation. It also helps maintain intrauterine safety by preventing umbilical cord compression. Tasew et al.[21] reported that polyhydramnios increased the risk of stillbirth 13-fold. Increased amniotic fluid distends the uterus, causing preterm birth and fetal malpresentation. When the membranes rupture, cord prolapse may occur. In addition, the risk of congenital anomalies is increased in cases of polyhydramnios. These factors increase the risk of stillbirth.

In this study, 9 (8.3%) stillborn fetuses were macrosomic. Salihu et al.[22] determined that the risk of stillbirth in fetuses weighing between 4500 and 5000 g increased 1.27-fold. In fetuses weighing >5000 g, the risk of stillbirth increased 5.97-fold compared with that in nonmacrosomic fetuses. Maternal diabetes increases insulin resistance and maternal blood glucose levels. As a result, excess glucose is transported to the fetus through the placenta. The fetus stores excess glucose as body fat, resulting in macrosomia. In our study, although the sexes of stillborn infants were similarly distributed, stillbirth was more common among female fetuses. Mondal et al.[23] showed that male fetal sex increased the risk of stillbirth by approximately 10%. Male fetal sex is considered a risk factor for stillbirth.

Eighty-four (77.1%) stillbirths occurred via vaginal delivery. Of the remaining 25 (22.9%) cesarean deliveries, 17 were elective. Dinoprostone vaginal ovules were most commonly used for labor induction. We also used misoprostol, cervical balloons, and oxytocin. Vaginal delivery was successfully achieved in all patients who underwent labor induction. Cervical balloons were used for labor induction in 15 pregnant women. The mean time to fetal delivery was 14.6±14.42 hours. In their study, Gawron et al.[24] used misoprostol, mifepristone, oxytocin, and Foley catheters for the induction of labor in third-trimester stillbirths. They found that the mean time to delivery was 11 hours. Vaginal delivery was achieved in 98% of patients. Pregnant women generally deliver within 24 hours, regardless of the induction agent used.

In our study, pathological examination of the placenta was performed in 70 (64.2%) patients. Among the placentas of stillborn fetuses examined, the most frequently detected histopathological findings were perivillous/intervillous fibrin accumulation, calcification, intraparenchymal hemorrhage/hematoma, decidual inflammation, increased syncytial knots, and necrotic decidua. In the study conducted by Patel et al.,[25] the most frequently detected pathological lesions in the placentas of stillborn fetuses were uteroplacental vascular pathology, calcific changes, and retroplacental clots. Not all of these lesions are placental autopsy findings specific to stillbirth; however, they are more common in the placentas of stillborn fetuses. Pathological findings contribute significantly to determining the cause of stillbirth. There is no clear consensus on whether histopathological lesions occur before or after stillbirth. These lesions may initially develop and cause stillbirth. In addition, fibrin deposits, inflammatory cells, and fragmented erythrocytes that accumulate in the placental parenchyma after intrauterine fetal death may contribute to the development of histopathological lesions.[26]

In this study, stillbirths were classified according to the Relevant Condition at Death (ReCoDe) classification system. We found that fetal risk factors were the most common causes of stillbirth, accounting for 40 (36.7%) cases. Among the fetal risk factors, the leading cause was FGR, followed by infection, lethal congenital anomalies, and nonimmune hydrops. Placental risk factors were the second most common category, accounting for 20 (18.4%) stillbirths. Placental abruption was the most common placental risk factor. Amniotic fluid-related risk factors were the third most common category, accounting for 18 (16.5%) stillbirths. Oligohydramnios was the leading amniotic fluid-related risk factor. Maternal risk factors were the fourth most common category, accounting for 9 (8.3%) stillbirths. In our study, the unexplained/unclassifiable stillbirth rate was 18 (16.5%). In their study classifying stillbirths using the ReCoDe system, Kashif et al.[27] showed that FGR was the leading factor associated with stillbirth, followed by maternal disorders. They reported an unclassifiable stillbirth rate of 18.8%, which was similar to that in our study.

There is no internationally accepted classification system for evaluating the causes of stillbirth. All classification systems have advantages and disadvantages. The most important consideration is the appropriate and accurate use and assessment of whichever stillbirth classification system is selected. The ReCoDe stillbirth classification system has the lowest rate of unexplained stillbirth. Approximately 85% of stillbirths can be classified using the ReCoDe system.[28] Determining the causes of stillbirth is essential for informing families and alleviating their anxiety. Establishing the etiology of stillbirth is also of great importance in identifying risk factors that may affect future planned pregnancies.

The strengths of our study include the presentation of data on stillbirths occurring at a tertiary hospital over approximately six years and the detailed examination of placental pathology reports. However, the study has several limitations, including its retrospective design and the absence of placental examination in approximately one-third of cases. This may have limited our ability to determine the underlying etiologies of stillbirth, as placental pathology plays a crucial role in understanding the mechanisms of fetal death.

CONCLUSION

Stillbirth rates are among the leading indicators of the quality of obstetric care. Stillbirth causes emotional devastation and grief among parents. To reduce stillbirth rates, specific risk factors in women should be identified, and strategies for preventing pregnancy complications should be established during antenatal visits. Pathological examination of the placenta should be performed as part of the evaluation of stillbirths. Pregnant women should be educated about the importance of obstetric care.

Statement

Ethics Committee Approval: The study was approved by Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital Ethics Committee (No: 2023/209, Date: 11.10.2023).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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ORIGINAL ARTICLE

Comparison of maternal serum Sestrin2 (SESN2) protein levels between healthy pregnancies and missed abortion cases at 7–13 weeks of gestation

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ABSTRACT

Objective: This study aimed to compare maternal serum Sestrin2 levels between women diagnosed with missed abortion and those with healthy pregnancies at 7–13 weeks of gestation and to investigate the possible association between Sestrin2 levels and missed abortion.

Material and Methods: This prospective study included 45 pregnant women diagnosed with missed abortion and 45 healthy pregnant women who presented to the obstetrics and gynecology outpatient clinic or emergency department of our hospital between January and June 2023. Maternal blood samples were collected to measure serum Sestrin2 levels. Demographic and clinical data, including age, body mass index (BMI), gravidity, parity, history of abortion, gestational age, chorionic localization, last menstrual period (LMP), uterine artery pulsatility index (PI), and crown–rump length (CRL), were recorded. The groups were compared in terms of these parameters.

Results: The mean age and BMI of the participants were 30.52 years and 24.15 kg/m^2, respectively. The mean maternal serum Sestrin2 level was 787.4±504.6 ng/mL in the missed abortion group and 609.6±449.1 ng/mL in the healthy pregnancy group. The right and left uterine artery PI values were significantly higher in the missed abortion group, indicating increased vascular resistance compared with the healthy pregnancy group. No statistically significant differences were observed between the groups in terms of age, gravidity, parity, history of abortion, chorionic localization, or LMP. Additionally, no significant difference was found in maternal serum Sestrin2 levels between the missed abortion and healthy control groups.

Conclusion: This study found no significant difference in maternal serum Sestrin2 levels between women with missed abortion and those with healthy pregnancies. These findings suggest that maternal serum Sestrin2 may not play a significant role in the pathophysiology of missed abortion. Further large-scale, multidisciplinary, prospective studies are needed to confirm these results and provide more comprehensive insights into the role of Sestrin2 in early pregnancy outcomes.

Keywords: Miscarriage, missed abortion, oxidative stress, pregnancy, Sestrin2.

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INTRODUCTION

Pregnancy loss is defined as an intrauterine pregnancy with no chance of survival before 20 weeks of gestation. It is also known as miscarriage or spontaneous abortion. The most common type is early pregnancy loss, which occurs during the first trimester. The most commonly recognized causes include advanced maternal age, maternal medical conditions, certain medications, and environmental factors.

Missed abortion is one type of early pregnancy loss. It is defined as a condition in which a nonviable fetus remains in the uterus for weeks despite a closed cervix.[1] Missed abortion differs from other types of pregnancy loss in that typical symptoms, such as bleeding and abdominal cramps, are absent.

Etiological factors may be of maternal or fetal origin. The most common fetal factors are chromosomal abnormalities.[2,3] Maternal factors include maternal age, chronic diseases, infections, radiation exposure, uterine anomalies, surgical procedures, and social or behavioral factors.[2–5]

The incidence of missed abortion varies between 11% and 22% between 5 and 20 weeks of gestation. However, higher rates may be observed during the earlier weeks.[6] Serum beta-human chorionic gonadotropin levels and transvaginal ultrasonography (TVUS) can be used for diagnosis.

SESN2 (Sestrin2) is a stress-responsive, evolutionarily conserved protein found in many vertebrates. It is strongly affected by conditions such as prolonged hypoxia, oxidative stress, and DNA damage.[6]

Under stressful conditions, such as oxidative stress and hypoxia, SESN2 exerts a cytoprotective effect by activating adenosine monophosphate-activated protein kinase (AMPK), inhibiting mammalian target of rapamycin (mTOR), and reducing reactive oxygen species (ROS) levels. Studies in the literature have shown that this molecule plays a cytoprotective role in various diseases, including neurodegenerative, cardiovascular, and metabolic disorders and cancer.[2]

Studies in the literature have shown that oxidative stress plays an active role in many obstetric complications, such as preeclampsia, intrauterine growth restriction, and miscarriage.[7–9] Trophoblast invasion and placental development during pregnancy are highly sensitive to the balance of oxidative stress. The Sestrin2 (SESN2) molecule protects against oxidative damage that may occur at the cellular level. These are critical processes for a healthy pregnancy. Consequently, changes in SESN2 expression or activity may negatively affect these processes and cause pregnancy loss.

Given that oxidative stress is among the causes of early pregnancy loss, our study aimed to evaluate the association between the SESN2 molecule, whose response to oxidative stress has been demonstrated in scientific studies, and missed abortion and to determine whether this molecule may be a predisposing factor.

MATERIAL AND METHODS

Study Design and Participants

Following approval from the Ethics Committee of the University of Health Sciences Ümraniye Training and Research Hospital (approval no.: B.10.1.TKH.4.34.H.GP.0.01/413), this prospective cross-sectional study was conducted in the Department of Obstetrics and Gynecology in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants. Between January 10, 2023, and July 10, 2023, a total of 90 pregnant women were included in the study: 45 healthy pregnant women who presented to our obstetrics outpatient clinic for routine antenatal follow-up and 45 pregnant women diagnosed with missed abortion who presented to the obstetric emergency department. All participants were between 7 and 13 weeks of gestation, aged 18–45 years, had no systemic diseases, and did not use tobacco or alcohol.

Gestational age was determined based on the last menstrual period (LMP). In cases of discrepancy between the LMP and ultrasonographic findings, gestational dating was performed using sonographic measurements.

Inclusion Criteria

Pregnant women aged 18–45 years with a singleton pregnancy between 7 and 13 weeks of gestation, no systemic diseases, and no history of smoking or alcohol consumption were included in the study.

Transvaginal ultrasonography (TVUSG) was performed, and serum beta-hCG levels were measured. These findings were used for diagnosis.

Normally, the gestational sac can be visualized using transvaginal ultrasonography when the serum beta-hCG level reaches approximately 1500–2000 mIU/mL.[10] In a normally progressing pregnancy, serum beta-hCG levels should increase by at least 52–66% every 48 hours.[11] Conversely, a decrease of >50% in beta-hCG levels within 48 hours is associated with a completed miscarriage.[12] In most pregnancies at 5–6 weeks of gestation, a 1–2 mm embryo can be visualized adjacent to the yolk sac. Fetal cardiac activity (FCA) is generally detected at approximately 6–6.5 weeks of gestation, when the crown–rump length (CRL) measures 1–5 mm and the mean sac diameter (MSD) ranges from 13 to 18 mm.[13] Pregnancy loss should be suspected if the yolk sac diameter is ≥6 mm before 10 weeks of gestation.[14] Moreover, if no fetal cardiac activity is observed when the CRL is ≥7 mm on ultrasonography, the embryo is considered nonviable. M-mode ultrasonography was used to assess the presence and rate of fetal cardiac activity.[15] Patients who met these diagnostic criteria for abortion were included in the study.

Exclusion Criteria

Pregnant women aged <18 or >45 years, those who were not between 7 and 13 weeks of gestation, those with multiple pregnancies, including pregnancies that began as multiple gestations but continued as singletons, and those with chronic hypertension, gestational diabetes, pregestational diabetes, hypothyroidism or hyperthyroidism, known vascular disease, thrombophilia, autoimmune disease, uterine anomalies, or a history of recurrent pregnancy loss were excluded from the study.

Data Collection

At the beginning of the study, detailed medical histories were obtained from both healthy pregnant women and those diagnosed with missed abortion between 7 and 13 weeks of gestation, and informed consent forms were signed by all participants. Following

ultrasonographic assessment using a Mindray ultrasound device available at our hospital, crown–rump length (CRL) was measured. Subsequently, peripheral venous blood samples were collected for the analysis of Sestrin2 levels.

Blood samples were left at room temperature for 1 hour and then centrifuged at 2000 rpm for 20 minutes. After centrifugation, the serum supernatant was carefully transferred into Eppendorf tubes using an automatic pipette. The tubes were labeled and stored at -80°C in the Biochemistry Laboratory of the University of Health Sciences Ümraniye Training and Research Hospital.

On the day of analysis, the serum samples were transported via a cold chain to an external laboratory, Farmasina Medical and Chemical Products Industry and Trade Limited Company, located in Ataşehir, Istanbul, Türkiye. Serum Sestrin2 levels were measured using an enzyme-linked immunosorbent assay method (Human SESN2 ELISA Kit, Sunred) with a Diagnostic Automation, Inc. DAR800 device and KCjunior software.

Statistical Analysis and Data Processing

SPSS version 25.0 statistical software was used to analyze the data. The Kolmogorov–Smirnov test was used to assess whether the data were normally distributed. Descriptive statistical methods, including the mean, standard deviation, median, interquartile range (IQR), frequency, and percentage, were used to evaluate the study data.

For comparisons between two groups with parametric distributions, the independent-samples t-test was used, whereas one-way analysis of variance was applied for comparisons among more than two groups. For nonparametric distributions, the Mann–Whitney U test was used to compare two groups, and the Kruskal–Wallis test was used for comparisons among more than two groups. Spearman and Pearson correlation analyses were conducted to assess relationships between variables. The chi-square test was used to evaluate categorical data. A p-value of <0.05 was considered statistically significant for all analyses.

Power analysis was performed using G*Power software, version 3.1.9, to determine the sample size. The power of the study was defined as 1−β, with β representing the probability of a type II error, and was set at 80%. Based on the effect size coefficients defined by Cohen and assuming a medium effect size (d=0.30), it was determined that a minimum of 45 participants would be required in each group.

A post hoc power analysis was performed using G*Power version 3.1. Based on the observed mean and standard deviation of the uterine artery PI values, the effect size (Cohen's d) was calculated as 1.49, corresponding to a statistical power of 99.8% (α=0.05, two-tailed) with 45 participants per group.

RESULTS

The study population consisted of a total of 90 participants, including 45 individuals in the missed abortion group and 45 in the healthy pregnancy group.

Table 1 presents the demographic and obstetric characteristics of all 90 participants. Upon detailed evaluation, the mean age was 28.83±4.77 years (range, 19–40 years), and the mean BMI was 24.67±3.50 kg/m².

Table 1: Descriptive statistics of participants' demographic and obstetric characteristics

Variable	Mean±SD	Median (Min–Max)
Age	28.83±4.77	29 (19–40)
Height (cm)	164.01±5.66	163 (154–176)
Weight (kg)	66.21±8.75	65 (48–87)
BMI (kg/m²)	24.67±3.50	24.07 (18.71–36.21)
Gravida	2.33±1.09	2 (1–5)
Parity	1.12±1.00	1 (0–4)
LMP (days)	70.64±10.65	69.5 (49–91)
CRL (mm)	25.86±14.10	19 (10–64)
Right uterine PI	2.28±0.51	2.35 (1.52–3.32)
Left uterine PI	2.34±0.52	2.33 (1.52–3.25)
Sestrin2 Level	6.09±5.79	3.58 (1.86–28.08)
	n	**%**
Parity		
Nulliparous	22	24.4
Multiparous	68	75.6
History of abortion		
Yes	19	21.1
No	71	78.9
Chorionic location		
Anterior	48	53.3
Posterior	42	46.7

SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index; LMP: Last menstrual period; CRL: Crown–rump length; PI: Pulsatility Index.

Regarding the obstetric parameters, the mean right uterine artery PI was 2.28±0.51, the mean left uterine artery PI was 2.34±0.52, and the mean Sestrin2 level was 6.09±5.79. Among all participants, 24.4% (n=22) were nulliparous, and 75.6% (n=68) were multiparous. A history of abortion was present in 21.1% (n=19) of the participants. Chorionic location was anterior in 53.3% (n=48) and posterior in 46.7% (n=42) of the cases.

As shown in Table 2, there was no statistically significant difference between the two groups in terms of age or body mass index (BMI) (p>0.05). Similarly, no significant differences were found between the groups in terms of gravidity, parity, last menstrual period (LMP), or crown–rump length (CRL) (p>0.05).

However, the right and left uterine artery PI values were significantly higher in the missed abortion group than in the healthy pregnancy group (p=0.001 for both; p<0.01). The mean right uterine artery PI was 2.58±0.45 in the missed abortion group and 1.98±0.35 in the healthy pregnancy group. Similarly, the mean left uterine artery PI was 2.66±0.45 in the missed abortion group and 2.02±0.36 in the healthy pregnancy group.

Table 2: Intergroup comparison of demographic and obstetric variables

Variable	Missed abortion (n=45)	Healthy Pregnancy (n=45)	p
Age (years)	29.02±5.01	28.64±4.57	0.710*
BMI (kg/m²)	24.63±3.25	24.71±3.77	0.913*
Gravida	2.31±1.24	2.16±0.93	0.472**
Parity	1.13±0.99	0.98±0.78	0.544**
LMP (days)	71.58±10.64	69.71±10.71	0.409*
CRL (mm)	24.22±12.12	27.49±15.81	0.500**
Right uterine PI	2.58±0.45	1.98±0.35	0.001*
Left uterine PI	2.66±0.45	2.02±0.36	0.001**
Categorical variable	**Missed abortion**	**Healthy pregnancy**	**p**
Nulliparous	11 (47.8%)	12 (52.2%)	0.809***
Multiparous	34 (50.7%)	33 (49.3%)	
Abortion history present	9 (47.4%)	10 (52.6%)	0.796***
Abortion history absent	36 (50.7%)	35 (49.3%)	
Chorionic location - anterior	22 (45.8%)	26 (54.2%)	0.398***
Chorionic location - posterior	23 (54.8%)	19 (45.2%)	
Sestrin2 (ng/mL), Median (Min–Max)	3.5 (1.9–25.1)	4.3(1.9–28.1)	0.451**

*: Independent t test; **: Mann-Whitney U test; ***: Chi Square. Data are presented as median (min–max) due to non-normal distribution (Shapiro–Wilk p<0.05). Min: Minimum; Max: Maximum; BMI: Body mass index; LMP: Last menstrual period; CRL: Crown–rump length; PI: Pulsatility Index

Table 3: Diagnostic screening tests and ROC curve results for right uterine and left uterine PI according to missed abortion status

	Diagnostic scan					ROC curve		p
	Cut-off	Sensitivite	Spesifisite	Positive predictive value	Negative predictive value	Area	95% CI	
Right uterin PI	≥2.34	77.78	77.78	77.8	77.8	0.846	0.755–0.914	<0.0001
Left uterin PI	≥2.54	73.33	88.89	86.8	76.9	0.859	0.769–0.923	<0.0001

ROC: Receiver operating characteristic; CI: Confidence interval; PI: Pulsatility Index.

There were no statistically significant differences between the groups in terms of parity distribution (nulliparous/multiparous) (p=0.809), previous abortion history (p=0.796), or chorionic location (p=0.398).

There was no statistically significant difference in Sestrin2 levels between the missed abortion and healthy pregnancy groups (p>0.05).

Given the significant differences in uterine artery PI values between the groups, receiver operating characteristic (ROC) curve analyses were performed to assess their diagnostic potential for predicting missed abortion (Table 3).

In the ROC analysis, the cutoff value for the left uterine artery PI in cases of missed abortion was determined to be ≥2.54. At this cutoff value, the sensitivity was 73.33%, specificity was 88.89%, positive predictive value was 86.8%, and negative predictive value was 76.9%. The cutoff value for the right uterine artery PI in cases of missed abortion was determined to be ≥2.34. At this cutoff value, the sensitivity was 77.78%, specificity was 77.78%, positive predictive value was 77.8%, and negative predictive value was 77.8% (Fig. 1, 2).

DISCUSSION

In this study, we investigated the relationship between serum Sestrin2 (SESN2) levels and missed abortion by comparing patients who presented to the Department of Obstetrics and Gynecology at our hospital with missed abortion with those with healthy pregnancies.

Missed abortion is a type of early pregnancy loss characterized by the embryo or fetus remaining in the uterus for days or weeks without

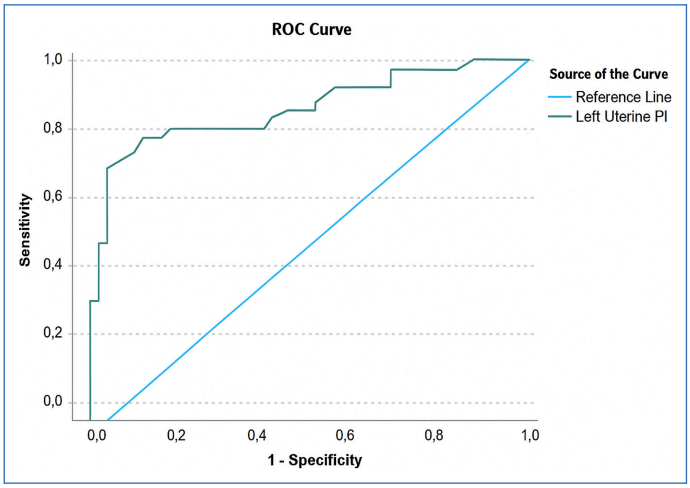

Figure 1: Receiver Operating Characteristic (ROC) curve demonstrating the diagnostic performance of the Left Uterine Pulsatility Index (PI).

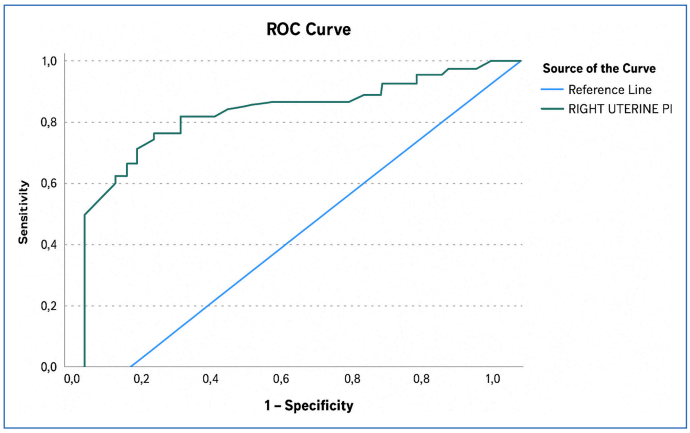

Figure 2: Receiver Operating Characteristic (ROC) curve demonstrating the diagnostic performance of the Right Uterine Pulsatility Index (PI).

causing any symptoms while the cervical canal remains closed. The most common causes include chromosomal abnormalities and maternal medical conditions. Missed abortus tanısı serum beta-hCG düzeyleri ve transvajinal ultrasonografi ile konulur. İnsidansı ise gebeliğin 5. ile 20. haftaları arasında %11 ile %22 arasında değişmektedir.

Sestrin proteins are a family of proteins induced by stressful conditions caused by factors such as hypoxia, oxidative stress, and genotoxic agents. SESN2 is well known to play a cytoprotective role by activating AMPK, inhibiting mammalian target of rapamycin (mTOR), and preventing the accumulation of reactive oxygen species (ROS).[16] Recently, SESN2 has been investigated in many gynecological and obstetric studies on preeclampsia, intrauterine growth restriction (IUGR), uterine fibroids, and polycystic ovary syndrome.[17–20]

Although the association between missed abortion and oxidative stress is known and the cytoprotective functions of SESN2 under oxidative stress have been demonstrated, no significant difference was found between the two groups in terms of serum SESN2 levels. These data suggest that the SESN2 molecule does not play an active role in the pathogenesis of missed abortion.

In a retrospective study conducted in 2020, inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were examined in 80 pregnant women between 6 and 14 weeks of gestation, including 40 diagnosed with missed abortion and 40 with healthy pregnancies. When the data were compared, NLR and PLR levels were found to be significantly higher in pregnancies diagnosed with missed abortion, and this finding was associated with systemic inflammation.[21] Based on these data, we hypothesized that SESN2, an anti-inflammatory and antioxidant marker, might also play a role in the pathogenesis of missed abortion. However, our study found no statistically significant difference in SESN2 levels between the missed abortion and healthy pregnancy groups.

Oxidative stress can negatively affect trophoblast invasion and placentation, leading to adverse outcomes such as miscarriage, preeclampsia, and intrauterine growth restriction (IUGR).[7,22] SESN2 is known to reduce oxidative stress by activating AMP-activated protein kinase (AMPK) and inhibiting the mechanistic target of rapamycin (mTOR) signaling pathways, thereby reducing reactive oxygen species (ROS) levels.[23,24] Based on this information, we hypothesized that SESN2 levels would be altered in pregnancies that ended in miscarriage; however, the data obtained from the study did not support our hypothesis.

In a study conducted in 2018, SESN2 levels were compared among patients with severe preeclampsia, healthy pregnant women, and patients with mild preeclampsia. SESN2 levels were found to be significantly higher in the severe preeclampsia group. This finding suggests that SESN2 may play a role in the pathogenesis of severe preeclampsia.[20] Li et al.[25] reported a retrospective study that analyzed SESN2 and placental growth factor (PIGF) levels in 134 pregnant women and found that both markers were correlated with the severity of preeclampsia. This study supported the potential utility of these two biomarkers in predicting disease progression. However, such an association between SESN2 levels and missed abortion was not observed in our study.

The relationship between preeclampsia and SESN2 is based on the concepts of abnormal placentation and placental ischemia. Ischemia–reperfusion injury caused by impaired placentation leads to placental oxidative stress and disruption of the syncytiotrophoblast structure, resulting in systemic inflammatory responses and elevated serum markers, as demonstrated in the aforementioned studies.[26] In a study conducted in 2001 involving 56 women divided into four groups—healthy pregnant women, women with preeclampsia, women who had miscarried, and nonpregnant women—the levels of selectins, a family of adhesion molecules associated with leukocyte transport and endothelial responses, were analyzed.

The study found that selectin levels were significantly elevated in both the preeclampsia and miscarriage groups, indicating increased endothelial activation in both conditions.[27] Intrauterine growth restriction (IUGR) is another serious complication of pregnancy. Its pathophysiology is complex and not yet fully understood. Fetuses with IUGR are at high risk of hypoxia, and early detection of this condition is critical for optimal perinatal management.[27] In a prospective study conducted by Agaoğlu et al.[18] in 2023, serum SESN2 levels were evaluated in 44 pregnant women diagnosed with IUGR and 43

low-risk controls at similar gestational ages. The study demonstrated significantly higher SESN2 levels in the IUGR group. These findings suggest the potential use of SESN2 as a novel biomarker for IUGR. In contrast to this study, our study found no significant difference in serum SESN2 levels between the missed abortion and healthy pregnancy groups.

Previous studies have reported altered oxidative stress markers in cases of spontaneous abortion and recurrent pregnancy loss.[27] For instance, elevated malondialdehyde (MDA) levels and reduced total antioxidant capacity (TAC) have been consistently reported.[28] Despite these findings, evidence specifically addressing SESN2 in early pregnancy complications remains limited. To our knowledge, only a few experimental studies have investigated the role of SESN2 in pregnancy-related oxidative damage, primarily using animal models or placental tissue analyses.[29] The absence of a significant difference in SESN2 levels in our study may indicate that maternal circulating SESN2 does not accurately reflect local oxidative stress at the maternal–fetal interface or that compensatory antioxidant mechanisms may obscure such changes in the systemic circulation.[30]

In our study, venous blood samples were obtained from patients diagnosed with missed abortion, and serum SESN2 levels were analyzed. No significant difference in SESN2 levels was observed between patients with missed abortion and healthy pregnant controls. However, future multicenter studies with larger sample sizes and longitudinal follow-up, including blood samples obtained before and after diagnosis, may provide further insight into whether dynamic changes in SESN2 are relevant to early pregnancy loss.

The receiver operating characteristic (ROC) analyses demonstrated that both right and left uterine artery PI values had good diagnostic accuracy, with area under the curve (AUC) values >0.84, supporting their potential use as predictive markers of early pregnancy loss.

In a study by Li et al.,[30] uterine artery PI values were higher in pregnancies complicated by preeclampsia, and inhibin A and activin A levels were also elevated compared with those in the control group. In contrast, placental growth factor (PlGF) levels were lower in pregnancies complicated by preeclampsia than in the control group.

Although no significant difference was observed in Sestrin2 levels between the groups, the small effect size and low statistical power indicate that this nonsignificant finding should be interpreted with caution and that larger studies are warranted.

CONCLUSION

Many studies have shown that various molecules play a role in pregnancy loss. The involvement of Sestrin2 in oxidative stress pathways, its inducibility by stress, and its potential contribution to the etiopathogenesis of pregnancy loss led us to conduct this study. In our investigation, maternal serum Sestrin2 levels remained stable, with no significant difference observed between the missed abortion and healthy pregnancy control groups. In conclusion, further studies with larger sample sizes are needed to better understand the role of Sestrin2 in pregnancy loss.

Statement

Ethics Committee Approval: The study was approved by University of Health Sciences Ümraniye Training and Research Hospital Ethics Committee (No: B.10.1.TKH.4.34.H.GP.0.01/413, Date: 22.12.2022).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Evaluation of perinatal outcome of monochorionic twin pregnancies in a single perinatology clinic

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ABSTRACT

Objective: Monochorionic twin pregnancies carry high perinatal risks due to shared placental circulation, predisposing them to complications such as twin-to-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), and selective fetal growth restriction (sFGR). Early recognition and timely intervention are essential to improve neonatal survival. This study evaluates the perinatal outcomes of monochorionic twin pregnancies managed at a single perinatology center.

Material and Methods: A retrospective cross-sectional study was conducted using medical records from January 2020 to December 2023. Forty-six monochorionic twin pregnancies were analyzed for maternal factors, obstetric complications, and neonatal outcomes. Statistical analyses included Pearson correlation, t-tests, and chi-square tests.

Results: The mean gestational age at delivery was 32.46±4.48 weeks. The average birth weight of the first twin was 1809.76±797.37 g and that of the second twin was 1683.13±887.06 g. Mean APGAR scores were 7.15±2.74 and 8.41±2.69 for the first twin, and 6.80±3.12 and 8.11±3.14 for the second twin, at one and five minutes, respectively. TTTS occurred in 8.7% and sFGR in 50% of pregnancies. Higher birth weights were significantly correlated with better APGAR scores ($p<0.01$), whereas advanced TTTS and sFGR were associated with lower birth weights and adverse neonatal outcomes.

Conclusion: Monochorionic twin pregnancies are associated with increased risks of prematurity, low birth weight, and neonatal distress, particularly in the presence of TTTS and sFGR. Reporting outcomes with measures of variability highlights the substantial heterogeneity in neonatal status. Routine surveillance and timely interventions remain essential to improving perinatal survival.

Keywords: Monochorionic twins, neonatal morbidity, perinatal outcomes, selective fetal growth restriction, twin anemia-polycythemia sequence, twin-to-twin transfusion syndrome.

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INTRODUCTION

Monochorionic twin pregnancies account for about 1–2% of all pregnancies worldwide, with approximately 20% of all twin pregnancies being monochorionic, representing about 1 in 5 twin pregnancies.[1,2] These pregnancies originate from a single egg, which, upon fertilization, splits to form one or more embryos, resulting in a shared placenta.[3] Monochorionic twins, as opposed to dichorionic twins, share placental circulation, which exposes them to severe hemodynamic imbalances and vascular complications, resulting in fetal morbidity and mortality.[4,5] The perinatal mortality rates of monochorionic twin pregnancies are 3–5 times higher compared to those of dichorionic pregnancies, with more complex cases experiencing fetal loss rates of up to 30%.[6] There has been a continuous rise in the frequency of twin pregnancies during the last few decades due to increasing maternal age at childbirth as well as infertility treatments.[7] Although twin pregnancies account for 1–3% of all registered live births, a significant proportion of approximately 20–30% are monochorionic, which further exacerbates the clinical complications posed by this more complicated type of placental structure.[8] Even with improvements in fetal medicine, monochorionic twin pregnancies continue to pose a high risk in low- and middle-income regions (LMICs), where perinatal mortality rates hover around 50% as opposed to 10–15% in high-income countries (HICs).[9] The substantial difference in the outcomes of monochorionic pregnancies strongly suggests that the availability of specialized maternal-fetal medicine, early screening, and fetal therapy are necessary interventions to enhance neonatal survival and improve pregnancy outcomes.[10]

Discrepancy in blood supply is one of the major causes of selective fetal growth restriction (sFGR), which occurs in 10–15% of monochorionic twin pregnancies.[11] In practice, these discrepancies in blood and nutritional supply also have a negative impact on fetal weight, where the significant weight difference between the twins is more than 20%, often causing detrimental health issues for the fetus by increasing the chances of perinatal morbidity, intrauterine death, and premature labor.[12,13]

Monochorionic twin pregnancies present a significant risk because of the presence of anastomosing placental vessels, which can cause unequal distribution of blood between the fetuses, resulting in twin-to-twin transfusion syndrome (TTTS), which affects 9–15% of monochorionic diamniotic (MCDA) twin pregnancies worldwide.[14,15] TTTS arises from unbalanced intertwin blood flow, causing polyhydramnios and volume overload in the recipient twin and oligohydramnios with hypovolemia in the donor twin, often leading to severe outcomes if untreated.[16] TTTS has a mortality rate of 80–100%; however, with the advent and proper optimization of fetoscopic laser coagulation, overall mortality rates have drastically changed, leading to improved fetal survival.[17] TAPS causes extreme fetal anemia in one twin and excessive polycythemia in the other, resulting in cardiac dysfunction, hydrops fetalis, and stillbirth.[18] Single fetal demise (SFD) occurs in 3–6% of pregnancies involving monochorionic twins. Considering the shared circulation, the surviving twin has a 20–30% chance of suffering from neurological impairment.[6,19] This greatly raises the risk of neonatal illnesses such as respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and neonatal sepsis.[20]

In addition to placental factors, other maternal conditions such as diabetes mellitus, hypertension, and obesity can worsen existing issues in monochorionic twin pregnancies.[21] Monochorionic pregnancies have an increased prevalence of hypertension, including preeclampsia, which has been associated with placental insufficiency, fetal distress, and higher perinatal mortality.[22]

Pregnancies with monochorionic twins have significantly worse outcomes without medical intervention. Research suggests that unmanaged monochorionic twins, particularly in low-resource settings, face perinatal mortality rates above 30–50%.[23,24]

This study will determine the perinatal outcomes of monochorionic twin pregnancies managed at a single perinatology center.

MATERIAL AND METHODS

This study is a retrospective cohort study evaluating the perinatal outcomes of monochorionic twin pregnancies. This design was selected to determine maternal, obstetric, and neonatal characteristics at a single point in time using existing medical records. This methodology permits the examination of multiple pregnancy-related complications and their corresponding neonatal outcomes within a defined study timeframe.

The study was conducted in a tertiary care hospital's perinatology unit, which specializes in high-risk obstetric care and fetal medicine. The participants' information was collected retrospectively from electronic medical records and hospital obstetric databases from January 2020 to December 2023. The study population included all patients with monochorionic twin pregnancies who attended the center during the study period.

The participants were pregnant women with monochorionic twin pregnancies, which were verified by first-trimester ultrasound and confirmation of a single placenta. The study was retrospective and based on available hospital records, and 46 monochorionic twin pregnancies were included. No formal sample size calculation was performed for this descriptive retrospective study; all eligible twin cases during the specified period were analyzed, thus forming the sample size. All participants meeting the criteria were included, with no selection bias. The eligibility criteria were as follows:

- Confirmed monochorionic twin gestation diagnosed via first-trimester ultrasonography.
- Singleton pregnancies and dichorionic twin pregnancies were excluded to maintain the homogeneity of the study population.
- Only pregnancies with completely available medical records from prenatal care to delivery were included.
- Most major congenital life-threatening anomalies were excluded.
- Twin-to-twin transfusion syndrome (TTTS) was staged according to the Quintero classification, based on ultrasound findings of amniotic fluid discordance, bladder filling, Doppler abnormalities, hydrops, and cardiac dysfunction. Selective fetal growth restriction (sFGR) was defined and staged using the Delphi consensus criteria, incorporating estimated fetal weight discordance, umbilical artery Doppler indices, and fetal growth centiles. Twin anemia–polycythemia sequence (TAPS) was staged according to middle cerebral artery peak systolic velocity

(MCA-PSV) Doppler criteria, defined as >1.5 MoM in the anemic twin and <1.0 MoM in the polycythemic twin, with confirmation by intertwin hemoglobin differences at birth when available.

The analysis focused on various maternal, obstetric, and neonatal factors.

- Maternal Factors: Maternal age, number of previous pregnancies, number of previous births, abortion history, method of conception (spontaneous or IVF [*in vitro* fertilization]), history of labor, presence of gestational diabetes mellitus, and preeclampsia.
- Obstetric Complications and Treatments: Diagnosis of twin-to-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), selective intrauterine growth restriction (sFGR), discordant anomaly, laser ablation, and radiofrequency ablation.
- Neonatal Outcomes: Week of birth, birth weight of each twin, and APGAR scores at one and five minutes.

All data were collected retrospectively from electronic medical records, hospital databases, and obstetric and neonatal records. These records captured most maternal characteristics, complications during pregnancy, and delivery outcomes related to newborn health indicators. Some of the measurements of interest included:

- Gestational age at delivery (weeks): Fetal growth was confirmed from the last ultrasound scan prior to delivery, which corresponded with the clinical dating of pregnancy.
- Birth weight (grams): Neonatal nurses measured weights directly from neonatal birth records using standardized neonatal scales.
- APGAR scores at one and 5 minutes: These were recorded in the case report form by the attending pediatricians in the neonatal department or trained staff from the delivery area.
- Ultrasound and Doppler examinations: Retrospective analysis of existing prenatal ultrasound reports and Doppler studies was performed by specialists. All measurements were obtained under institutional regulations, ensuring the accuracy of these evaluations. Periodic quality measures were followed.

To minimize selection bias, all eligible monochorionic twin pregnancies within the study period were included consecutively, ensuring comprehensive coverage of the sample. Information bias was minimized through standardized hospital records and validated measurement devices.

This study was approved by the Scientific Research Ethics Committee of Eskişehir City Hospital (approval code: ESH/BAEK 2025/77) and was conducted in accordance with the Declaration of Helsinki and institutional research policies. As this was a retrospective study based on previously collected data, the requirement for informed consent was waived by the ethics committee. All patient identifiers were removed to ensure confidentiality, and the data were securely stored and accessed only by authorized researchers.

Statistical Analysis

The study data were analyzed using SPSS software Version 26. Maternal, obstetric, and neonatal attributes were described using descriptive statistics. Continuous variables were recorded as mean and standard deviation, whereas categorical variables were recorded as percentages.

Table 1: Descriptive statistics of maternal and neonatal characteristics

Variables	Mean	SD
The mother's age	29.72	4.843
The total number of times the mother has been pregnant	2.33	1.461
The number of live births the mother has had	1.13	1.439
The number of abortions the mother has had	0.26	0.535
Week of birth	32.46	4.476
1st baby 1 min Apgar	7.15	2.740
1st baby 5 min Apgar	8.41	2.688
2nd baby 1 min Apgar	6.80	3.117
2nd baby 5 min Apgar	8.11	3.143
1st baby's birth weight	1809.76	797.372
2nd baby's birth weight	1683.13	887.059

SD: Standard deviation.

Comparisons between variables were performed using the independent t-test for continuous, normally distributed variables, the Mann–Whitney U test for continuous, non-normally distributed variables, the chi-square (χ^2) test, and Fisher's exact test for categorical data. Correlations concerning gestational age at birth, birth weight discordance, and certain neonatal outcomes were assessed using Pearson's or Spearman's correlation coefficients according to the normality status.

RESULTS

The data provide insights into various medical conditions and outcomes associated with pregnancies. Most pregnancies (93.5%) were conceived naturally, while only 6.5% were achieved through IVF. Preeclampsia, a serious pregnancy complication, affected 15.2% of mothers. Most pregnancies (97.8%) did not end in termination, while 2.2% did. Selective fetal growth restriction (sFGR) was equally present and absent at 50.0%. Stage 1 FGR was observed in 37.0% of cases, while Stages 2 and 3 were less common at 8.7% and 4.3%, respectively. Gestational diabetes mellitus was diagnosed in 17.4% of mothers. Delivery methods indicated that 95.7% of births occurred through cesarean section (CS), with only 4.3% delivered spontaneously.

Table 1 contains descriptive details of 46 monochorionic twin pregnancies, focusing on maternal characteristics, obstetric history, and neonatal outcomes. Maternal age ranged from 19 to 39 years, with a mean age of 29.72 years (SD: 4.84). Mothers had been pregnant between 1 and 8 times, with a mean of 2.33 pregnancies, an average of 1.13 live births, and abortion or miscarriage numbers ranging from 0 to 2, with a mean of 0.26 among all participants. The average gestational age at delivery was 32.46 weeks (SD: 4.48), corresponding to the increased risk of prematurity in monochorionic twins. APGAR scores at one and five minutes after birth showed

Table 2: Descriptive statistics of monochorionic pregnancy complication and treatment

Variables	Category	Frequency	Frequency %	Variables	Category	Frequency	Frequency %
Whether the pregnancy was achieved through IVF	No	43	93.5	TTTS	No	42	91.3
	Yes	3	6.5		Yes	4	8.7
Mother suffered from preeclampsia	No	39	84.8	TTTS 1	No	46	100.0
	Yes	7	15.2		Yes	0	0.0
Termination of pregnancy	No	45	97.8	TTTS 2	No	45	97.8
	Yes	1	2.2		Yes	1	2.2
Selective fetal growth restriction	No	23	50.0	TTTS 3	No	43	93.5
	Yes	23	50.0		Yes	3	6.5
Stage 1 fetal growth restriction	No	29	63.0	TAPS	No	40	87.0
	Yes	17	37.0		Yes	6	13.0
Stage 2 fetal growth restriction	No	42	91.3	TAPS stage	No	40	87.0
	Yes	4	8.7		Yes	4	8.7
Stage 3 fetal growth restriction	No	44	95.7		2	1	2.2
	Yes	2	4.3		5	1	2.2
Gestational diabetes mellitus	No	38	82.6	Radiofrequency ablation	No	43	93.5
	Yes	8	17.4		Yes	3	6.5
Mode of delivery	SVD	2	4.3%	Laser ablation	No	45	97.8
	CS	44	95.7%		Yes	1	2.2
	Abortions	0	0.0%	Discordant anomaly	No	44	95.7
					Yes	2	4.3

IVF: *In vitro* fertilization; SVD: Spontaneous vaginal delivery; CS: Cesarean section; Ttts: Twin to twin transfusion syndrome; TAPS: twin arterial perfusion sequence.

improvement, with the mean scores of the first twin being 7.15 and 8.41, respectively, while the second twin scored 6.80 and 8.11, respectively, suggesting effective neonatal adaptation, although they appeared to be in distress initially. The first twin had an average birth weight of 1809.76 g, and the second twin had an average birth weight of 1683.13 g, with some cases showing notable intrauterine growth restriction.

Twin-to-twin transfusion syndrome (TTTS) was present in 8.7% of cases, but Stages 1 and 2 were rare (0.0% and 2.2%, respectively), while Stage 3 occurred in 6.5%. Twin anemia-polycythemia sequence (TAPS) affected 13.0% of cases, with Stages 2 and 5 occurring in 2.2% of cases each.

Treatments such as radiofrequency ablation were performed in 6.5% of cases, and laser ablation was less frequent at 2.2%. Discordant anomalies were observed in 4.3% of cases. These findings provide a comprehensive view of the participants' pregnancies and associated conditions.

The correlation table demonstrates significant associations between maternal factors, neonatal APGAR scores, and birth weights of neonates in monochorionic twin pregnancies. There were strong and statistically significant correlations between APGAR scores at 1 and 5 minutes for both twins, with r values ranging from 0.726 to 0.937 ($p<0.01$), signifying the comparability of neonatal condition and recovery after birth. Furthermore, birth weight showed a strong positive correlation with neonatal APGAR scores (up to $r=0.770$, $p<0.01$), indicating that higher birth weight was associated with better neonatal outcomes (Table 1).

Maternal age, IVF, and preeclampsia did not show any significant correlation with APGAR scores or birth weights, indicating a limited impact on neonatal outcomes in this population. These findings underline the predominance of fetal growth parameters compared to maternal factors in determining neonatal health in monochorionic twin pregnancies (Table 2).

In this analysis, the focus was on comparing gestational age, APGAR scores, and birth weights according to IVF conception, preeclampsia, pregnancy termination, and selective fetal growth restriction (sFGR). Compared to non-IVF pregnancies, gestational age at birth, APGAR scores, and birth weights were higher in IVF pregnancies (34.67 vs. 32.30). Preeclampsia cases appeared to have lower gestational ages at birth (32.00 vs. 32.54) and birth weights compared with non-preeclampsia cases. However, APGAR scores of both groups were approximately equal (Table 2).

Table 3: Correlation analysis of maternal factors, Apgar, and birth weights in monochorionic twin pregnancies

	Mother age	IVF	Pre-eclampsia	1. baby 1 min Apgar	1. baby 5 min Apgar	2. baby 1 min Apgar	2. baby 5 min Apgar	1 baby birth weight	2 baby birth weight
The mother's age									
Pearson correlation	1	0.236	0.151	0.157	0.260	0.230	0.278	0.051	0.157
Sig. (2-tailed)		0.114	0.315	0.296	0.081	0.124	0.061	0.734	0.298
IVF									
Pearson correlation	0.236	1	-0.112	0.115	0.125	0.131	0.132	0.145	0.186
Sig. (2-tailed)	0.114		0.459	0.446	0.410	0.386	0.380	0.337	0.217
Preeclampsia									
Pearson correlation	0.151	-0.112	1	0.043	0.025	0.145	0.102	-0.085	-0.146
Sig. (2-tailed)	0.315	0.459		0.776	0.868	0.337	0.500	0.572	0.332
1. Baby 1 min Apgar									
Pearson correlation	0.157	0.115	0.043	1	0.926*	0.826*	0.726*	0.770*	0.661*
Sig. (2-tailed)	0.296	0.446	0.776		0.000	0.000	0.000	0.000	0.000
1. baby 5 min Apgar									
Pearson correlation	0.260	0.125	0.025	0.926*	1	0.771*	0.786*	0.728*	0.630*
Sig. (2-tailed)	0.081	0.410	0.868	0.000		0.000	0.000	0.000	0.000
2. baby 1 min Apgar									
Pearson correlation	0.230	0.131	0.145	0.826*	0.771*	1	0.937*	0.619*	0.802*
Sig. (2-tailed)	0.124	0.386	0.337	0.000	0.000		0.000	0.000	0.000
2. baby 5 min Apgar									
Pearson correlation	0.278	0.132	0.102	0.726*	0.786*	0.937*	1	0.536*	0.776*
Sig. (2-tailed)	0.061	0.380	0.500	0.000	0.000	0.000		0.000	0.000
1 baby birth weight									
Pearson correlation	0.051	0.145	-0.085	0.770*	0.728*	0.619*	0.536*	1	0.746*
Sig. (2-tailed)	0.734	0.337	0.572	0.000	0.000	0.000	0.000		0.000
2 baby birth weight									
Pearson correlation	0.157	0.186	-0.146	0.661*	0.630*	0.802*	0.776*	0.746*	1
Sig. (2-tailed)	0.298	0.217	0.332	0.000	0.000	0.000	0.000	0.000	
N	46	46	46	46	46	46	46	46	46

IVF: *In vitro* fertilization; *: Correlation is significant at the 0.01 level (2-tailed).

For pregnancy termination, there was a marked reduction in neonatal health outcomes, as exemplified by extremely low values for gestational age (20 weeks vs. 32.73 weeks), APGAR scores (zero), and no reported birth weight. In sFGR cases, both twin infants had lower birth weights than expected (first twin: 1658.65 g vs. 1960.87 g; second twin: 1458.48 g vs. 1907.78 g), although infants were born with comparable gestational ages and APGAR scores (Table 2).

In conclusion, better health outcomes were observed in IVF pregnancies compared to the negative consequences associated with preeclampsia and sFGR, while the most detrimental effects on birth outcomes were observed among pregnancies in which termination was performed.

The correlation analysis indicates that TTTS, FGR, neonatal distress, and birth weight in monochorionic pregnancies are strongly associated. Severe TTTS was closely linked with the progression of FGR. In the analysis, strong correlations between Stage 2 FGR and TTTS ($r=0.452$, $p=0.002$) and between Stage 3 FGR and TTTS ($r=0.313$, $p=0.034$) suggest that TTTS accelerates fetal growth restriction. The progression of TTTS was sequential, with Stage 2 and Stage 3 showing a high level of correlation ($r=0.856$, $p<0.001$), reinforcing the progressive nature of the condition (Table 3).

Neonates with severe TTTS had significantly lower APGAR scores than those without TTTS. Stage 3 TTTS demonstrated a strong negative relationship (-0.600 and -0.604; $p<0.001$ at 1 and 5 minutes, respectively),

Table 4: t-Test results for the impact of IVF, preeclampsia, pregnancy termination, and sFGR on neonatal outcomes

	IVF					Preeclampsia					Pregnancy termination			Selective fetal growth restriction				
	Levene's Test for equality of variances		t-test for equality of means			Levene's Test for equality of variances		t-test for equality of means			t-test for equality of means			Levene's Test for equality of variances		t-test for equality of means		
	F	Sig.	t	df	Sig. (2-tailed)	F	Sig.	t	df	Sig. (2-tailed)	t	df	Sig. (2-tailed)	F	Sig.	t	df	Sig. (2-tailed)
Week of birth	2.288	0.138	-0.882	44	0.382	1.093	0.301	0.290	44	0.773	3.065	44	0.004	0.009	0.924	0.754	44	0.455
			-2.447	8.341	0.039			0.411	13.031	0.688						0.754	43.647	0.455
1. baby 1 min Apgar	1.961	0.168	-0.769	44	0.446	1.326	0.256	-0.287	44	0.776	2.838	44	0.007	0.012	0.915	-0.053	44	0.958
			-1.595	3.956	0.187			-0.394	12.324	0.700						-0.053	43.938	0.958
1. baby 5 min Apgar	1.656	0.205	-0.833	44	0.410	0.314	0.578	-0.167	44	0.868	3.549	44	0.001	0.063	0.804	-0.054	44	0.957
			-2.499	11.989	0.028			-0.220	11.407	0.830						-0.054	43.717	0.957
2. baby 1 min Apgar	3.411	0.071	-0.876	44	0.386	7.351	0.010	-0.970	44	0.337	2.311	44	0.026	0.024	0.877	0.140	44	0.889
			-1.982	4.632	0.109			-1.622	19.438	0.121						0.140	43.968	0.889
2. baby 5 min Apgar	1.952	0.169	-0.886	44	0.380	2.256	0.140	-0.680	44	0.500	2.800	44	0.008	0.032	0.860	0.046	44	0.963
			-2.807	16.438	0.012			-1.145	19.834	0.266						0.046	43.725	0.963
1 baby birth weight	0.974	0.329	-0.970	44	0.337	3.051	0.088	0.569	44	0.572	2.415	44	0.020	0.185	0.669	1.295	44	0.202
			-1.489	2.818	0.239			0.794	12.686	0.442						1.295	43.906	0.202
2 baby birth weight	2.251	0.141	-1.254	44	0.217	2.498	0.121	0.982	44	0.332	1.980	44	0.054	0.297	0.589	1.757	44	0.086
			-2.424	3.564	0.080			1.456	14.321	0.167						1.757	43.052	0.086

IVF: *In vitro* fertilization; sFGR: Selective fetal growth restriction.

Table 5: Correlation analysis between TTTs, FGR stages, and neonatal outcomes in monochorionic twin pregnancies

	Stage 1 FGR	Stage 2 FGR	Stage 3 FGR	TTTS	TTTS 2	TTTS 3	1. baby 1 min Apgar	1. baby 5 min Apgar	2. baby 1 min Apgar	2. baby 5 min Apgar	1 baby birth weight
Stage 2 FGR											
Pearson correlation	-0.236										
Sig. (2-tailed)	0.114										
Stage 3 FGR											
Pearson correlation	-0.163	-0.066									
Sig. (2-tailed)	0.278	0.664									
TTTS											
Pearson correlation	-0.236	0.452**	0.313*								
Sig. (2-tailed)	0.114	0.002	0.034								
TTTS 2											
Pearson correlation	-0.114	-0.046	0.699**	0.483**							
Sig. (2-tailed)	0.450	0.761	0.000	0.001							
TTTS 3											
Pearson correlation	-0.202	0.543**	-0.056	0.856**	-0.039						
Sig. (2-tailed)	0.178	0.000	0.710	0.000	0.795						
1. baby 1 min Apgar											
Pearson correlation	0.356*	-0.473**	-0.169	-0.530**	-0.008	-0.600**					
Sig. (2-tailed)	0.015	0.001	0.261	0.000	0.956	0.000					
1. baby 5 min Apgar											
Pearson correlation	0.305*	-0.512**	0.007	-0.512**	0.033	-0.604**	0.926**				
Sig. (2-tailed)	0.040	0.000	0.963	0.000	0.828	0.000	0.000				
2. baby 1 min Apgar											
Pearson correlation	0.297*	-0.381**	-0.229	-0.506**	-0.136	-0.497**	0.826**	0.771**			
Sig. (2-tailed)	0.045	0.009	0.127	0.000	0.369	0.000	0.000	0.000			
2. baby 5 min Apgar											
Pearson correlation	0.234	-0.408**	-0.007	-0.433**	-0.005	-0.491**	0.726**	0.786**	0.937**		
Sig. (2-tailed)	0.117	0.005	0.961	0.003	0.973	0.001	0.000	0.000	0.000		
1 baby birth weight											
Pearson correlation	0.196	-0.454**	-0.307*	-0.582**	-0.220	-0.535**	0.770**	0.728**	0.619**	0.536**	
Sig. (2-tailed)	0.191	0.002	0.038	0.000	0.142	0.000	0.000	0.000	0.000	0.000	
2 baby birth weight											
Pearson correlation	0.043	-0.390**	-0.190	-0.457**	-0.113	-0.455**	0.661**	0.630**	0.802**	0.776**	0.746**
Sig. (2-tailed)	0.777	0.007	0.205	0.001	0.456	0.002	0.000	0.000	0.000	0.000	0.000
N	46	46	46	46	46	46	46	46	46	46	46

*: Correlation is significant at the 0.05 level (2-tailed); **: Correlation is significant at the 0.01 level (2-tailed); TTTS: Twin to twin transfusion syndrome; FGR: Fetal growth restriction.

suggesting increased birth distress. Conversely, Stage 1 mild FGR did not negatively affect APGAR scores; however, advanced stages of FGR had significant adverse impacts on neonatal outcomes (Table 4).

Increased birth weight and 5-minute APGAR scores were significantly correlated, indicating improved neonatal stabilization ($r=0.536$, $p<0.001$ for the first twin and $r=0.746$, $p<0.001$ for the

second twin). In contrast, TTTS led to a considerable reduction in birth weight. This supports the argument that TTTS substantially contributes to fetal growth restriction (Table 5).

Overall, severe TTTS and advanced FGR are likely to result in adverse neonatal outcomes, reinforcing the importance of early diagnosis, surveillance, and effective intervention in monochorionic twin pregnancies to improve survival rates and decrease complications.

DISCUSSION

The research highlights the significant aspects of perinatal outcomes of monochorionic twin pregnancies, particularly focusing on the effects of selective fetal growth restriction (sFGR), twin-to-twin transfusion syndrome (TTTS), and twin anemia-polycythemia sequence (TAPS) on neonatal health. The study results correspond with previous studies, supporting the notion of early detection, close follow-up, and prompt treatment for the effective management of complex monochorionic twin pregnancies.

The results indicate the presence of stage 1 FGR as the principal pregnancy complication, presented in 50% of pregnancies. Prior studies have reported that sFGR affects 10–15% of pregnancies involving monochorionic twins and is linked with higher incidences of poor fetal outcomes.[4,25] In the current study, sFGR was associated with deteriorating neonatal health outcomes according to its correlation with birth weight and markedly low APGAR scores. It has been reported that monochorionic twins with substantial fetal growth discordance have increased chances of premature delivery as well as a risk for poor neonatal outcomes.[22]

TTTS was observed in 8.7% of cases in the study, which aligns with the literature reporting its prevalence in monochorionic twin pregnancies ranging between 9-15%.[15] This study found a significant relationship between TTTS and negative neonatal outcomes, highlighting that Stage 3 TTTS had a significant negative correlation with 1- and 5-minute APGAR scores of -0.600 ($p<0.001$) and -0.604 ($p<0.001$), respectively, adding to research indicating that higher stages of TTTS are the main causes of adverse neonatal outcomes.[24,26]

TAPS was found in more than 13% of cases in the study; it is a rarely documented but serious transfusion-related issue. Other reports show that it affects 3-5% of monochorionic pregnancies, which can result in fetal anemia, cardiac dysfunction, and even stillbirth.[15] Cases with TAPS in the study were observed to have a greater incapacity for neonatal adaptation, as shown by decreased birth weight.

Neonatal distress, evaluated by APGAR scores, was an important aspect of the study. At one minute, the first twin's APGAR score was 7.15, and the second scored 6.80. The scores improved at five minutes to 8.41 and 8.11, respectively. This progress suggests that the measures taken to resuscitate the neonate were successful. Research shows that monochorionic twins, especially those affected by TTTS and sFGR, have low 1-minute APGAR scores but improve significantly at the 5-minute mark; this improvement is seen when appropriately managed.[27] Also, the association between weight and APGAR scores reinforces findings from other studies, which noted that low birth weight is associated with increased odds of neonatal instability and greater NICU admissions.[28]

The delivery methods for twins sharing a placenta are still a matter of discussion. As per this research, cesarean delivery was noted in 95.7% of cases, which aligns with global obstetric recommendations.[29] This suggests that in cases of high-risk pregnancies with monochorionic twins, cesarean sections are preferred to optimize outcomes for these patients.[8]

The average gestational age at delivery in this research was 32.46 weeks, emphasizing the concern of prematurity in monochorionic twin pregnancies. This finding supports previously published data showing that a good proportion of monochorionic twins are born preterm due to conditions such as TTTS and sFGR. In this cohort, the lower gestational age at delivery is likely associated with increased chances of RDS and IVH.[30]

This study observed obstetric complications such as preeclampsia (15.2%) and gestational diabetes mellitus (17.4%). Although these conditions are well documented to have an impact on fetal development and pregnancy outcomes, their effects on neonatal APGAR scores and birth weights in the cohort appear insignificant.[31] This could stem from the adverse effects of TTTS and sFGR in determining neonatal outcomes in cases of monochorionic twin pregnancies.

The outcome of this study emphasizes the need for systematic surveillance protocols for the clinical management of monochorionic twin pregnancies, which are considered high-risk pregnancies.[11,32] Early detection of TTTS, sFGR, and TAPS can increase neonatal survival. Doppler ultrasound, fetal echocardiography, and periodic growth measurements have been suggested for the management of these pregnancies.[2,15] In addition, greater availability of fetoscopic laser ablation surgery in resource-limited regions may greatly improve the morbidity and mortality rates of TTTS.[17]

The study's retrospective design limits the findings, as it depends on previously recorded medical data, which may have reporting bias. Furthermore, the small sample size restricts the generalizability of the results to larger populations.

CONCLUSION

This study demonstrates the significant impact of TTTS, sFGR, and TAPS on perinatal outcomes in monochorionic twin pregnancies. The strong correlation between the severity of TTTS, fetal growth restriction, and neonatal distress highlights the need for strict prenatal surveillance and prompt interventions. Cesarean section remains the main mode of delivery, in line with current obstetric guidelines, to minimize intrapartum risks. The study confirms the need for standardized screening and management protocols to enhance neonatal survival rates and reduce morbidity in monochorionic twin pregnancies.

Statement

Ethics Committee Approval: The study was approved by Eskişehir City Hospital Ethics Committee (No: ESH/BAEK 2025/77, Date: 29.12.2023).

Informed Consent: In this study, previously collected data were analyzed; informed consent was not obtained because it was not deemed necessary.

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ORIGINAL ARTICLE

Natural evolution of cervical intraepithelial lesions and high-risk human papillomavirus infection during pregnancy

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ABSTRACT

Objective: The aim of this study was to investigate the pregnancy course, outcomes, and the progression, persistence, or regression status of postpartum cervical intraepithelial lesions (SIL) and high-risk Human Papillomavirus (HR-HPV) positivity in pregnant women who were diagnosed with cervical intraepithelial lesions and/or HR-HPV positivity detected through cervical Pap smear testing shortly before or at the onset of pregnancy.

Material and Methods: The study was conducted between 2018 and 2021 at Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, including seventy pregnant women who were identified either with preinvasive cervical lesions in cervical cytology tests or with high-risk Human Papillomavirus (HR-HPV) positivity through Real-Time PCR testing. Pregnancy outcomes were evaluated. A control group of 146 non-pregnant patients comparable in terms of age, parity, cytology, and HPV typing results was selected. The natural evolution of cervical intraepithelial lesions and HR-HPV infection in both groups was compared using samples obtained 12–18 months after the first evaluation.

Results: In the pregnant group, the regression rate of squamous intraepithelial lesions was 87.1%, whereas the rate of HPV infection regression was 68.8%. Comparatively, these rates in the control group were 64.6% and 43.0%, respectively. The regression rate of abnormal cervical cytology was significantly higher in the pregnant group (3.2%) than in the control group (23.8%), with a minimal progression rate (p=0.001). The regression rate of HR-HPV infection was significantly higher in the pregnant group than in the control group (p=0.009). When both groups were analyzed, the regression rate of squamous intraepithelial lesions in the presence of other HR-HPV types (72.6% (n=61)) was significantly higher than that in HPV 16–18-positive cases (54.1% (n=33)) (p=0.021). Of the total pregnancies, 14.7% resulted in abortion, 11.4% resulted in preterm birth, 8.7% resulted in post-term birth, and 65.2% resulted in term birth. Regarding the increase in the rate of preterm birth, there was no significant difference in preterm birth rates among HR-HPV types. There was no significant difference in the frequency of pregnancy-related complications based on HR-HPV types and the regression status of HR-HPV infection.

Conclusion: Preinvasive lesions of the cervix and HR-HPV infection exhibit a high rate of spontaneous regression after pregnancy. In cases of low-grade lesions and situations without suspicion of invasive cancer, histopathological examination and definitive treatment may be considered for postponement until after pregnancy. This observed regression appears to be associated with progesterone dominance during pregnancy. Further advanced molecular and histopathological studies are required to elucidate the impact of progesterone on squamous intraepithelial lesions and cervical HR-HPV infection.

Keywords: Cervical cytology, cervical intraepithelial neoplasia, human papillomavirus, pregnancy, squamous intraepithelial lesion.

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INTRODUCTION

The presence of abnormal cervical cytology and HPV infection can complicate the implementation of standard care algorithms during pregnancy. Although colposcopy is considered safe to perform during pregnancy, endocervical curettage is contraindicated. Aggressive interventions for cytological abnormalities and HPV infection can generally be postponed in most cases.[1]

The management of squamous intraepithelial lesions during pregnancy is determined by the severity of the lesion. Colposcopy is preferred for pregnant women diagnosed with LSIL. Postponing colposcopy until up to 6 weeks postpartum is acceptable. Pregnant women diagnosed with HSIL should undergo a colposcopic evaluation. Pregnant women who do not show signs of cervical intraepithelial neoplasia (CIN) 2+ on colposcopy or histology should undergo postpartum follow-up. The only diagnosis that can alter management during pregnancy is invasive cancer. The primary goal of cytology, colposcopy, and histology is to rule out invasive cancer. Pregnant women who have been histologically diagnosed with CIN 2, CIN 3, or CIN 2,3 may nevertheless undergo repeated colposcopy examinations and cytology testing at intervals of up to 12 weeks, despite the general recommendation against these procedures during pregnancy. Repeat biopsy is only acceptable in the presence of suspected invasive cancer, and treatment is contraindicated until invasive cancer is confirmed.[2]

Performing a colposcopy during pregnancy is challenging due to cervical hyperemia, marked normal epithelial changes mimicking the appearance of preinvasive disease, obscured mucus, contact with prolapsed vaginal walls, and bleeding after biopsy. Additionally, cervical treatments designed to eliminate CIN can lead to miscarriage, premature birth, and maternal bleeding.[2]

Squamous intraepithelial neoplasia can regress during the interval between antenatal cytology testing and postpartum examination. In women who have been diagnosed with CIN 2 during pregnancy, the likelihood of developing microinvasive cancer at the postpartum visit is extremely low. However, for those diagnosed with CIN 3, the risk is less than 10%, and deep invasive cancer types are rare.[3] Although postpartum colposcopy is recommended to be performed at least 4 weeks after delivery to allow time for cervical healing, reassessment with cytology and colposcopy should be performed at the latest by the 6th week postpartum.[2,4]

HPV is considered the most common sexually transmitted agent worldwide, with a prevalence of 10.4%.[5] HPV genotypes are classified as high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and low-risk (6, 11, 42, 43, and 44) based on their relationship with CIN development. The prevalence of HPV, particularly HPV type 16, increases during pregnancy.[6]

The impact of pregnancy on the course of cervical cytology and HPV infection, as well as the association between abnormal cervical cytology and adverse pregnancy outcomes, remains debated. In our study, we aimed to evaluate postpartum cytological findings in women with abnormal cervical cytology and HPV infection during pregnancy, examining the rates of persistence, progression, and regression. Additionally, we aimed to assess the impact of abnormal cervical cytology and HPV infection on cervix-related adverse pregnancy outcomes during pregnancy.

MATERIALS AND METHODS

Our prospective case-control study was conducted at Zeynep Kamil Women's and Children's Diseases Training and Research Hospital between March 5, 2020, and February 28, 2022. The study was approved by the Ethics Committee of Zeynep Kamil Women's and Children's Diseases Training and Research Hospital (Ethics Committee reference number 40) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the study.

Pregnant women who presented to the Obstetrics and Gynecology clinic in the first trimester with a confirmed pregnancy status were evaluated. The initial medical history included age, height, weight, obstetric history, date and results of the last cervical cytology and HR-HPV test, and a history of previous cervical surgery. Pregnant women who had undergone cervical cytology and HR-HPV testing within the last 6 months and were diagnosed with epithelial cell abnormalities (according to Bethesda II) and/or HPV positivity (83 patients) were included in the pregnant group. Thirteen patients who did not continue routine pregnancy follow-ups during the study period or did not undergo a control smear test between 6 weeks and 3 months postpartum were excluded. Seventy patients meeting all inclusion criteria and follow-up requirements were included in the study.

During the same period, a control group consisting of non-pregnant women who presented for routine health check-ups and had epithelial cell abnormalities (Bethesda II) in the cervical cytology test and/or HPV positivity reported within the last 6 months was examined. The control group was matched for age and parity with the pregnant group (170 patients). Those with a history of cervical surgery were excluded from both groups. Twenty-four patients in the control group who did not present for a control smear test within 12–18 months after the initial smear were also excluded. A total of 146 patients meeting all inclusion criteria were included in the control group.

Cervical cytology results, colposcopy findings, cervical biopsy results if available, HPV-DNA test results, and the presence of genital condyloma were recorded for participants in both the pregnant and control groups. Cervical cytology screening was performed using the ThinPrep cytological test, which involves the use of a specific cytological brush to obtain samples from the cervical canal (TCT; Hologic). Participants with confirmed abnormal ThinPrep cytological test results were included in the study. All included smear reports were evaluated using the 2014 Bethesda system in different pathology laboratories. Results were categorized as negative for intraepithelial lesions or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL).

HPV-DNA analysis in all participants was performed using the real-time polymerase chain reaction (RT-qPCR) technique. All samples were analyzed for the presence of 13 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Therefore, a positive HPV test result indicates positivity for one or more of the 13 high-risk HPV genotypes. HPV test results were further analyzed as HPV16,18 and HPV OTHER (non16,18-HPV).

Following the guidelines of ACOG 2013 and ASCCP 2021–22, patients with LSIL and above lesions and/or positive HR-HPV test results in both the pregnant and control groups were recommended to undergo colposcopy examination. In the pregnant group, fifteen patients consented to undergo colposcopy, and biopsies were taken from eleven patients. Colposcopy examinations in the pregnant group were conducted between the 14th and 28th weeks of gestation. In the control group, colposcopy was performed on 121 patients, and biopsies were taken from all patients. Colposcopy examinations were conducted by experienced professional gynecologic oncologists. Cervical pathology and colposcopy classifications were performed according to the 2011 colposcopy terminology of the International Federation for Cervical Pathology and Colposcopy (IFCPC).[7]

Patients who did not accept colposcopy examination accepted the liquid-based cytology results, whereas in patients undergoing colposcopy and biopsy, the most severe pathology results from liquid-based cytology and cervical biopsy were considered the definitive cytological status.

Pregnant patients were followed according to the algorithm of the Turkish Ministry of Health for uncomplicated pregnancies.[8] Treatments applied due to first-, second-, and third-trimester vaginal bleeding, cervical length in the second trimester, cervical shortening, or bleeding during pregnancy were recorded. Prelabor rupture of membranes (PROM) was defined and recorded as the rupture of fetal membranes before the onset of regular uterine contractions. Pregnancies that ended before 20 weeks were recorded as abortions. Births that occurred between 20 weeks 0 days and 36 weeks 6 days were considered preterm births, births that occurred between 37 weeks and 41 weeks were considered term births, and births that occurred after 41 weeks were considered post-term births. The mode of delivery was recorded as normal vaginal delivery or cesarean section, and birth outcomes were recorded as live birth, stillbirth, or abortion. Postpartum bleeding and the need for transfusion were also recorded.

In the pregnant group, patients were called for follow-up liquid-based cytology and HR-HPV real-time PCR testing 6–12 weeks after the end of pregnancy. Patients included in the control group were called for control smear screening tests between 12 and 18 months after the initial smear, consistent with the post-pregnancy control period. ThinPrep cytological tests were performed on samples obtained from the cervical canal using a specific cytological brush for the control smear. HPV-DNA of 13 types was screened in real time using PCR from the same sample. All cytological and histological samples were examined by independent cytopathologists who were unaware of the patients' findings.

The duration between the first and second control smears and HPV results, as well as the regression, persistence, and progression status of abnormal cervical cytology and HR-HPV infection, were compared between the study and control groups. In a sub-analysis of obstetric outcomes defined in the pregnant group, the group with regression of abnormal cytology was compared with the group without regression. The frequency of pregnancy complications was compared according to HPV type and the regression status of HPV infection (Fig. 1).

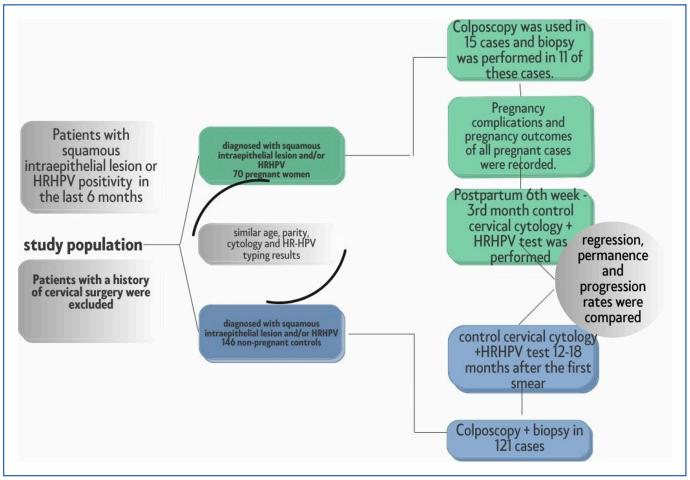

Figure 1: Flowchart of the study population.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 26 was used for statistical analyses. Descriptive statistical methods, such as mean, standard deviation, median, min, and max values for quantitative variables and frequency and percentage for qualitative variables, were used to evaluate study data. The normality of the data was assessed using the Shapiro–Wilk test and Box Plot graphs. Student's t-test was used for the evaluation of two groups of numerical variables showing normal distribution. For the comparison of qualitative data, the Chi-square test, Fisher's Exact test, and Fisher–Freeman–Halton test were used. Results were evaluated at the 95% confidence interval, and statistical significance was considered at $p<0.05$.

RESULTS

The study was conducted with a total of 216 cases, including 70 cases in the pregnant group and 146 cases in the non-pregnant control group. The ages of the cases ranged from 20 to 41 years, with a mean of 30.28±5.03. The average gestational age at inclusion in the pregnant group was 10.4±3.5 weeks.

Age, parity, and the presence of condyloma were similar between the pregnant and control groups. The distribution of abnormal cervical cytology types (ASCUS, LSIL, ASCH, HSIL) was similar among the groups. In the pregnant group, isolated HPV positivity was detected in 8.6% of cases, whereas in the control group, it was detected in 18.5%. Isolated abnormal cervical cytology was present in 12.9% of the pregnant group and 12.3% of the control group. The distribution of HR-HPV types in HR-HPV-positive cases was similar between the groups. Among pregnant women with a negative HPV test, 7 of 9 had ASCUS, 1 had LSIL, and 1 had HSIL in cervical cytology (Table 1).

In the pregnant group, colposcopy was performed on 15 patients, and colposcopic biopsies were obtained from 11 patients. In the control group, colposcopy was performed on 121 patients, and biopsies were obtained from all patients. Pathological results revealed advanced cervical lesions compared to cytology in 41 patients (pregnant group: 1, control group: 40), and 63.4% of these cases were positive for HPV types 16 or 18. The agreement between biopsy and cytology results was similar between the groups. The rate of obtaining a normal

Table 1: Comparisons of patients characteristics

	Study group (n=70)	Control group (n=146)	p
Age	29.77±5.15	30.53±4.97	[a]0.303
Gential condyloma	9 (12.9)	27 (18.5)	[b]0.298
LSIL, cytology	27 (38.6)	58 (39.7)	[b]0.871
HSIL, cytology	6 (8.6)	4 (2.7)	[c]0.056
ASCUS, cytology	28 (40)	51 (34.7)	[b]0.469
ASC-H, cytology	3 (4.3)	6 (4.1)	[c]0.952
NILM, cytology	6 (8.6)	27 (18.5)	[b]0.058
HPV 16 or 18	12 (17.1)	43 (29.5)	[b]0.058
HPV, other	49 (70)	85 (58.2)	[b]0.066
HPV, negative	9 (12.9)	18 (12.3)	[b]0.912

LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; ASCUS: Atypical squamous cells of undetermined significance; ASC-H: Atypical squamous cells, cannot exclude HSIL; NILM: Negative for intraepithelial lesion or malignancy; HPV: Human papillomavirus.

biopsy result despite abnormal cytology was higher in the pregnant group compared to the control group (27.3% vs. 9.9%), and the rate of detecting a more advanced cervical lesion by cytology was higher in the control group (33.1% vs. 9.1%). However, these differences were not statistically significant (p=0.082 and p=0.100).

The average number of visits during pregnancy in the pregnant group was 10±3 (2–16).

Among the pregnant participants, 34.3% reported vaginal bleeding in the first trimester, 4.3% in the second trimester, and 8.6% in the third trimester. The average cervical length in the second trimester was 33.44±4.48 millimeters, with cervical shortening detected in only 4.28% of cases. Progesterone therapy was administered to 34.3% of pregnant cases, mainly for bleeding (28.6%) and cervical shortening (5.7%). Pregnancy outcomes included 14.7% abortion, 11.4% preterm birth, 8.7% post-term birth, and 65.2% term birth. The rate of premature birth in HPV-negative cases with abnormal cervical cytology (33.3%) was significantly higher than that in HPV16,18 (16.7%) and HPV Other (8.3%) positive cases (p<0.001) (Table 2).

The average gestational week at abortion was 8.6±3.7 (5–17). The gestational weeks at delivery for pregnancies other than abortion ranged from 20 to 42 weeks, with an average of 37.58±4.18 (20–42). Two patients had stillbirths (2.8%). Of the cases, 45.6% (n=31) had normal vaginal delivery, and 39.7% (n=27) had cesarean section (Table 2).

There was no significant difference in the frequency of pregnancy complications based on the regression status of HPV infection and HPV types. The frequency of preterm labor and prelabor rupture of membranes (PROM) was significantly higher (p=0.008 and p=0.007) in the group where cytological abnormalities regressed (Table 2).

The time between the two smear tests ranged from 8.63 to 24.77 months, with similar durations between the groups. There was no statistically significant difference in the presence of recurrent vaginitis between the groups (Table 3).

Compared to the pre-pregnancy period, there was a statistically significant decrease in high-grade cytological abnormalities and HPV positivity after childbirth. The pregnant group had a significantly higher regression rate and a lower progression rate in cervical cytology compared to the control group. Similarly, the regression rate of HPV infection was significantly higher in the pregnant group (p=0.009; p<0.01) (Table 3).

In the pregnant group, the regression rate of abnormal cervical cytology was 87.1%, and the negativity rate of HPV infection was 68.6%, whereas in the control group, these rates were 64.5% and 43.1%, respectively (Table 3).

When all cases were analyzed, the regression rate of squamous intraepithelial lesions in the presence of other HR-HPV types (72.6% (n=61)) was significantly higher than that in HPV16,18-positive cases (54.1% (n=33)) (p=0.021) (Table 3).

DISCUSSION

The age group with the highest prevalence of HPV infection similarly exhibits the highest birth rate.[9] Although the majority of cases resolve spontaneously after a period of 1–2 years, follow-up is required due to the risk of persistent infection. In our study, we evaluated cases recently diagnosed with squamous intraepithelial lesions and/or high-risk HPV (HR-HPV) positivity that had not undergone any treatment procedures. We aimed to investigate the potential effects of pregnancy on abnormal cytology and the status of HR-HPV infection.

The objective of our study was to evaluate cervical intraepithelial lesions and HPV infections, revealing lower rates of persistence and progression as well as higher rates of spontaneous regression in the pregnant group compared to the non-pregnant group. The regression rate of cervical squamous intraepithelial lesions was 87.1%, and the negativity rate for HPV infection was 68.6% in the pregnant group, whereas these rates in the control group were 64.5% and 43.1%, respectively. The regression rate for abnormal cytology and HR-HPV infection was significantly higher, and the progression rate (2.9% vs. 23.9%) was significantly lower in the pregnant group (p=0.001). Despite an exceptionally low rate of disease progression, no cases of invasive cancer were observed.

Our findings support the notion that histopathological evaluation and treatment can be postponed until after pregnancy in patients with no suspicion of invasive cancer based on a risk-based rather than a diagnosis-based approach.

A cervical biopsy during pregnancy can be a source of concern for pregnant women. There are few studies focusing on the natural course of cervical intraepithelial lesions during pregnancy. In a study published in 2001, 279 pregnant cases were evaluated, including 32 with atypical glandular cells of undetermined significance (11%), 178 with low-grade squamous intraepithelial lesions (61%), 69 with high-grade squamous intraepithelial lesions (23.6%), and 2 with malignancy (1%). Only 27 patients (9%) underwent colposcopy-directed biopsy, and among 91 patients scheduled for follow-up colposcopy during pregnancy, only 24 (26%) complied. In four cases, invasive cervical carcinoma was diagnosed within 12 months after delivery.[10]

Table 2: Pregnancy outcomes of the study group according to the detected HPV type

	n (%)	HPV 16,18	HR-HPV other	p
Vaginal bleeding				
1st trimester	24 (34.3)	16.7%	36.7%	0.334
2nd trimester	3 (4.3)	0.0%	6.1%	0.511
3rd trimester	6 (8.6)	8.3%	10.2%	0.603
2nd trimester cervical length (CXL) (n=55), Mean±SD		33.44±4.48		
Prelabor rupture of the membranes (PROM)	6 (8.7)	16.7%	8.2 %	0.683
Preterm labor	12 (17.1)	16.7%	18.4%	0.945
Progesterone treatment during pregnancy	24 (34.3)	16.7%	34.7%	0.294
Reason for progesterone therapy				0.557
Vaginal bleeding	20 (28.6)	16.7%	32.7%	
Cervical shortening	4 (5.7)	0.0%	6.1%	
Age of birth				
Abortion	10 (14.7)	10.0%	40.0%	0.741
Preterm	9 (11.4)	16.7%	8.3%	0.324
Term	45 (65.2)			
Postterm	6 (8.7)			

HPV: Human papillomavirus; HR-HPV: High-risk human papillomavirus; CXL: Cervical length; PROM: Prelabor rupture of the membranes; SD: Standard deviation.

Table 3: Comparison of control cytology and HPV results

	Study group (n=70) (%)	Control group (n=146) (%)	p
Time between cervical cytology tests (months), Mean±SD	19.65±7.8	15.61±7.56	[a]**0.522**
Cytology results			[d]**0.002***
ASCH	1 (1.4)	1 (0.7)	
ASCUS	2 (2.9)	16 (11.0)	
HSIL	3 (4.3)	11 (7,.5)	
LSIL	3 (4.3)	27 (18.5)	
NILM	60 (87.0)	91 (62.3)	
HR-HPV tests			[b]**0.001***
Negative	57 (85.1)	66 (46.2)	
Positive	10 (14.9)	77 (53.8)	
Recurrent vaginitis	10 (14.5)	33 (22.8)	[b]**0.158**
Control cytology			[d]**0.001***
Regression	60 (87.1)	94 (64.5)	
Persistence	7 (10.0)	17(11.6)	
Control HRHPV tests			[b]**0.009***
Regression	48 (68.6)	63 (43.1)	
Persistence	22 (31.4)	83 (56.9)	

a: Sutudent-t Test; b: Pearson Chi-Square Test; d: Fisher Freeman Halton Test; *: P<0.01. HPV: Human papillomavirus; HR-HPV: High-risk human papillomavirus; ASCUS: Atypical squamous cells of undetermined significance; ASC-H: Atypical squamous cells, cannot exclude HSIL; HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion.

The impact of HPV infection on pregnancy development and outcomes is not fully understood in the literature. While some studies have found no relationship, others have highlighted various adverse pregnancy outcomes. One study reported the frequency of PROM in the presence of HR-HPV infection as 27.3%, and HR-HPV infection was associated with an increased risk of PROM.[11,12] In our study, the frequency of PROM in pregnant cases was 8.7% (n=6), and four of these patients had abnormal cervical cytology with negative HPV results.[11,12] PROM was found to be significantly higher in patients with regression of cervical cytology. This situation may be coincidental, or it may be related to cell apoptosis, changes in the microenvironment, and inflammation that occur during the regression of cytological abnormalities in cervical cells.[13]

Our study showed a higher rate of preterm birth (11.4%) compared to the general rates of 4.3% to 8.7% reported for singleton pregnancies in Europe in 2008.[14] Previous studies also reported that the prevalence of HR-HPV is higher among women who delivered prematurely (18.1%) compared to women who delivered at term (4%). Furthermore, infection with HR-HPV is associated with an increased risk of preterm birth. In these studies, HPV 16,18 positivity was found to be significantly higher in women with preterm birth than in those with other HR-HPV types.[15,16] However, our study did not find a significant relationship between HPV types, infection remission status, and preterm birth.

You et al.[17] also discovered that HPV infection leads to a reduction in trophoblast cell numbers through HPV receptors, inhibiting their ability to adhere to endometrial cells. It has potential effects on embryo loss, as it promotes apoptosis in trophoblasts (abortion risk). In our study, 14.7% of pregnancies resulted in abortion. This rate is higher than the 10% abortion prevalence reported in the literature for pregnancies between the ages of 20 and 25.[18]

Human papillomavirus infection does not cause a measurable inflammatory reaction. However, it may be associated with general changes in the vaginal microbiota, which may trigger an immune-inflammatory process leading to PROM and preterm birth. Additionally, the role of trophoblasts in preventing HPV infection and the interaction between the immune system and HPV are not fully understood. Understanding the interaction between the immune system and HPV during pregnancy, as well as the potential impact of hormonal changes during pregnancy, is crucial for understanding the natural history of HPV infection of the cervix and the impact of infection on pregnancy outcomes.[9]

In our study, the regression rate of HR-HPV infection was significantly higher in the pregnant group than in the control group (68% vs. 43%, p=0.009). Værnesbranden et al.,[19] in their study evaluating 757 pregnant women, reported that a low viral load in the middle of pregnancy was associated with clearance of HPV infections at birth and reported HPV persistence as 52%.This rate was lower (31%) in our study. Our findings are consistent with the results reported by Chen et al.,[20] who demonstrated that HR-HPV levels and cervical cytological abnormalities decrease during the third trimester. Epithelial sloughing of the cervix or increased localized immunological response are proposed theories that may explain this regression phenomenon.[21]

During pregnancy, cervical columnar and stratified squamous epithelium undergoes intense proliferation and differentiation; it provides a physical and immunological barrier against external factors. Progesterone supplementation studies in cervical insufficiency show that both the epithelial barrier and cervical stroma play an endocrine role in maintaining cervical integrity.[22] Progesterone synthesis is high throughout pregnancy. Both cervical stromal and epithelial cells express progesterone receptors (PR). PR is necessary for the occurrence of apoptosis and suppression of proliferation in the cervical epithelium.[23]

HPV infection often causes different humoral and cellular immune responses.[24] CIN I and II precancerous lesion cells are generally cleared by apoptotic pathways as a result of innate and adaptive cytotoxic responses. Viral antigens released by HPV-infected cells that initiate programmed apoptosis are presented to CD4+ and CD8+ T cells by Langerhans cells. Activated CD8+ T cells also secrete cytolytic granules, and programmed cell death is induced in target cells.[24] Women with persistent dysplasia have been found to have biopsy samples with significantly lower numbers of Langerhans cells and T helper cells, which are specific to the inflammatory wound-healing process.[25]

The progestogenic environment present for a long time during pregnancy may contribute to the regression of lesions and infection by mediating the apoptosis of infected cells.

Two studies published in 2019 drew attention to the importance of progesterone during cervical intraepithelial lesions. In the first study, it was reported that the use of progesterone reduced nuclear atypia and pleomorphism in the cervical superficial and middle epithelial layers.[26] In the second study, it was reported that 17β-estradiol induced cancer progression in CIN lesions in infected transgenic mice, whereas medroxyprogesterone acetate prevented it.[27] These findings support our view that progesterone contributes to the regression of cervical lesions. The high rate of regression of lesions and infection during pregnancy reported in our study highlights the need for studies with large case series investigating the effect of progesterone treatment on the regression of cervical intraepithelial lesions and HPV infection.

There are publications in the literature that recommend routine histological evaluation of abnormal cervical cytology.[28] It was reported that all 28 patients with prenatal HSIL had persistent HSIL after birth, and three of them were diagnosed with microinvasive carcinoma.[29] However, the widespread use of guidelines and common terminology has reduced this requirement. In a study examining 76 pregnant women, postnatal colposcopy and colposcopy-directed biopsies were recommended because the prevalence of HPV or CIN was 21% in patients with abnormal postnatal cytology.[30] Another similar study suggested that, in the presence of a low-grade cervical intraepithelial lesion, antepartum colposcopy does not contribute to treatment.[31]

Our findings support the notion that histopathological evaluation and treatment can be postponed until after pregnancy in patients with no suspicion of invasive cancer using a risk-based strategy rather than a diagnosis-based approach. The possibility of developing invasive cervical cancer during pregnancy due to low-grade cervical dysplasia is negligible.[32] Considering the higher rates of persistence and progression in cases of HPV16-18 positivity and high-grade cervical intraepithelial neoplasia, colposcopy evaluation and histopathological sampling may be encouraged in this population.

This study also has some limitations, including the limited number of cases, lack of smoking data in the case and control groups, and the inability to determine the date of lesion occurrence or the time at which the infection first appeared from the smear obtained prior to or at the beginning of pregnancy. Smoking history was not included in the study due to missing and questionable data in the study group regarding the tendency to quit smoking during pregnancy, duration of previous smoking habits, and the date of cessation. This study constitutes one of the limited number of studies comparing pregnant women with non-pregnant women who have identical cervical intraepithelial lesions and are positive for HR-HPV types.

CONCLUSION

In conclusion, our study reveals the complex relationship between HPV infection, cervical intraepithelial lesions, and pregnancy outcomes. The findings suggest that histopathological evaluation may be deferred until after pregnancy in cases of cervical intraepithelial lesions detected during pregnancy, supporting the idea that pregnancy-related changes, especially the progestogenic environment, contribute to lesion regression.

Further research with larger sample sizes is needed to understand the relationship between HPV infection and pregnancy and the effect of progesterone on squamous intraepithelial lesions and HPV infection.

Statement

Ethics Committee Approval: The study was approved by Zeynep Kamil Women's and Children's Diseases Training and Research Hospital Ethics Committee (No: 40, Date: 04.03.2020).

Informed Consent: Written informed consent was obtained from all patients before participation in the study.

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ORIGINAL ARTICLE

Parents' knowledge and attitudes regarding fever management and antipyretic use in children presenting to the pediatric emergency department with fever complaints

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ABSTRACT

Objective: Fever is one of the most common symptoms in childhood and a major reason for pediatric emergency department visits. Despite being a natural defense mechanism, misconceptions and heightened anxiety among parents may lead to unnecessary healthcare utilization and inappropriate interventions. This study aimed to determine the knowledge and attitudes of parents of children aged 6 months to 6 years regarding fever management and the use of antipyretic medications.

Material and Methods: This descriptive study was conducted with 322 parents who presented to the pediatric emergency department of a university hospital with their children because of fever complaints. Data were collected through face-to-face interviews using a questionnaire developed by the researcher. Analyses were performed using SPSS version 21.0, with descriptive statistics and chi-square tests, and the significance level was set at $p<0.05$.

Results: The mean age of the children was 2.7±1.49 years, and 57.6% were girls. Nearly all parents (97.2%) measured their child's body temperature when fever was suspected, with 73.6% preferring a digital axillary thermometer. Although 93.5% of parents reported knowing the normal temperature range, 24.2% identified values below 37°C as fever. In cases of high fever, 75.8% of parents removed the child's clothing, 58.7% gave the child a lukewarm bath, and 58.7% administered an antipyretic. Paracetamol was the most commonly used antipyretic (57.5%), but only 47.8% of parents reported being aware of medication side effects. A significant association was found between a child's history of febrile illness and the parents' practice of recording temperature measurements ($p<0.05$).

Conclusion: Although parents' practices regarding temperature measurement and antipyretic use were generally appropriate, misconceptions about fever thresholds and nonevidence-based practices, such as wiping the child with vinegar, persist. The high level of anxiety related to fever complications indicates the persistence of "fever phobia." These findings highlight the need for structured, guideline-based education programs for parents, which may reduce inappropriate practices and unnecessary healthcare visits.

Keywords: Antipyretic use, child, fever; nursing care, patient care management, pediatric emergency.

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INTRODUCTION

Fever is defined as a natural immune response developed by the body against bacteria, viruses, or other pathogens and is characterized by an elevation in body temperature above normal limits.[1] The Centers for Disease Control and Prevention (CDC) considers a temperature of 38.0°C (≥100.4°F) or higher to indicate fever, whereas the World Health Organization (WHO) sets this threshold at 37.5°C.[2,3]

In childhood, fever is one of the most frequently encountered clinical symptoms and a major cause of pediatric emergency department visits. Particularly in cases of high fever, parental anxiety increases significantly, often resulting in unnecessary emergency department visits.[4–6] In the literature, exaggerated fear and misconceptions surrounding fever have been defined as "fever phobia," a phenomenon that leads to inappropriate medical interventions, unnecessary use of antipyretics, overprescription of antibiotics, and an increased burden on healthcare systems.[6–8] While the global rate of emergency department admissions among children aged 0–5 years due to febrile illnesses ranges from 20% to 40%, this rate has been reported to be as high as 71% in Türkiye.[9,10]

Pediatric fever management guidelines emphasize the accurate measurement of body temperature, appropriate evaluation and monitoring of symptoms, maintenance of adequate hydration, use of nonpharmacological comfort measures, recognition of warning signs requiring medical intervention, and proper dosing and timing of antipyretic administration.[11,12]

Nevertheless, parents and caregivers often resort to unnecessary or inappropriate interventions because of concerns that fever may cause brain damage, trigger febrile seizures, or become life-threatening if left untreated.[13] Despite cultural differences in fever management practices, the frequency of antipyretic use, and levels of knowledge, anxiety surrounding fever remains widespread across societies.[14] Educational initiatives have improved parental awareness of fever; however, persistent fever phobia continues to manifest through incorrect practices, unrealistic fears, and heightened anxiety.[13,15]

Early recognition and appropriate management of fever in childhood are critical for preventing fever-related complications.[16] Evaluating parents' knowledge and experiences, identifying gaps and inappropriate practices, and examining their approaches to fever management, antipyretic use, and awareness of medication effects and side effects are essential. Moreover, understanding parents' information and support needs in these situations will contribute to the development of effective educational and intervention programs on fever management.

This study was conducted to assess the knowledge levels and attitudes of parents of children aged 6 months to 6 years in Türkiye regarding fever and antipyretic use.

MATERIAL AND METHODS

Study Design

This descriptive study was conducted to determine the knowledge levels and attitudes of parents of children aged 6 months to 6 years regarding fever management and antipyretic use among those who presented to the pediatric emergency department.

Study Sample

The study population consisted of parents who presented with their children aged 6 months to 6 years to the tertiary-level pediatric emergency department of a training and research hospital in Istanbul because of fever complaints. The sample size was calculated as 322 using the formula $Nt^2pq/[d^2(N-1)+t^2pq]$, considering a 0.5% margin of error. The study was conducted with parents who presented during daytime working hours (08:00–16:00) and provided both verbal and written informed consent.

Inclusion Criteria

- Parents with a child aged between 6 months and 6 years
- Parents who presented to emergency healthcare services because of their child's fever
- Parents of children with no history of chronic illness or continuous medication use
- Parents who could speak, read, and understand Turkish
- Parents with no communication barriers, such as hearing or speech impairments
- Parents who provided both verbal and written informed consent

Exclusion Criteria

- Parents who left the data collection form incomplete
- Parents whose interviews could not be completed because of the child's condition

Data Collection Form

The data collection form was prepared by the researcher based on a review of the literature to evaluate parents' knowledge of fever and their attitudes regarding antipyretic use in children aged 6 months to 6 years. The form consisted of 11 questions on parental demographic characteristics, 5 questions about the child, 17 questions assessing parental knowledge of fever, and 11 questions assessing attitudes and knowledge regarding antipyretic use.[17–19]

Study Procedure

Parents were informed about the study, and their verbal and written informed consent was obtained using an "Informed Consent Form." Data were collected through face-to-face interviews, each lasting approximately 40 minutes (minimum, 30 minutes; maximum, 50 minutes). Data collection was conducted during the observation period after all necessary examinations and treatments in the pediatric emergency department had been completed and the child's condition had stabilized.

Statistical Analysis

The data obtained in this study were analyzed using SPSS (Statistical Package for the Social Sciences) for Windows, version 21.0. Analyses were performed at a 95% confidence level, and statistical significance was set at $p<0.05$. Descriptive statistics were used to analyze percentages and distributions, while relationships between categorical variables were examined using the chi-square test.

Ethical Considerations

Ethics committee approval was obtained from the Istanbul Medipol University Non-Interventional Ethics Committee (decision no.: 149; date: March 9, 2016). Institutional permission was also obtained from the Istanbul Provincial Health Directorate (decision no.: 39038; date: June 27, 2016). The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

The mean age of the children participating in the study was 2.7±1.49 years, and 57.6% were female. Among the children, 37.9% had previously experienced a febrile illness, and 14.0% had experienced febrile seizures.

Of the 322 parents, 64.3% (n=208) were mothers. The parents' ages ranged from 18 to 45 years, with 51.6% aged between 31 and 40 years. Regarding educational level, 41.9% were primary school graduates. Among the parents, 49.4% reported that they were unemployed, including homemakers, and 38.2% reported working as laborers (Table 1).

Among the parents, 97.2% reported measuring their child's body temperature whenever they suspected a fever. The most commonly preferred method was a digital axillary thermometer (73.6%). Furthermore, 93.5% of the parents stated that they knew the normal body temperature range, and 61.2% identified a temperature of ≥38°C as fever. The proportion of parents who reported feeling concerned when their child's temperature reached ≥38°C was 55.3% (Table 2).

An examination of parental attitudes toward high fever revealed that 38.5% had previously received education on this topic. When their child had a fever, 75.8% reported removing the child's clothing, 58.7% gave the child a lukewarm bath, and 58.7% administered an antipyretic medication. The proportion of parents who stated that they would wipe their child's body with vinegar water as an intervention was 15.2%.

In addition, 68.6% of the parents reported measuring their child's temperature every 15 minutes during febrile episodes, and 64.6% stated that they recorded the temperature measurements. Regarding febrile seizures, 36% of the parents reported having knowledge of the appropriate actions to take; 67.1% indicated that they would take their child to the nearest healthcare facility, 37% stated that they would call emergency services (112), and 22.4% reported that they would place the child in a position that ensured airway patency. Moreover, 68.3% of the parents reported remaining at their child's bedside to monitor them during febrile episodes (Table 3).

Regarding the use of antipyretic medications, 52.2% of the parents administered them according to a physician's prescription. A total of 93.8% of the participants reported reading the medication package insert, and 80.4% stated that they reviewed the storage instructions. Antipyretics were stored at room temperature (<25°C) by 62.1% of the parents.

Regarding the duration of use after opening, 35.7% of the parents used the medication for up to 1 month, 30.7% used it until it was finished, and 7.2% continued to use it until its expiration date. Overall, 48.4% stated that they administered medications strictly in accordance with physician recommendations.

Table 1: Characteristics of the child and parents

	n	%
Data pertaining to the child		
Age (min–max) = 6 month-6 years), Median±SD	2.7±1.49	
Gender		
Girl	186	57.76
Boy	136	42.24
Weight		
3–6 weight	28	8.7
7–12 weight	147	45.7
13–20 weight	89	27.6
21–30 weight	58	18.0
History of febrile illness		
Yes	122	37.9
No	200	62.1
History of seizures		
Yes	45	14.0
No	277	86.0
Parental characteristics		
Participating parent		
Mother	208	64.3
Father	115	35.7
Parental age		
18–24	23	7.1
25–30	101	31.4
31–40	166	51.6
41–45	32	9.9
Parental education level		
Illiterate	2	0.6
Primary education	135	41.9
High school	112	34.8
Parental occupation		
Undergraduate and graduate	73	22.6
Worker	123	38.2
Officer	40	12.4
Not working	159	49.4
Total	**322**	**100**

Min: Minimum; Max: Maximum; SD: Standard deviation.

Regarding the temperature threshold for antipyretic use, 64.3% of the parents reported administering medication at ≥38°C. The most frequently used antipyretic was paracetamol (57.5%), followed by the alternating use of paracetamol and ibuprofen (14.6%). The most commonly reported dosing frequency was every 4 hours (65.2%) (Table 4).

Table 2: Distribution of parental practices regarding fever

		n	%
Responses to the question: "how do you recognize when your child has a fever?"*	If the body feels warmer than usual	**200**	**62.1**
	By touching the skin	105	32.6
	If the hands and feet feel cold	92	28.6
	If he is still cold even though he is covered	53	16.5
	By observing the child's overall appearance	41	12.7
Practice of measuring the child's temperature when fever is suspected	Yes	**313**	**97.2**
	No	9	2.8
Preferred device for measuring fever	With an ear (tympanic) digital thermometer	51	15.8
	With an axillary digital thermometer	**237**	**73.6**
	With a forehead (temporal) thermometer	27	8.4
	With a mercury thermometer (axillary, rectal, or oral use)	7	2.2
Preferred site for temperature measurement when fever is suspected	Axillary	**234**	**72.7**
	Oral	13	4.0
	Rectal	6	1.9
	Ear (tympanic)	39	12.1
	Forehaad (temporal)	30	9.3
Respondents who report knowing the normal limits of body temperature	Yes	**301**	**93.5**
	No	21	6.5
Knowledge of high fever thresholds	≥36°C	23	7.1
	≥37°C	57	17.7
	≥38°C	**197**	**61.2**
	≥39°C	45	14
Fever threshold of concern	≥37°C	38	11.8
	≥38°C	178	55.3
	≥39°C	106	32.9
Total		**322**	**100**

*: Multiple responses selected.

In addition, 47.8% of the parents reported being aware of the potential side effects of the antipyretics they used. The most frequently reported side effects were rash (36.4%) and vomiting (34.4%). In the event of side effects, 85.5% of the parents stated that they would take their child to a healthcare facility (Table 5).

The study found no statistically significant association ($p>0.05$) between a child's history of febrile illness and the following variables: parental concern about fever, frequency of temperature measurement, knowledge of the normal temperature range, perception of high fever thresholds, thresholds for concern, education on fever management, knowledge of febrile seizure management, storage duration of opened medication, review of package inserts and storage instructions, or awareness of medication side effects.

However, a statistically significant association ($p<0.05$) was found between a child's history of febrile illness and the parents' practice of recording temperature measurements during febrile episodes (Table 6).

DISCUSSION

The primary aim of this study was to determine how parents assess fever in their children, which temperature measurement methods they prefer, their level of knowledge about fever, their attitudes toward febrile conditions, their interventions during febrile episodes, and their practices regarding the use of antipyretic medications. In our study, 97.2% of the parents reported measuring their child's temperature when they felt that the child's body was warmer than normal, and

Table 3: Parents' attitudes and practices in response to high fever

		n	%
Status of having received education on the management of high fever	Yes	124	38.5
	No	198	61.5
Initial ınterventions when the child develops a fever*	I remove excess clothing	244	75.8
	I give a lukewarm bath / apply lukewarm compresses	189	58.7
	I administer an antipyretic	189	58.7
	I seek medical care / visit a healthcare facility	127	39.4
	I encourage increased fluid intake	65	20.2
	I wipe the body with vinegar water	**49**	**15.2**
	I cool the room	39	12.1
Frequency of temperature reassessment when high fever ıs detected	Every 15 minutes	**221**	**68.6**
	Every 30 minutes	19	5.9
	Every 60 minutes	71	22
	Every 2 hours or more	11	3.4
Status of recording the child's temperature during febrile episodes	Yes	**208**	**64.6**
	No	114	35.4
Knowledge of seizure management in children	Yes	**116**	**36**
	No	206	64
Actions to take ıf the child has a seizure*	Take the child to the nearest healthcare facility	**216**	**67.1**
	Place the child in a bath	126	39.1
	Call emergency services (112)	120	37.3
	Position the child to ensure airway patency and facilitate breathing	**72**	**22.4**
	Splash water on the child's face	71	22.0
	Try to keep the child's mouth open	49	15.2
	Attempt to administer an antipyretic	38	11.8
	Try to give fluids and put the child to sleep	45	14
Nighttime monitoring practices when the child has a fever	Stay by the child's side	**220**	**68.3**
	Monitor temperature every 30 minutes throughout the night	88	27.3
	Check every 3–4 hours and administer medication as needed	9	2.8
	Take the child to the emergency department	5	1.6
Total		322	100

*: Multiple responses selected.

73.6% stated that they used a digital axillary thermometer for this purpose. A study conducted by Sağer et al.[20] in Türkiye, which examined fever management practices over the past decade, similarly reported a preference for digital thermometers for measuring body temperature in children. The NICE 2022 guidelines also recommend measuring body temperature in children aged between 4 weeks and 5 years using an electronic thermometer in the axilla, a chemical thermometer, or an infrared tympanic thermometer.[21]

In this study, 75.5% of the parents considered a body temperature >38°C to indicate fever, and 55.3% reported feeling concerned at this threshold. Similarly, studies in the literature have found that parents generally define fever as a temperature between 37.7°C and 38.6°C. [6,8,10] The CDC defines fever as a body temperature >38.0°C. [2] While most parents in our study demonstrated perceptions of fever consistent with the literature, it is noteworthy that 24.2% considered body temperatures <37°C to indicate fever, suggesting a considerable level of misconception. This misconception may lead to unnecessary anxiety and inappropriate management approaches, highlighting the need for more comprehensive parental education regarding the correct definition and management of fever.

Our findings also showed that parents were primarily concerned about febrile seizures (90.4%), followed by concerns about brain

Table 4: Parental attitudes toward antipyretic use

		n	%
Attitudes toward antipyretic medication use	Administer according to a doctor's prescription	**168**	**52.2**
	Give medication previously prescribed during an earlier febrile episode	111	34.5
	Administer medication recommended by a pharmacist	4	1.2
	Give medication recommended by relatives or acquaintances	6	1.9
	Administer whichever antipyretic medication is available at home	33	10.2
Storage conditions for antipyretic medication	On a refrigerator shelf/door	122	37.9
	At room temperature below 25°C / In a medicine cabinet	**200**	**62.1**
Storage duration of an opened antipyretic medication	Until the medication is finished	99	30.7
	1–3 weeks	76	23.6
	One month	**115**	**35.7**
	Three months	9	2.8
	Until the expiration date	23	7.2
Rate of reading medication package inserts	Yes	**302**	**93.8**
	No	20	6.2
Rate of reading medication storage instructions	Yes	**259**	**80.4**
	No	63	19.6
Interval for administering antipyretic medication	According to the doctor's recommendation	**156**	**48.4**
	Every 4 hours	126	39.1
	According to the interval stated in the medication package insert	23	7.1
	Whenever I perceive the child's temperature to be elevated	17	5.4
Temperature threshold for administering antipyretics	≥37°C	70	21.7
	≥38°C	**207**	**64.3**
	≥39°C	40	12.4
	≥40°C	5	1.6
Rate of the most commonly used antipyretic	Parasetamol	**185**	**57.5**
	İbuprofen	56	17.4
	Paranox+Paranox S	20	6.2
	Aferin	13	4
	Parasetamol ve ibuprofen karışık	48	14.9
	Aspirin	**0**	**0.0**
Interval of antipyretic administration	Every 1–3 hours	24	7.5
	Every 4 hours	**210**	**65.2**
	2–3 times per day	88	77.3
Total		322	100

damage (58.7%) and death (34.2%) during febrile illnesses. Similar findings have been reported in previous studies, which noted that mothers frequently feared febrile seizures and even the possibility of death during episodes of fever.[8,14,20,22,23] In this study, no statistically significant association was found between the parents' age or educational level and their level of anxiety about fever, which is consistent with findings reported in the literature.[23]

In this study, 75.8% of the parents reported that their first intervention during a febrile episode was to remove their child's clothing, 58.7% stated that they gave their child a lukewarm bath, and the same proportion reported administering an antipyretic medication. Similar to our findings, studies in the literature indicate that parents typically remove their child's clothing first, followed by giving a lukewarm bath or applying a compress and administering an antipyretic medication.[6,8,10,24] In this study, 15.2% of the parents reported wiping their child's body with vinegar water to reduce fever. Sert et al.[10] similarly reported that, although at a lower rate, some mothers used alcohol- or vinegar-based solutions to reduce fever.

Table 5: Parents' knowledge regarding the adverse effects of antipyretic drugs

		n	%
Knowledge of the side effects of antipyretic medications	Yes	**154**	**47.8**
	No	168	52.2
Actions to take when experiencing side effects of antipyretic medications	I do not know	22	6.8
	Take the child to a healthcare facility	**276**	**85.7**
	Call emergency services (112)	24	7.5
Total		322	100
Side effects*	Rash	**56**	**36.4**
	Vomiting	**53**	**34.4**
	Drowsiness	**12**	**7.8**
	Dizziness	9	5.9
	Fatigue	7	4.5
	Diarrhea	6	3.9
	Respiratory distress	7	4.5
	Hallucinations	4	2.6
Total		**154**	**100**

*: Open-ended responses on side effects from parents reporting knowledge of side effects.

The NICE 2021 guidelines do not recommend the use of lukewarm compresses because they can cause peripheral vasoconstriction, agitation, and shivering.[17] Instead, the guidelines recommend ensuring that children are not overdressed and that antipyretics are administered based on the child's general condition.[25,26] These findings demonstrate that some parents continue to resort to non-evidence-based and potentially harmful practices.

In this study, 68.6% of the parents reported measuring their child's temperature every 15 minutes, while 64.9% stated that they recorded body temperature measurements. Additionally, 68.3% of the parents reported remaining at their child's bedside throughout the night during febrile episodes. This frequent monitoring and overnight bedside observation reflect high levels of parental anxiety and concern during febrile illnesses, which may lead to excessive vigilance, unnecessary interventions, and disrupted sleep routines.

Regarding attitudes toward antipyretic use during febrile episodes, 52.2% of the parents reported administering medications according to a physician's prescription, 64.3% reported giving antipyretics at temperatures >38°C, and 65.2% administered them every 4 hours. Although the rate of appropriate medication practices was generally high, the remaining proportions indicate that inappropriate use continues to be a significant issue. Clinical guidelines recommend the use of antipyretics based on the child's overall condition rather than a specific temperature threshold; however, in practice, physicians often prescribe antipyretics at temperatures ranging from 37°C to 40.5°C.[21,27]

The most commonly used antipyretic medication was paracetamol (57.5%), followed by ibuprofen (17.4%) and alternating paracetamol and ibuprofen (14.4%). Similar findings have been reported in the literature, showing that paracetamol is most frequently selected as the first-line treatment.[14,23,24,27] A study by Charde et al.,[28] conducted among children aged 6 months to 18 years, demonstrated that paracetamol, ibuprofen, and combinations of the two were equally effective in alleviating fever- and pain-related symptoms over 48 hours. Furthermore, the study reported that the combined use of paracetamol and ibuprofen resulted in a longer fever-free period over 48 hours than the use of either medication alone. However, both the NICE 2019 guidelines and the Italian Pediatric Society guidelines do not recommend alternating or combining two different antipyretics in children younger than 5 years.[29,30] Similarly, a meta-analysis conducted by Trippella et al.,[31] which included 9 studies and 2,026 children, concluded that there was insufficient evidence to support the combined or alternating use of antipyretics over monotherapy, emphasizing the importance of adherence to established clinical guidelines.

A systematic review conducted by Arias et al.[13] examined 36 studies on parental management of childhood fever and found that, in 29 of these studies, parents most frequently relied on the experiences of friends and family. However, because these sources often contain inaccurate or outdated information, they may contribute to inappropriate practices and exacerbate fever phobia, emphasizing the importance of providing parents with accurate and up-to-date education on fever management. Physicians were also reported to be a primary source of both written and verbal information.

In this study, no statistically significant differences were found between a child's history of febrile illness and parental anxiety levels, antipyretic preferences, knowledge of medication side effects, or frequency of temperature measurement. However, a significant association was observed between a child's previous febrile illness and the parents' practices of monitoring and recording

Table 6: Distribution of knowledge on febrile illnesses by the child's febrile illness history

		History of febrile illness				χ^2	p
		Yes		No			
		n	%	n	%		
A child's fever ıs a cause for concern	Yes	117	95.9	191	95.5	0.029	0.864
	No	5	4.1	9	4.5		
Practice of measuring the child's temperature when fever occurs	Yes	121	99.2	192	96.0	2.821	0.093
	No	1	.8	8	4.0		
High fever threshold	≥36°C	11	9.0	12	6.0	2.154	0.708
	≥37°C	23	18.9	34	17.0		
	≥38°C	74	60.7	123	61.5		
	≥39°C	12	9.8	25	12.5		
	≥40°C	2	1.6	6	3.0		
Fever threshold of concern	≥37°C	19	15.6	19	9.5	3.056	0.383
	≥38°C	63	51.6	115	57.5		
	≥39°C	33	27.0	52	26.0		
	≥40°C	7	5.7	14	7.0		
Recording the child's temperature when fever occurs	Yes	71	58.2	137	68.5	3.517	**0.040***
	No	51	41.8	63	31.5		
Storage conditions of opened antipyretic medication	Until the medication is finished	37	30.3	62	31.0	2.442	0.655
	1–3 weeks	27	22.1	49	24.5		
	1 month	42	34.4	73	36.5		
	3 months	5	4.1	4	2.0		
	Until the expiration date	11	9.0	12	6.0		
Practice of reading medication package inserts	Yes	113	92.6	189	94.5	0.458	0.498
	No	9	7.4	11	5.5		
Practice of reading medication storage instructions	Yes	100	82.0	159	79.5	0.293	0.588
	No	22	18.0	41	20.5		

χ^2: Pearson Chi-Square (Fischer test).

temperature measurements ($p<0.05$). This finding suggests that previous experiences with febrile illnesses may positively influence systematic monitoring behaviors, such as tracking and documenting febrile episodes.

According to our findings, no significant association was found between a mother's educational level and her knowledge of the normal temperature range, antipyretic preferences, review of medication package inserts, or knowledge of potential side effects ($p>0.05$). This result suggests that mothers, regardless of their educational level, have similar levels of knowledge and attitudes toward fever management and antipyretic use. This finding indicates that educational programs on fever management should be planned not only for a specific educational group but for all mothers.

Limitations

This study was conducted in a pediatric emergency department setting among parents of children aged 6 months to 6 years. Given that emergency departments are inherently high-stress environments, parents' anxiety levels may have been elevated, potentially influencing their reported behaviors and attitudes. Future

research conducted in calmer, less stressful environments could provide a more objective assessment of parents' knowledge and attitudes and make an important contribution to the field.

CONCLUSION

This study provides valuable insights into how parents assess fever in their children, their preferred methods of temperature measurement, their knowledge and attitudes toward fever, their interventions during febrile episodes, and their antipyretic medication practices. Although most parents measured body temperature using evidence-based methods and identified a temperature of ≥38°C as fever, a considerable proportion incorrectly considered temperatures <37°C to indicate fever, and anxiety regarding severe fever-related complications remained high. These findings highlight the need for accurate, evidence-based educational programs to address misinformation and inappropriate practices in fever management.

The use of non-evidence-based methods, such as wiping the child with vinegar water, further underscores the importance of guidance from healthcare professionals. Although most parents generally demonstrated appropriate practices regarding fever monitoring, recording, and antipyretic use, inappropriate dosing and excessive interventions remain areas of concern. The association between previous experiences with febrile illnesses and improved monitoring practices suggests that real-life experiences may positively influence certain parental behaviors. The limited influence of educational level on knowledge and attitudes emphasizes the need for fever management education programs to reach all demographic groups.

In conclusion, comprehensive educational initiatives designed to improve parental knowledge, attitudes, and practices regarding fever should be implemented in objective and supportive environments outside high-stress emergency settings. Promoting adherence to current evidence-based guidelines may help reduce unnecessary healthcare visits and harmful practices, ultimately protecting children's health and alleviating the burden on healthcare systems.

Statement

Ethics Committee Approval: The study was approved by Istanbul Medipol University Non-Interventional Ethics Committee (No: 149, Date: 09.03.2016).

Informed Consent: The study was conducted with parents who presented during daytime working hours (08:00–16:00) and provided both verbal and written informed consent.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Breastfeeding beyond infancy: Are the barriers too hard to overcome, even for physicians?

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ABSTRACT

Objective: The World Health Organization (WHO) recommends continued breastfeeding up to two years of age and beyond. However, breastfeeding beyond infancy remains uncommon and is often hindered by cultural barriers and misconceptions. Physicians play a crucial role in guiding families on infant feeding practices; yet, limited evidence exists regarding their knowledge and attitudes toward breastfeeding beyond two years. This study aimed to evaluate the knowledge and attitudes of physicians from different specialties toward breastfeeding beyond two years and to identify factors influencing their awareness and counseling practices.

Material and Methods: This multicenter, descriptive, cross-sectional study was conducted in four hospitals among physicians working in pediatrics, family medicine, obstetrics and gynecology, and other clinical specialties. Data were collected using a face-to-face structured questionnaire assessing demographic characteristics, personal breastfeeding experience, knowledge of WHO recommendations, perceived benefits and challenges of extended breastfeeding, and counseling behaviors. Data were analyzed using descriptive statistics and chi-square tests.

Results: Although 95.9% of participants correctly identified the WHO recommendation for exclusive breastfeeding, only 17.9% accurately recognized the total recommended duration of breastfeeding. Knowledge levels were significantly higher among pediatricians and family physicians and among those who frequently provided breastfeeding counseling. While 90% of pedodontists believed that extended breastfeeding could contribute to dental caries, most physicians remained uncertain about its protective effects on maternal health. Only 19.9% reported recommending breastfeeding beyond two years. Both knowledge and attitudes varied significantly across medical specialties.

Conclusion: Physicians' knowledge and attitudes toward breastfeeding beyond two years were limited. Integrating evidence-based breastfeeding education into medical curricula, residency programs, and continuing professional training may strengthen physicians' ability to support mothers who breastfeed beyond infancy.

Keywords: Baby-friendly hospital initiative, breastfeeding beyond two years, breastfeeding education, extended breastfeeding, maternal and child health.

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INTRODUCTION

The World Health Organization (WHO) recommends exclusive breastfeeding for the first six months of life and continued breastfeeding until two years of age or beyond.[1] Although many countries, including Türkiye, endorse these recommendations, breastfeeding rates at two years vary widely across regions—reported as 88% in Bangladesh, 72% in India, 7% in China, and 32% in Türkiye.[2–5]

The benefits of exclusive breastfeeding during the first six months are well established. Moreover, growing evidence highlights the positive impact of prolonged breastfeeding on the health of both the mother and the child.[6] Longitudinal studies have shown that the concentrations of protective components such as lysozyme, lactoferrin, and secretory immunoglobulin A increase over time in breast milk beyond the first year.[7–9] Additionally, neurotrophic growth factors supporting neurological development remain present after the first year.[10]

All healthcare professionals in contact with the mother–baby dyad, especially pediatricians, play a crucial role in the initiation and continuation of breastfeeding; therefore, they must be well educated about breastfeeding and act as advocates for it.[6,11] However, physicians may hold differing attitudes toward breastfeeding beyond two years, and insufficient professional support can contribute to early cessation. Mothers may also perceive that healthcare providers disapprove of or lack knowledge about breastfeeding beyond infancy, which may discourage them from seeking professional guidance.[12]

Although the WHO recommends breastfeeding up to two years and beyond, the concept of extended breastfeeding—defined as breastfeeding beyond 12 months—has not yet been fully embraced by healthcare professionals. This attitude among healthcare workers has, at times, led mothers to conceal the duration of their breastfeeding practices, a phenomenon referred to as "closet nursing".[6,13]

Studies examining healthcare workers' attitudes toward the duration of breastfeeding remain limited.[11,14] Therefore, this study aimed to evaluate physicians' knowledge, attitudes, and practices regarding breastfeeding beyond two years.

MATERIALS AND METHODS

Study Design

This multicenter, cross-sectional study was conducted in Istanbul, Türkiye, over a two-month period between February and March 2020. The study protocol was approved by the Kartal Lütfi Kırdar Training and Research Hospital ethics committee (Protocol No: 2020/514/172/12). Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Setting and Sample

The study population included specialists in pediatrics, obstetrics and gynecology, family medicine, internal medicine, child and adolescent psychiatry, and pedodontics who frequently counsel breastfeeding mothers. The study was conducted in the outpatient clinics of two university hospitals and two training hospitals. The inclusion criteria were being a physician from one of the listed specialties and actively practicing in the outpatient setting of the participating hospitals.

Table 1: Demographic characteristics and breastfeeding experiences of the physicians

Demographic characteristics (n=241)	n (%)
Gender	
Female	171 (71)
Age, years	
Mean±SD / Median (min-max)	31±7.1 / 28 (23–64)
Institution	
University hospital	136 (56.4)
Training and research hospital	105 (43.5)
Work experience	
0–2 years	69 (28.6)
3–5 years	93 (38.6)
6–10 years	38 (15.8)
11–15 years	14 (5.8)
16–20 years	13 (5.4)
>20 years	14 (5.8)
Parenthood	
Yes	66 (27.4)
Speciality	
Pediatrics	70 (29)
Obstetrics&gynecology	37 (15.4)
Family medicine	34 (14.1)
Child and adolescent psychiatry	30 (12.4)
Internal medicine	28 (11.6)
Pedodontics	42 (17.4)
Breastfeeding advice frequency (n=235)	
Every day	57 (24.3)
2–3 times a week	59 (25.1)
Once a week	17 (7.2)
Once every two weeks	10 (4.2)
Once a month	30 (12.8)
Less	62 (26.4)

SD: Standard deviation; Min: Minimum; Max: Maximum.

A sample size of 240 participants was calculated to provide 95% power (effect size=0.304, α=0.05) based on the study by Baranowska et al.[14]

Outcome Measures and Data Collection

A structured questionnaire was developed by the researchers based on relevant literature and reviewed by social pediatricians and breastfeeding specialists.[14–17] The questionnaire included 24 items assessing demographics, personal breastfeeding experience, and physicians' knowledge and attitudes toward breastfeeding beyond two years.

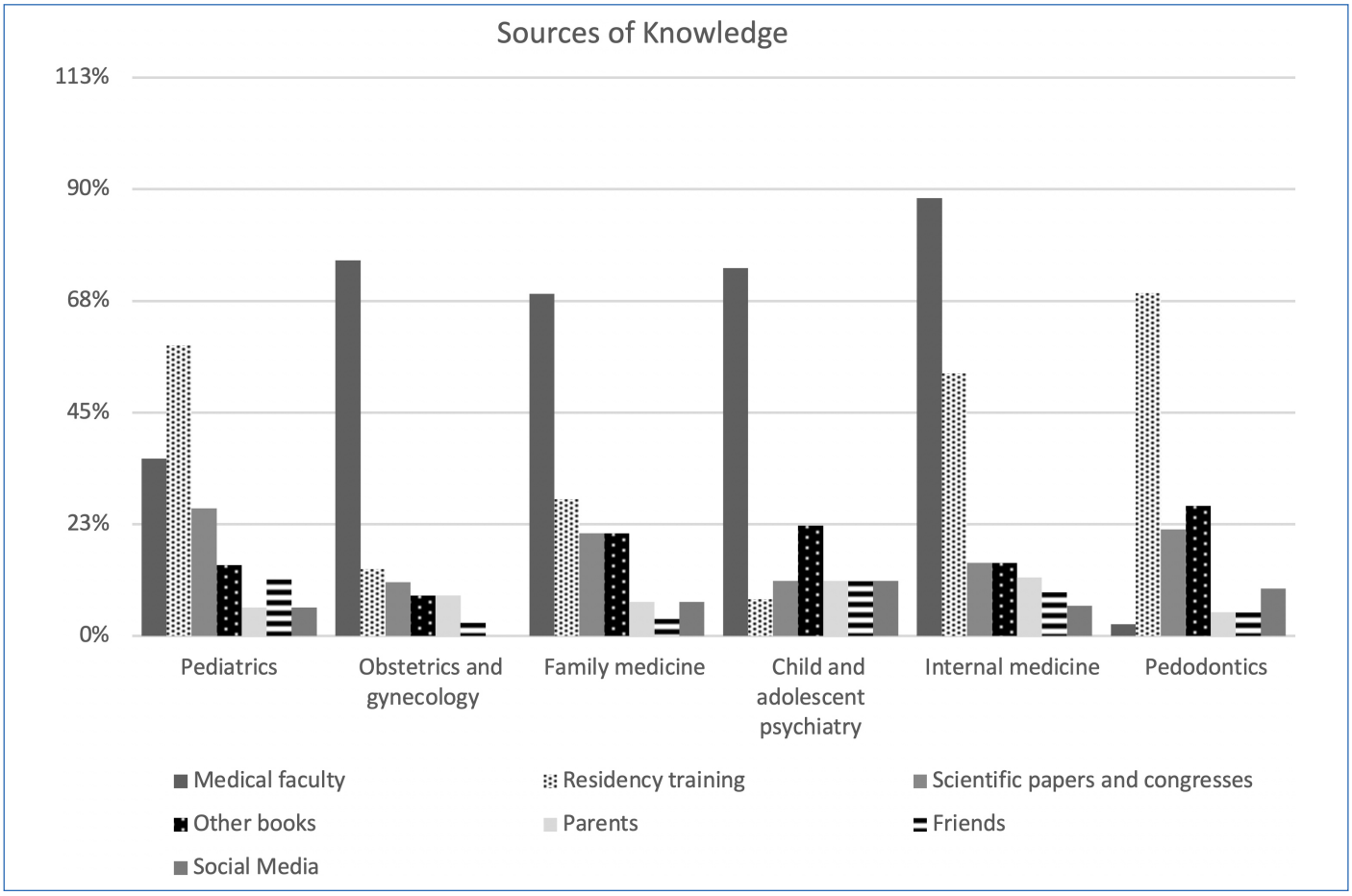

Figure 1: Sources of knowledge about breastfeeding.

Ten items addressed demographic and social characteristics. Two questions evaluated personal experience, including the longest breastfeeding duration for one's own child and the frequency of providing breastfeeding counseling in clinical practice. Knowledge was assessed through four questions covering the WHO recommendations for exclusive breastfeeding duration (EBD) and total breastfeeding duration (TBD), sources of information about breastfeeding beyond two years, and awareness of their institution's "Baby-Friendly Hospital (BFH)" status.

Attitudes were evaluated through eight questions: two addressed physicians' recommendations regarding weaning time and breastfeeding beyond two years in healthy mother–infant dyads, while the remaining six used a five-point Likert scale (strongly agree, agree, undecided, disagree, strongly disagree) to assess beliefs about the effects of breastfeeding beyond two years on mother–infant attachment, dental caries, sleep problems, appetite, maternal breast and ovarian cancer risk, and the child's later obesity risk.

Unanswered questions were considered missing data. Physicians were visited in their outpatient clinics and asked to complete the questionnaire, which required approximately seven minutes. After completion, participants were informed about WHO recommendations and the dose-dependent effects of breastfeeding duration.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population. Relationships between categorical variables were analyzed using Fisher's exact test, Yates' correction test, or Pearson's chi-square test, as appropriate. A p-value<0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 20.0; IBM Corp., Armonk, NY, USA, 2010).

RESULTS

A total of 241 voluntary physicians completed the questionnaire. The median age was 28 years (range: 23–64 years), and 71% were female. Sixty-six participants (27%) had at least one child. Fifty-three physicians (22%) had personal breastfeeding experience: 20.8% (n=11) breastfed for less than 12 months, 43.4% (n=23) breastfed for 12–24 months, and 35.8% (n=19) breastfed beyond two years. The demographic characteristics and breastfeeding experience of participants are summarized in Table 1.

Among the participants, 231 (95.9%) correctly identified the WHO recommendation for EBD. However, only 17.9% correctly recognized the WHO recommendation for TBD as two years or beyond. Knowledge of recommended TBD was higher among

Table 2: Physicians knowledge about breastfeeding

	Participants							p
	Total (n=241) n (%)	Pediatrics (n=70) n (%)	Obstetrics gynecology (n=37) n (%)	Family medicine (n=34) n (%)	Child & adolescent psychiatry (n=30) n (%)	Internal medicine (n=28) n (%)	Pedodontics (n=42) n (%)	
Knowledge of the WHO definition regarding EBD								0.098
Yes	**231(95.9)**	67 (95.7)	37 (100)	34 (100)	29 (100)	26 (92.8)	38 (92.4)	
No	**10 (4.1)**	3 (4.3)	0 (0)	0 (0)	0 (0)	2 (7.2)	4 (7.6)	
Knowledge of the WHO definition regarding TBD								**0.008**
Yes	**43 (17.9)**	20 (46.5)	5 (11.6)	9 (20.9)	1 (2.3)	1 (2.3)	7 (16.3)	
No	**197 (82.1)**	50 (25.4)	32 (16.2)	25 (12.7)	28 (14.2)	27 (13.7)	35 (17.8)	
Sources of the knowledge on breastfeeding beyond two years								
Medical/dentistry faculty	**124 (51.9)**	25 (35.7)	28 (75.7)	30 (88.2)	20 (69)	20 (74.1)	1 (2.4)	**<0.001**
Residency training	**103 (43.1)**	41 (58.6)	5 (13.5)	18 (52.9)	8 (27.6)	2 (7.4)	29 (69)	**<0.001**
Scientific papers and congresses	**45 (18.8)**	18 (25.7)	4 (10.8)	5 (14.7)	6 (20.7)	3 (11.1)	9 (21.4)	0.368
Awareness of the institutions' BFH status								**<0.001**
Aware	**165 (69)**	67 (98.5)	35 (94.6)	25 (73.5)	21 (70)	16(57.1)	1 (2.4)	
Not aware	**74 (31)**	1 (1.5)	2 (5.4)	9 (26.5)	9 (30)	12 (42.9)	41 (97.6)	

WHO: World Health Organization; EBD: Exclusive breastfeeding duration; TBD: Total breastfeeding duration; BFH; Baby friendly hospital.

pediatricians (46.5%) and family physicians (20.9%) (p=0.008). Knowledge of TBD was higher among pediatricians (46.5%) and family physicians (20.9%) (p=0.008), as well as among physicians who provided breastfeeding counseling daily or two to three times per week (34.9% and 44.2%, respectively) compared with those who counseled once a month or less (7% and 7%, respectively) (p=0.001).

Regarding sources of knowledge, the proportion of physicians reporting medical or dental school as their primary source was lower among pedodontists and pediatricians (p<0.001), whereas those reporting residency training as their main source were more common among pedodontists, pediatricians, and family physicians (p<0.001). The sources of physicians' breastfeeding knowledge are presented in Figure 1.

Except for pedodontics clinics, all participating departments had been certified as Baby-Friendly Hospitals (BFHs). A total of 165 participants (69%) were aware of whether their institution held BFH status, with significant differences observed between specialties (p<0.001). Physicians' awareness of BFH certification is shown in Table 2.

The most frequently recommended weaning period across all specialties was 12–24 months (p=0.001). Only 19.9% of physicians recommended breastfeeding beyond two years. Six Likert-type questions were used to evaluate attitudes toward breastfeeding beyond two years. Ninety percent of pedodontists agreed or strongly agreed that prolonged breastfeeding could cause dental caries in infants (p<0.001), while most physicians were undecided about its potential protective effect against maternal breast and ovarian cancer (p=0.048). Physicians' attitudes toward extended breastfeeding are presented in Table 3.

DISCUSSION

Although the vast majority of participating physicians (95.9%) were aware of the WHO recommendation regarding EBD, only 17.9% correctly identified the recommended TBD, indicating a significant knowledge gap. The higher rates of accurate knowledge among pediatricians and family physicians suggest that medical specialty may influence familiarity with breastfeeding guidelines. Moreover, physicians who provided breastfeeding counseling more frequently

Table 3: Physicians attitudes toward extended breastfeeding

	Total (n=241) n (%)	Pediatrics (n=70) n (%)	Obstetrics gynecology (n=37) n (%)	Family medicine (n=34) n (%)	Child & adolescent psychiatry (n=30) n (%)	Internal medicine (n=28) n (%)	Pedodontics (n=42) n (%)	p
Breastfeeding recommendation beyond 2 years								0.322
Yes	48 (19.9)	23 (33.8)	6 (16.2)	11 (32.3)	0 (0)	3 (11.1)	5 (11.9)	
No	172 (71.4)	41 (60.2)	25 (67.5)	20 (58.8)	28 (96.5)	22 (81.4)	36 (85.7)	
Pumped milk	17 (7.1)	4 (5.8)	6 (16.2)	3 (8.8)	1 (3.4)	2 (7.4)	1 (2.3)	
Breastfeeding recommendation on weaning time								**0.001**
12 months	15 (6.4)	0 (0)	3 (8.1)	0 (0)	1 (3.3)	3 (10.7)	8 (19)	
12–24 months	181 (76.7)	48 (72.7)	31 (83.8)	26 (78.8)	27 (90)	1 (67.9)	30 (71.4)	
>24 months	40 (16.9)	18 (27.3)	3 (8.1)	7 (21.2)	2 (6.7)	6 (21.4)	4 (9.5)	
Breastfeeding beyond two years may have a negative effect on mother-infant attachment								0.110
Strongly agree	27 (11.3)	8 (11.8)	6 (16.2)	2 (5.9)	2 (6.7)	1 (3.6)	8 (19.1)	
Agree	77 (32.2)	13 (19.1)	12 (32.5)	11 (32.4)	16 (53.3)	13 (46.4)	12 (28.6)	
Undecisive	76 (31.8)	25 (36.8)	10 (27)	13 (38.2)	8 (26.7)	6 (21.4)	14 (33.3)	
Disagree	49 (20.5)	16 (23.5)	8 (21.6)	5 (14.7)	4 (13.3)	8 (28.6)	8 (19)	
Strongly disagree	10 (4.2)	6 (8.8)	1 (2.7)	3 (8.8)	0 (0)	0 (0)	0 (0)	
Breastfeeding beyond two years may cause dental carries in infant								**<0.001**
Strongly agree	30 (12.6)	5 (7.4)	1 (2.7)	2 (5.9)	1 (3.33)	2 (7.1)	19 (45.2)	
Agree	55 (23)	11 (16.2)	6 (16.2)	3 (8.8)	10 (33.3)	6 (21.4)	19 (45.2)	
Undecisive	66 (27.6)	19 (27.9)	15 (40.6)	12 (35.3)	9 (30)	10 (35.7)	1 (2.4)	
Disagree	74 (31)	27 (39.7)	13 (35.1)	13 (38.2)	8 (26.7)	10 (35.7)	3 (7.1)	
Strongly disagree	14 (5.6)	6 (8.8)	2 (5.4)	4 (11.8)	2 (6.7)	0 (0)	0 (0)	
Breastfeeding beyond two years may cause sleep problems in infant								0.101
Strongly agree	30 (12.6)	11 (16.2)	3 (8.1)	3 (8.8)	4 (13.3)	2 (7.4)	7 (16.7)	
Agree	78 (32.8)	22 (32.4)	10 (27)	6 (17.7)	12 (40)	9 (33.3)	19 (45.2)	
Undecisive	80 (33.6)	17 (25)	13 (35.1)	16 (47.1)	6 (20)	13 (48.2)	15 (35.7)	
Disagree	35 (14.7)	13 (19.1)	9 (24.3)	5 (14.7)	6 (20)	2 (7.4)	0 (0)	
Strongly disagree	15 (6.3)	5 (7.3)	2 (5.4)	4 (11.7)	2 (6.7)	1 (3.7)	1 (2.4)	

Table 3 (cont): Physicians attitudes toward extended breastfeeding

	Total (n=241) n (%)	Pediatrics (n=70) n (%)	Obstetrics gynecology (n=37) n (%)	Family medicine (n=34) n (%)	Child & adolescent psychiatry (n=30) n (%)	Internal medicine (n=28) n (%)	Pedodontics (n=42) n (%)	p
Breastfeeding beyond two years may cause appetite problems in infant								0.131
Strongly agree	35 (14.6)	12 (17.7)	5 (13.5)	2 (5.9)	4 (13.3)	5 (17.9)	7 (16.7)	
Agree	96 (40.1)	26 (38.2)	15 (40.5)	11 (32.3)	11 (36.7)	12 (42.9)	21 (50)	
Undecisive	59 (24.7)	10 (14.7)	8 (21.6)	11 (32.3)	10 (33.3)	7 (25)	13 (30.9)	
Disagree	36 (15)	14 (20.6)	7 (18.9)	6 (17.6)	4 (13.3)	4 (14.2)	1 (2.4)	
Strongly disagree	13 (5.4)	6 (8.8)	2 (5.4)	4 (11.8)	1 (3.3)	0 (0)	0 (0)	
Breastfeeding beyond two years may decrease mammary and ovarian cancer risk in mother								**0.048**
Strongly agree	19 (7.9)	10 (14.7)	2 (5.4)	4 (11.7)	1 (3.33)	0 (0)	2 (4.7)	
Agree	60 (25.1)	20 (29.4)	10 (27)	9 (26.4)	12 (40)	7 (25)	2 (4.7)	
Undecisive	120 (50.2)	26 (38.2)	19 (51.3)	13 (38.2)	13 (43.3)	16(57.1)	33 (78.5)	
Disagree	36 (15)	9 (13.2)	6 (16.2)	7 (20.5)	4 (13.3)	5 (17.8)	5 (11.9)	
Strongly disagree	4 (1.6)	3 (4.4)	0 (0)	1 (2.9)	0 (0)	0 (0)	0 (0)	
Breastfeeding beyond two years may decrease risk of obesity in infant's later years.								0.781
Strongly agree	17 (7.1)	8 (11.8)	4 (10.8)	2 (5.9)	0 (0)	0 (0)	3 (7.1)	
Agree	33 (13.9)	12 (17.7)	4 (10.8)	9 (26.5)	4 (13.8)	2 (7.1)	2 (4.8)	
Undecisive	112 (47.1)	23 (33.8)	20 (54)	11 (32.3)	14 (48.3)	14 (50)	30 (71.4)	
Disagree	68 (28.6)	23 (33.8)	8 (21.6)	11 (32.3)	9 (31)	11 (39.3)	6 (14.3)	
Strongly disagree	8 (3.3)	2 (2.9)	1 (2.7)	1 (2.9)	2 (6.9)	1 (3.6)	1 (2.4)	

demonstrated significantly better knowledge, highlighting the positive impact of clinical engagement on awareness. Notably, while most physicians remained undecided about the long-term maternal health benefits of extended breastfeeding, 90% of pedodontists agreed or strongly agreed that breastfeeding beyond two years may lead to dental caries. These findings underscore the variation in knowledge and attitudes across specialties and emphasize the need for standardized, evidence-based breastfeeding education at both undergraduate and postgraduate levels.

In a study conducted among physicians (gynecologists, neonatologists) and midwives, only 5.9% of physicians had accurate knowledge of TBD, underlining the widespread lack of awareness.[14] The slightly higher rate (17.9%) in our study may be attributed to the higher proportion of pediatricians and family physicians among our participants; however, it remains unsatisfactory. Although there was no significant difference in EBD knowledge across specialties, pediatricians and family physicians were more familiar with TBD, possibly due to differences in educational sources and the frequency of applying their knowledge through counseling. Previous studies have shown that physicians acquire their breastfeeding knowledge from medical faculty, residency training, scientific meetings, publications, personal experience, and social media. These studies show medical faculty and residency training as sources of knowledge in 39–49.4% and 46.9–67% of physicians, respectively.[15,16] Consistent with these findings, 51.9% of participants in our study cited medical or dental school and 43.1% cited residency training as their primary knowledge sources.

All departments except pedodontics were certified as BFHs. Pediatricians and obstetricians were well aware of their hospital's BFH status, whereas awareness was lower among other specialties,

suggesting that breastfeeding education under the BFH initiative may not equally reach all professionals. Similarly, Yılmazbaş et al.[18] reported that many healthcare workers lacked proper breastfeeding training, with awareness varying significantly between professions.

A qualitative study on women's experiences with breastfeeding beyond infancy found that many perceived healthcare providers as disapproving of or uninformed about breastfeeding beyond infancy.[12] Studies have also shown that healthcare professionals often hold negative attitudes toward breastfeeding after the first year of life.[11,14] In a Polish study, only 15.7% of physicians recommended breastfeeding beyond two years,[14] compared with 19.9% in our study. Given the limited knowledge and ambivalent attitudes observed, our findings highlight the urgent need to reinforce the importance of breastfeeding beyond two years in both undergraduate and postgraduate medical education.

A review evaluating breastfeeding duration and infant–mother attachment reported a positive association between breastfeeding duration and infant–mother attachment, although all included studies involved durations shorter than two years.[19] Another study of 900 twin pairs found that secure attachment was more common among twins breastfed longer than their siblings.[20] The American Academy of Family Physicians and the American Academy of Pediatrics affirm that there is no evidence of psychological or developmental harm associated with breastfeeding into the third year of life or beyond.[21,22] Nevertheless, 60% of child psychiatrists in our study believed that breastfeeding beyond two years could negatively affect infant–mother attachment. No published evidence supports physicians' concerns regarding potential psychological or emotional harm; further research is warranted to examine this relationship.

There was also significant variation between specialties in attitudes toward the statement that breastfeeding beyond two years may cause dental caries. While 90% of pedodontists agreed with this statement, 49% of pediatricians disagreed. Early childhood caries are multifactorial and caused by complex mechanisms. One population-based cohort found an association between continued breastfeeding and early childhood caries but did not account for confounders such as night feeds or oral hygiene habits.[23] The International Association of Paediatric Dentistry recommends discontinuing night feeds after one year to prevent early childhood caries.[24] Further studies considering socioeconomic factors, oral hygiene practices, and dietary habits are required to clarify this relationship.

Among participants, 45.4% believed breastfeeding beyond two years may cause sleep problems, 54.7% thought it could lead to appetite issues, and 47.1% were undecided about its effect on reducing obesity risk later in life. While studies specifically evaluating breastfeeding beyond two years are lacking, previous research has demonstrated a dose-dependent relationship between breastfeeding duration and reduced risk of childhood obesity.[25,26] In a study assessing obesity in two- to three-year-old children, a significant difference was found between children breastfed for more than one year and those breastfed for less than 17 weeks.[27] Similarly, a dose-response relationship was found between being overweight and the duration of breastfeeding. Each additional month of breastfeeding was associated with a 4% reduction in overweight risk.[28] It is reasonable to hypothesize that this protective effect may extend beyond two years as well.

Study Limitations and Strengths

To our knowledge, this is the first multicenter study evaluating the knowledge, experience, and attitudes of physicians from various specialties—including pedodontists—toward breastfeeding beyond two years. The multicenter design increased the sample size, heterogeneity, and generalizability of the findings, which are key strengths. However, the study included only physicians; expanding future research to include midwives, nurses, and other healthcare professionals would provide a more comprehensive understanding of multidisciplinary perspectives on breastfeeding.

CONCLUSIONS

Physicians' knowledge and attitudes regarding breastfeeding beyond two years were found to be insufficient, with significant variation across specialties. Medical school curricula, residency programs, and institutional in-service training should be revised to ensure that all specialties receive standardized, evidence-based education on breastfeeding recommendations. Further longitudinal studies are warranted to examine the long-term effects of breastfeeding beyond two years on both maternal and child health and to support the implementation of WHO recommendations.

Statement

Ethics Committee Approval: The study was approved by Kartal Lütfi Kırdar Training and Research Hospital Ethics Committee (No: 2020/514/172/12, Date: 26.02.2020).

Informed Consent: Written informed consent was obtained from all participants before enrollment.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Assessment of parental knowledge, attitudes, and practices regarding rational antibiotic use in children under six with upper respiratory tract infections

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ABSTRACT

Objective: This study aimed to assess parental knowledge, attitudes, and practices regarding rational antibiotic use in children under six years of age with upper respiratory tract infections and to examine their associations with sociodemographic factors.

Material and Methods: A cross-sectional survey was conducted among 399 parents who presented to the Pediatric Emergency Department of Göztepe Training and Research Hospital between February and March 2019. The questionnaire comprised 12 knowledge, 5 attitude, and 3 practice items, and responses were evaluated in relation to sociodemographic characteristics and parents' awareness of media campaigns on rational antibiotic use.

Results: Parents demonstrated an overall correct response rate of 78%, with accuracy being highest for practice items (89.2%), followed by attitude (84.2%) and knowledge (72.7%) items. Higher educational attainment and household income were significantly associated with better scores, whereas parental age, number of children, and relationship to the patient were not. Although most parents recognized that isolated symptoms such as sore throat, ear pain, or fever do not require antibiotics, nearly half incorrectly believed that antibiotics are indicated for the common cold or purulent nasal discharge. Notably, substantial knowledge gaps persisted even among university-educated parents regarding the appropriate use of antibiotics in streptococcal pharyngitis. Awareness of media campaigns was associated with a modest improvement, equivalent to one additional correct response.

Conclusion: Parental knowledge gaps regarding antibiotic use in children remain substantial. Education and income were the strongest predictors of accurate knowledge and attitudes. Strengthening accessible, targeted public education initiatives, particularly for socioeconomically disadvantaged families, is essential to promote rational antibiotic use.

Keywords: Antibiotic, media, parent, upper respiratory tract infection.

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INTRODUCTION

Childhood represents a period during which antibiotic use is particularly prevalent. Although most upper respiratory tract infections (URTIs), such as nasopharyngitis, tonsillopharyngitis, and otitis media, are caused by viral pathogens, numerous studies from Türkiye and other countries have consistently demonstrated a high rate of unnecessary antibiotic prescribing for these conditions.[1–3] High parental expectations regarding antibiotic treatment during URTIs, along with the pressure exerted on physicians to prescribe antibiotics, further contribute to inappropriate antibiotic use in pediatric populations.[4,5]

Rational antibiotic use requires prescribing antimicrobials only when clinically indicated, at the correct dose, and for an appropriate duration.[6] In this context, parental knowledge, attitudes, and behaviors play a pivotal role, often shaping both treatment expectations and physicians' prescribing decisions. Therefore, identifying misconceptions, inappropriate practices, and factors driving unnecessary antibiotic demand among parents is essential for developing effective public health strategies and educational initiatives aimed at promoting rational antibiotic use in Türkiye.

This study assessed parental knowledge, attitudes, and practices regarding rational antibiotic use in young children with URTIs and the factors influencing these outcomes.

MATERIAL AND METHODS

The participants were parents of children diagnosed with URTIs who presented to the Pediatric Emergency Department of Göztepe Training and Research Hospital between February and March 2019. Children with other acute or chronic diseases were excluded. Parents (mothers or fathers) who agreed to participate and provided informed consent were included. They were asked to complete a questionnaire prepared to evaluate the sociodemographic characteristics of the family, as well as basic knowledge of infectious diseases and antibiotics, attitudes, and practices. Parents who were unable to complete the questionnaire due to physical or mental disabilities were excluded.

The questionnaire consisted of two sections. In the first section, the data included age, educational level, occupation, parental status (mother or father), number of children, the child's age, kindergarten attendance, and monthly household income. Monthly income was categorized according to the 2019 national poverty and hunger threshold values.[7]

The second section comprised a total of 20 items regarding antibiotic use: knowledge (12 items), attitudes (5 items), and practices (3 items). Some questions employed a three-point response scale ("Almost always," "Sometimes," and "Almost never"), while others were evaluated using a five-point Likert scale. The proportions

Table 1: Sociodemographic characteristics of the participats

Variables	Category	n	%
Parent age	≥30 years	236	59.15
	<30 years	163	40.85
Parent	Mother	340	85.21
	Father	59	14.79
Number of children	1	154	38.60
	>1	245	61.40
Educational level	Illiterate	5	1.25
	Primary school	54	13.53
	Middle school–high school	141	35.34
	University	199	49.87
Occupation	Housewife	208	52.13
	Worker	51	12.78
	Civil servant	101	25.31
	Retired	2	0.50
	Self-employed	37	9.27
Educational level of housewives	University	56	26.92
	Other	152	73.08
Monthly household income	<2000 TL	95	23.81
	2000–6000 TL	235	58.90
	>6000 TL	69	17.29
Attendance of the child to kindergarten	Yes	130	32.58
	No	269	67.42

Table 2: The rate of right answers on knowledge, attitudes, and practices of parents regarding antibiotic use

Statement	Number (n)	Percentage (%)
Knowledge		
1. Necessity of antibiotics for sore throat	387	96.99
2. Necessity of antibiotics for the common cold / influenza	235	58.90
3. Necessity of antibiotics for ear pain	304	76.19
4. Necessity of antibiotics for watery/green nasal discharge	206	51.63
5. Necessity of antibiotics for cough	381	95.49
6. Necessity of antibiotics for every febrile child	345	86.47
7. Necessity of antibiotics for β-hemolytic streptococcal pharyngitis	132	33.08
8. Awareness that viral infection is the most common cause of the common cold	298	74.69
9. Disagreement with the statement "If antibiotics are not used, the cold will last longer"	317	79.45
10. Awareness that frequent antibiotic use leads to antimicrobial resistance	282	70.68
11. Awareness that antibiotics may cause serious allergic reactions	311	77.94
12. Awareness that antibiotics can disrupt gut flora and cause diarrhea	284	71.18
Attitude		
13. Not expecting antibiotics from the physician for common cold/influenza	241	60.40
14. Trusting the physician when antibiotics are deemed unnecessary	339	84.96
15. Not seeking another physician when antibiotics are not prescribed	332	83.21
16. Not inclined to initiate antibiotics on their own	371	92.98
17. Agreeing that the physician's recommendation is the most influential factor in antibiotic use	397	99.50
Practice		
18. Avoiding premature discontinuation of antibiotic therapy (correct behavior)	73	18.30
19. Not reusing leftover antibiotics	371	92.98
20. No intention to obtain antibiotics without prescription	377	94.49

of correct responses to the questionnaire items were compared according to the parents' sociodemographic characteristics and their awareness of the Ministry of Health's media campaigns promoting rational antibiotic use. Correct responses were defined based on national guidelines and previously published questionnaires.[8–10] The study was conducted in accordance with the Declaration of Helsinki and was approved by the Istanbul Medeniyet University, Göztepe Training and Research Hospital ethics committee (approval number/date: 2018/0338-12.09.2018).

Statistical Analysis

Data were analyzed using SPSS version 17.0. Normality was assessed using the Kolmogorov–Smirnov test. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann–Whitney U or Kruskal–Wallis test. Correlations were evaluated using Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 399 parents (340 mothers, 85.2%; 59 fathers, 14.8%) were included in the study. The sociodemographic characteristics of the participants are presented in Table 1. The mean total score for correct responses to the knowledge, attitude, and practice questions was 15.63±2.49 (minimum–maximum), corresponding to approximately 78% of all items. Across the subscales, parents correctly answered an average of 8.73±1.78 (72.7%) knowledge questions, 4.21±0.93 (84.2%) attitude questions, and 2.69±0.60 (89.2%) practice questions. These findings indicate that although parents generally exhibit positive attitudes and practices regarding antibiotic use, their level of knowledge remains comparatively lower (Table 2).

Parents who were university graduates or whose income exceeded the poverty threshold demonstrated greater accuracy regarding the necessity of antibiotic use, the etiology of infections (viral/bacterial), antibiotic resistance, and antibiotic-associated diarrhea (p<0.05 for all comparisons) (Table 3).

Table 3: The correlations between the knowledge scores and the levels of education and income of the participants

Knowledge item	Group with higher accuracy	p
Necessity of antibiotics for the common cold/influenza	University graduates	**0.040**
Necessity of antibiotics for ear infections	University graduates	**0.010**
Necessity of antibiotics in febrile illness	University graduates	**0.020**
Necessity of antibiotics for bacterial pharyngitis	Higher-income parents	**0.040**
Awareness that viral pathogens are the most common cause of the common cold	University graduates / higher-income parents	**<0.001 / 0.023**
Awareness of antibiotic resistance	University graduates / higher-income parents	**<0.001 / 0.003**
Awareness that antibiotics may cause diarrhea (gut flora disruption)	University graduates / higher-income parents	**0.002 / 0.001**

Table 4: The correlations between the attitude scores and the levels of education and income of the participants

Variables	Attitude Item	Group with higher accuracy	p
Educational level	Not expecting an antibiotic prescription for upper respiratory tract infections (URTIs)	University graduates	0.027
Income level	Not seeking another physician when antibiotics are not prescribed	Higher-income parents	0.007
Income level	Willingness to wait for the child to recover without antibiotics	Higher-income parents	0.046

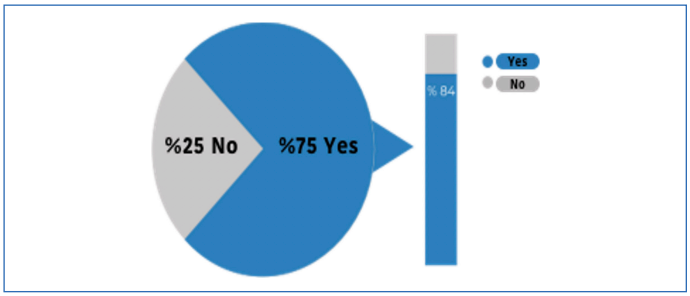

Figure 1: Awareness of media reports on rational antibiotic use and knowledge acquisition rates.

Although most parents recognized that antibiotics are not indicated for common symptoms of acute infections (90–95%), a substantial proportion continued to incorrectly attribute the need for antibiotics to viral conditions, including the common cold, influenza, and nasal discharge (41–48%). Notably, knowledge regarding streptococcal pharyngitis remained poor; almost 60% of parents with a university degree failed to provide the correct response.

Correct response rates for the attitude items were consistently high, with all but one exceeding 80%. Although 60.4% of parents correctly responded to the item evaluating expectations regarding antibiotic use in URTIs, nearly all participants (99.5%) identified physicians as the most authoritative source of guidance on antibiotic use. The results according to sociodemographic characteristics are summarized in Table 4.

Despite the overall high accuracy observed for the practice items, 81.7% of parents reported a tendency to discontinue antibiotics once symptoms subsided, and this behavior showed no significant association with sociodemographic characteristics. Poor adherence to the prescribed duration of therapy was the most prominent behavioral deficit.

Approximately 75% of parents reported being aware of recent media coverage related to rational antibiotic use, and among them, 84% indicated that they had acquired new information (Fig. 1). Awareness was significantly more common among parents with higher educational attainment and greater household income (p=0.039 and p=0.027, respectively). These parents also achieved significantly higher total correct response scores (15.85±2.38 vs. 14.96±2.69; p=0.005).

DISCUSSION

Although the vast majority of upper respiratory tract infections (URTIs) are caused by viral pathogens, the unnecessary and widespread use of antibiotics continues to represent a significant public health concern both in Türkiye and globally.[1,10] Our findings demonstrate that parents' level of knowledge remains lower than their attitudes and practices and that misconceptions regarding the necessity of antibiotics for viral infections persist. Moreover, the higher accuracy observed among parents with higher socioeconomic status and those who were aware of media campaigns underscores the importance of targeted public health interventions.

Regarding symptom-based expectations, previous studies have reported that parents frequently consider URTI symptoms such as ear pain, fever, cough, and nasal discharge to be indications for antibiotic use.[8,11–14] Similar findings have been documented in Türkiye, where parental expectations for antibiotics are particularly high in cases of fever and throat infections.[1] In our study, however, unlike in the existing literature, we found that parents correctly recognized at high rates (90–95%) that isolated symptoms such as sore throat, ear pain, cough, and fever do not require antibiotic treatment; yet, approximately half believed that antibiotics are necessary in the presence of the common cold, influenza, or watery/green nasal discharge alone.

Consistent with these observations, the literature has shown that parents are aware that the causative agents of the common cold and influenza are predominantly viral.[8,9,14,15] However, despite recognizing the viral origin, it is noteworthy that a high proportion (87%) believe that the illness lasts longer without antibiotic use. Similarly, in our study, although 75% of parents correctly identified the causative agent as viral, approximately half stated that antibiotics are necessary in these situations, revealing a marked knowledge–attitude discrepancy. This finding indicates that parents' knowledge regarding the unnecessary use of antibiotics for viral infections remains substantially inadequate.

When evaluating the level of knowledge regarding throat infections, our findings showed a marked divergence from the existing literature. Kuzujanakis and Vaz Elaine reported that parents were able to accurately determine the necessity of antibiotics for both simple sore throat and streptococcal pharyngitis.[8,16] In contrast, in our study, the fact that a high proportion of parents (96.9%) considered sore throat to require antibiotics and that the correct response rate for streptococcal infections remained at only one-third suggests that parents are unable to distinguish between bacterial and viral etiologies at the clinical level.

Our findings regarding antibiotic resistance were favorable. The fact that approximately three-quarters of parents were aware that frequent antibiotic use contributes to the development of resistance indicates a higher level of awareness than that reported in many other countries. Indeed, studies conducted in the United States and India have reported that parents have relatively low levels of knowledge about antibiotic resistance.[14,16] In Türkiye, although regional differences exist, our findings are consistent with the high awareness rates reported in İzmir and Ankara.[17,18]

A similar pattern was observed for awareness of antibiotic-related adverse effects. While the literature generally reports low levels of awareness regarding antibiotic side effects (10–45%),[14,16] the finding in our study that the majority of parents (70–78%) knew that antibiotics can cause allergies and diarrhea is noteworthy. This high proportion suggests that public awareness of antibiotic-related adverse effects has increased. Furthermore, the significantly higher level of knowledge among parents with higher educational attainment and income supports the influence of socioeconomic status on knowledge levels.

National and international studies have shown that parental attitudes toward antibiotic use vary considerably. While in some populations, parents may behave insistently or seek a second opinion when antibiotics are not prescribed by a physician (31–52%), other studies have reported very high levels of adherence to medical advice (90%).[8,14,19]

When examining the relationship between knowledge, attitudes, and practices, higher levels of parental knowledge were observed to be positively reflected in attitudes and behaviors. The fact that 84.2% of the attitude items and 89.2% of the practice items were answered correctly indicates that parents generally exhibit a favorable approach toward antibiotic use.

Furthermore, when examining parental attitudes and behaviors toward rational antibiotic use, our findings were generally consistent with the literature. Educational initiatives, such as informational brochures and media-based interventions, have been shown to improve parental understanding and reduce inappropriate expectations for antibiotics.[20,21] Recent studies from various countries have similarly demonstrated that parental misconceptions regarding the necessity of antibiotics remain widespread despite increased public awareness efforts.[22,23] Findings from the Antibiotic Use Questionnaire Parent Version study further indicate that parental decision-making is often guided by symptom interpretation rather than clinical diagnosis, highlighting a persistent gap between knowledge and practice.[24] Consistent with our results, contemporary evidence has also emphasized that socioeconomic disparities significantly shape parental knowledge and attitudes toward antibiotic use.[25,26] These recent contributions reinforce the need for multifaceted educational strategies targeting both misconceptions and the social determinants of health literacy.

In our study, the significantly higher knowledge scores observed among parents who had encountered national media campaigns, together with the positive influence of higher educational attainment and income, underline the critical role of accessible and targeted communication strategies. The alignment between our findings and recent global evidence suggests that strengthening visual and written media interventions may be an effective way to enhance rational antibiotic use at the population level. When interpreting these findings, however, differences across healthcare systems, survey methodologies, cultural norms, and sociodemographic structures should be taken into account. Overall, integrating large-scale public awareness efforts with tailored community-based educational approaches appears essential for improving parental knowledge, correcting persistent misconceptions, and promoting rational antibiotic use.

CONCLUSION

Our study revealed that parental knowledge regarding antibiotic use remains insufficient in certain areas, with notable deficiencies particularly in determining the necessity of antibiotics for viral infections and adhering to the prescribed treatment duration. Although higher educational attainment and income levels were associated with greater knowledge accuracy, the persistence of fundamental misconceptions even among highly educated parents is noteworthy. The positive impact of media-based information on knowledge supports the importance of community-oriented awareness initiatives. Therefore, developing targeted and sustainable educational strategies, especially for parents with lower levels of education and income, plays a critical role in promoting rational antibiotic use.

Statement

Ethics Committee Approval: The study was approved by Istanbul Medeniyet University, Göztepe Training and Research Hospital Ethics Committee (No: 2018/0338, Date: 12.09.2018).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Functional and structural outcomes after vitrectomy: The role of macular contour restoration

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ABSTRACT

Objective: Idiopathic epiretinal membrane (ERM) is a fibroglial proliferation on the retinal surface that distorts the macular contour and impairs visual acuity. Restoration of the foveal pit following pars plana vitrectomy (PPV) is considered a key determinant of postoperative outcomes. This study aimed to evaluate the relationship between macular contour recovery and functional improvement after ERM surgery.

Material and Methods: This retrospective study included 168 eyes of 155 patients who underwent PPV for idiopathic ERM between January 2009 and January 2011. Patients were grouped according to pre- and postoperative macular contour (MC) as regular or irregular. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were measured using the Snellen chart and spectral-domain optical coherence tomography (SD-OCT) before and 6 months after surgery. Statistical analyses were performed using paired t-tests, ANOVA, and Tukey's *post hoc* tests ($p<0.05$).

Results: The mean age differed significantly among groups ($p=0.03$). Preoperative BCVA was higher in patients with regular MC (0.37±0.23) than in those with irregular MC (0.16±0.11; $p=0.02$). Postoperative BCVA improved significantly in all groups ($p=0.01$). The greatest CMT reduction occurred in patients whose MC normalized postoperatively (CMT=-338.9±159.2 µm; $p=0.01$), indicating concordant structural and visual recovery.

Conclusion: PPV for idiopathic ERM provides significant visual and anatomical improvement. Postoperative restoration of the foveal pit is strongly associated with superior BCVA gain and CMT reduction, highlighting foveal morphology as a key prognostic marker for surgical success.

Keywords: Epiretinal membrane, foveal contour, optical coherence tomography, pars plana vitrectomy, visual acuity.

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INTRODUCTION

ERM is a pathology characterized by fibroglial proliferation on the retinal surface, typically developing over the internal limiting membrane (ILM). It predominantly affects elderly individuals and presents with decreased visual acuity, metamorphopsia, and impaired contrast sensitivity.[1] The incidence of ERM has been reported to range between 2% and 20% in populations over the age of 60.[2] The pathogenesis of ERM involves several contributing factors, including posterior vitreous detachment, retinal microtrauma, inflammation, and oxidative stress.[3] With the advancement of optical coherence tomography (OCT) technology, it has become possible to assess microstructural changes in the macular region, enabling a more objective analysis of surgical outcomes.[4] In particular, postoperative changes in CMT and macular contour following PPV have been shown to be closely related to functional recovery.[5]

Recent studies have emphasized that anatomical restoration after PPV is not limited to the removal of the epiretinal membrane itself but also involves remodeling of the inner retinal layers—especially the foveal contour—which plays a crucial role in determining visual prognosis.[6] The integrity of photoreceptor outer segments, preservation of the ellipsoid zone, and reformation of the foveal depression are considered key determinants of postoperative visual acuity.[7] Moreover, whether the macular contour returns to its normal architecture has been highlighted as a significant parameter influencing surgical success.[8] In some cases, despite adequate anatomical peeling of the membrane, the foveal contour fails to recover, and these patients experience limited visual improvement.[9] This finding indicates that the relationship between anatomical and functional outcomes is multifactorial and that the structural integrity of the macular contour plays a critical role in postoperative recovery.[10]

In this context, our study aimed to evaluate the relationship between preoperative and postoperative changes in the macular contour and functional outcomes in patients with ERM who underwent PPV. Through this approach, we sought to contribute to a better understanding of the interplay between anatomical and functional recovery and to support the optimization of surgical indications and patient counseling processes.

MATERIAL AND METHODS

Study Design and Population

This retrospective study included 168 eyes of 155 patients who underwent PPV for idiopathic ERM at the Retina Unit of the 1st Ophthalmology Clinic, Haydarpaşa Numune Training and Research Hospital, between January 2009 and January 2011. The difference between the number of eyes and patients was due to bilateral involvement; 13 patients underwent surgery in both eyes, and each eye was analyzed separately.

Patients with a history of previous vitrectomy, diabetic retinopathy, macular or retinal diseases unrelated to ERM, optic disc or corneal pathologies causing visual impairment, myopia greater than –6 diopters, or those who were not followed for at least six months postoperatively were excluded from the study.

Patient demographic data (age, sex), best-corrected visual acuity (BCVA), clinical findings, biomicroscopic and fundus findings, as well as macular morphology and CMT obtained by optical coherence tomography (OCT) before surgery (preoperative, PO) and at postoperative month six (PO6), were evaluated. The six-month postoperative follow-up period was chosen because anatomical and functional recovery after ERM surgery generally stabilizes within this timeframe, and further improvements beyond six months are usually minimal according to previous studies. Visual acuity was assessed using the Snellen chart. In phakic patients, the grade of nuclear sclerosis and cataract was subjectively evaluated by slit-lamp examination. Fundus examinations were performed using standard 90-D and 58-D macular contact lenses under both normal and red-free green illumination.

ERM morphology was classified according to the Gass system. Structural relationships between the ERM, retinal surface, and posterior hyaloid were analyzed using SD-OCT (RTVue Fourier-Domain Optical Coherence Tomography, Optovue Inc.). Macular thickness and contour maps were evaluated using the “MM6” and “Grid” protocols, respectively. Fluorescein angiography (FA) was performed when deemed necessary. Changes in CMT were analyzed preoperatively and postoperatively.

Patients were first divided into two groups according to the preoperative MC:

- Group 1: Regular macular contour
- Group 2: Distorted macular contour (due to vitreomacular traction syndrome or ERM)

Additionally, based on preoperative and postoperative MC changes, patients were categorized into three subgroups:

In this context, a “regular” macular contour refers to the preservation of the normal foveal depression with a smooth inner retinal surface, whereas an “irregular” contour indicates loss or distortion of the foveal pit due to epiretinal membrane traction or vitreomacular interface abnormalities.

- Group A: Both preoperative and postoperative regular MC
- Group B: Both preoperative and postoperative irregular MC
- Group C: Preoperative irregular MC with postoperative restoration of contour

Preoperative and postoperative BCVA and CMT values, as well as their intra- and intergroup changes, were analyzed for each classification.

Surgical Technique

All patients underwent standard 23-gauge three-port PPV. Internal limiting membrane (ILM) peeling was performed in cases with secondary membrane formation or ILM wrinkling observed after ERM removal. Trypan blue and brilliant blue dyes were used to assist in ERM and ILM visualization and peeling. In all cases, complete ILM peeling was performed after staining with brilliant blue, covering approximately three disc diameters around the macular area. When necessary, air, sulfur hexafluoride (SF_6), or perfluoroethane (C_2F_6) gas tamponades were used at the surgeon’s discretion.

Table 1: Demographic characteristics of the patients and distribution according to macular contour groups

Variables	Group 1 (regular MC) n=13	Group 2 (irregular MC) n=24	Group A (pre- and post-op regular MC) n=13	Group B (pre- and post-op irregular MC) n=10	Group C (pre-op irregular, post-op regular MC) n=14	p
Age (mean±SD)	67.07±6.15 (60–80)	60.66±11.13 (33–77)	67.07±6.15 (60–80)	61.40±10.06 (39–76)	60.14±12.18 (33–77)	**0.03***
Gender (M/F)	5 / 8 (38.5% M)	9 / 15 (37.5% M)	5 / 8 (38.5% M)	3 / 7 (30% M)	6 / 8 (42.9% M)	>0.05
Affected eye (right/left)	6 / 7	10 / 14	6 / 7	2 / 8	8 / 6	>0.05
Pre-operative BCVA (Median±SD)	0.37±0.23	0.16±0.11	0.37±0.23	0.13±0.12	0.18±0.10	**0.02***
Post-operative BCVA (6th month, Median±SD)	0.60±0.21	0.45±0.22	0.60±0.21	0.34±0.26	0.53±0.15	**0.01***
Pre-operative CMT (μm, Median±SD)	361.3±62.5	542.9±206.1	361.3±62.5	424.2±106.9	627.8±220.6	**0.01***
Post-operative CMT (6th Month, μm, Median±SD)	250.2±52.2	294.4±58.2	250.2±52.2	302.2±55.7	288.8±61.3	0.08
Change in CMT (μm)	-111.1±58.4	-248.5±147.9	-111.1±58.4	-122.0±69.5	-338.9±159.2	**0.01***

ANOVA and Chi-square tests were used. *: P<0.05 was considered statistically significant. BCVA: Best-Corrected Visual Acuity; CMT: Central macular thickness; MC: Macular contour; Pre-op: Preoperative; Post-op: Postoperative; SD: Standard deviation.

Optical Coherence Tomography Evaluation

All patients underwent OCT examination preoperatively and at six months postoperatively. To assess the structural effect of surgery on the macular region, the primary parameter analyzed was CMT within the central 3 mm² area of the "MM6" protocol. Reduction in CMT and macular edema after surgery was interpreted as indirect evidence of traction release from the ERM. Using the "Grid" protocol, macular contour integrity was further examined. Recurrent ERMs were assessed by the presence of hyperreflective surfaces on OCT images.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequency, percentage, mean, and standard deviation, were used to summarize the data. The Kolmogorov–Smirnov test was applied to assess the normality of data distribution. For variables following a normal distribution, paired-sample t-tests were used to compare preoperative and postoperative values within groups. For non-normally distributed variables, the Wilcoxon signed-rank test was employed. Comparisons among three or more groups were performed using one-way analysis of variance (ANOVA), and when statistically significant differences were detected, Tukey's Honestly Significant Difference (HSD) *post hoc* test was applied for multiple comparisons. A p-value <0.05 was considered statistically significant, and all results were reported with 95% confidence intervals (CI 95%).

Ethics Committee Approval

This study is derived from a medical specialty thesis completed in 2012. At the time the study was conducted, ethical committee approval was not mandatory according to national and institutional regulations. Therefore, no ethical approval number is available. All procedures were carried out in accordance with the principles of the Declaration of Helsinki. All patient data used in the study were anonymized to protect patient confidentiality and analyzed solely for scientific purposes.

RESULTS

A total of 155 patients (168 eyes) were initially screened for eligibility. After applying the exclusion criteria (inadequate follow-up, missing OCT data, prior ocular surgery, or low-quality imaging), 118 patients were excluded. Consequently, 37 patients were included in the final analysis. A statistically significant difference was found in the mean age among the groups (p=0.03). Patients in Group 1 and Group A were older compared to those in the other groups (mean 67.07±6.15 years; other groups ranged between 60.1 and 61.4 years). The preoperative best-corrected visual acuity (BCVA) was significantly higher in Group 1 compared to Group 2 (0.37±0.23 vs. 0.16±0.11; p=0.02). At the 6th postoperative month, BCVA showed improvement in all groups, and this increase was statistically significant (p=0.01). The preoperative CMT was significantly lower in Group 1 (361.3±62.5 μm) compared to Group 2 (542.9±206.1 μm) and Group C (627.8±220.6 μm) (p=0.01). In addition, the change in CMT was most pronounced in Group C (–338.9±159.2 μm), and this change was statistically significant (p=0.01) (Table 1).

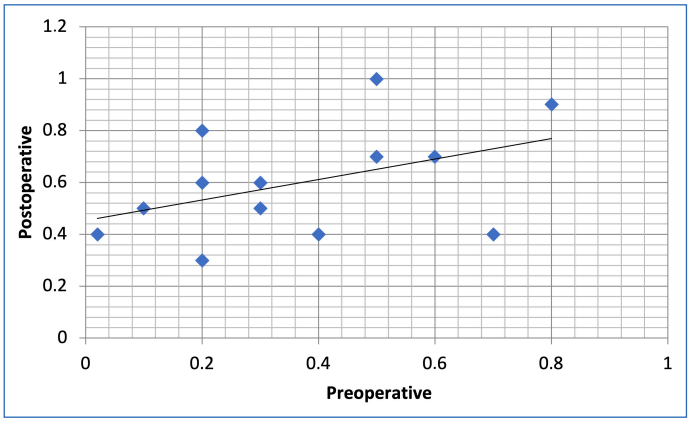

Figure 1: Distribution of Best-Corrected Visual Acuity (BCVA) on the snellen scale before and after surgery in group 1 patients.

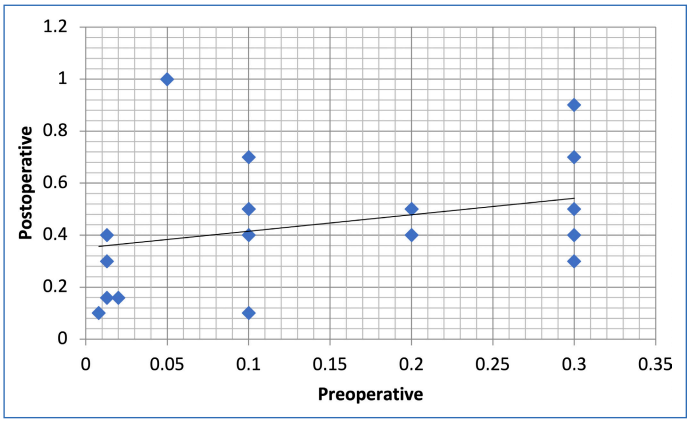

Figure 2: Distribution of Best-Corrected Visual Acuity (BCVA) on the snellen scale before and after surgery in group 2 patients.

In Group 1, the mean preoperative best-corrected visual acuity (BCVA) was 0.37±0.23, which improved to 0.60±0.21 at postoperative month 6. The increase in BCVA, measured using the Snellen chart, was statistically significant (p=0.016), corresponding to a mean gain of 0.22±0.23 lines. Figure 1 clearly illustrates the functional improvement achieved after surgery.

In Group 2, the mean preoperative BCVA was 0.16±0.11, improving to 0.45±0.22 at postoperative month 6. The difference between preoperative and postoperative BCVA values was statistically significant (p=0.01), with a mean visual gain of 0.29±0.22 lines. As shown in Figure 2, patients in Group 2 also demonstrated a marked postoperative improvement in visual function.

In Group 1, the mean preoperative CMT measured by OCT was 361.30±62.53 μm (range: 297–516 μm), which decreased to 250.23±52.19 μm (range: 157–337 μm) at postoperative month 6. The reduction in CMT was statistically significant (p=0.01). Figure 3 demonstrates the substantial postoperative thinning of the macula, indicating anatomical recovery that paralleled functional improvement.

In Group 2, the mean preoperative CMT was 542.95±206.10 μm (range: 306–954 μm), which significantly decreased to 294.41±58.16 μm (range: 185–394 μm) at postoperative month 6 (p=0.01). As depicted in Figure 4, the postoperative reduction in macular thickness reflects marked anatomical restoration following surgery.

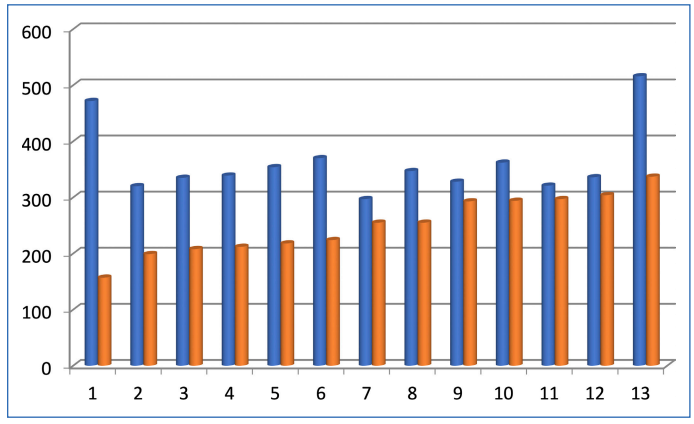

Figure 3: Preoperative and postoperative changes in Mean Macular Contour (MMC) in group 1 patients.

*Blue bars represent the preoperative MMC values, while orange bars indicate the postoperative MMC measurements obtained at the 6-month follow-up.
**Changes in central macular thickness (expressed in micrometers, μm) during follow-up.

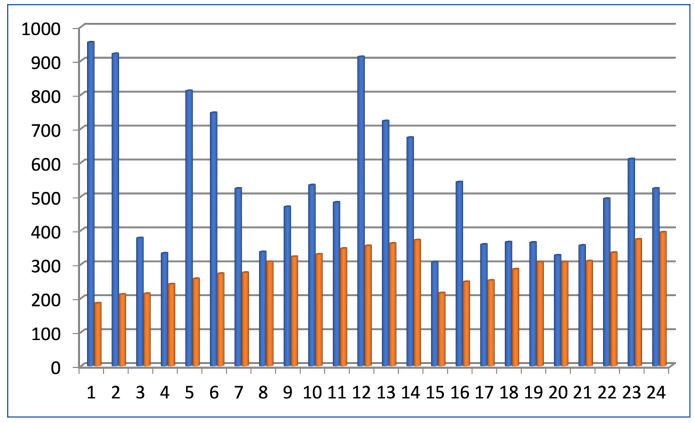

Figure 4: Preoperative and postoperative changes in Mean Macular Contour (MMC) in group 2 patients.

*Blue bars represent the preoperative MMC values, while orange bars indicate the postoperative MMC measurements obtained at the 6-month follow-up.
**Comparison of postoperative central macular thickness between groups (expressed in micrometers, μm).

In Group C, the mean preoperative CMT was 627.78±220.56 μm (range: 332–954 μm), which decreased to 288.85±61.32 μm (range: 185–371 μm) at postoperative month 6, representing a statistically significant improvement (p=0.01). Figure 5 demonstrates that patients with preoperatively distorted macular contours achieved significant postoperative thinning and restoration of normal macular structure.

DISCUSSION

In our study, significant improvements were observed in both visual and anatomical outcomes after pars plana vitrectomy in patients with ERM. Best-corrected visual acuity (BCVA) increased significantly after surgery, while CMT decreased. Visual gains were more pronounced, and anatomical recovery was greater in patients whose foveal pit contour was re-established. Although functional improvement was also observed in cases without foveal pit reformation, it was slower and less marked. These findings demonstrate that preoperative and postoperative

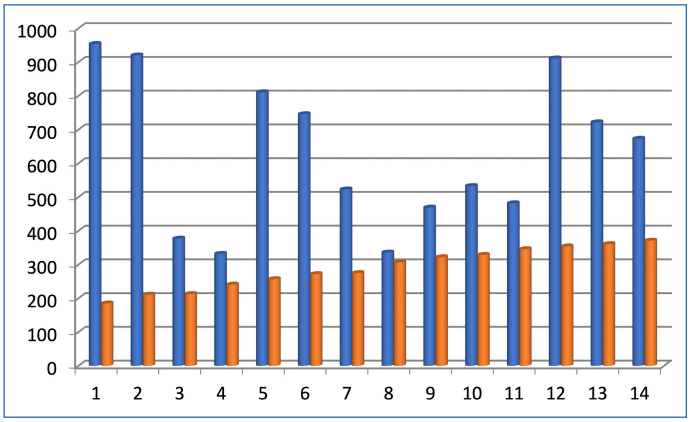

Figure 5: Preoperative and postoperative changes in Mean Macular Contour (MMC) in group c patients.

*Blue bars represent the preoperative MMC values, while orange bars indicate the postoperative MMC measurements obtained at the 6-month follow-up.
**MMC values are expressed in micrometers (μm).

changes in macular contour are closely associated with visual outcomes.

There is extensive evidence in the literature supporting significant postoperative improvement in BCVA. Kim et al.[11] reported a marked increase in BCVA up to 6 months after vitrectomy in all patients, although full visual normalization was rarely achieved. Indeed, visual acuity and metamorphopsia generally improve gradually after ERM surgery, and many patients do not regain completely normal vision.[12] In our series, while the mean improvement in vision was substantial, some patients—consistent with previous reports—experienced mild persistent visual loss or distortion. Bae et al.[9] showed that visual acuity improved rapidly in the early postoperative period but that the rate of improvement plateaued by 12 months. This suggests that postoperative anatomical adaptation and neurological rehabilitation may take several months. Similarly, improvement in metamorphopsia often lags behind visual recovery, with complete resolution being uncommon.[12] In elderly patients or those with concomitant photoreceptor damage, some degree of micropsia or metamorphopsia may persist even after successful surgery.

Postoperative macular anatomical changes were also prominent in our results. Following membrane peeling, a significant reduction in macular thickness was noted, a finding that has been widely confirmed in the literature. In a series of 54 cases, Mafi et al.[13] reported a decrease in mean CMT from approximately 510 μm preoperatively to 415 μm at 6 months, representing a statistically significant reduction. Similarly, Kim et al.[11] observed a marked postoperative decrease in central foveal thickness in all patients at 6 months. This decrease is attributed to the release of epiretinal traction, allowing relaxation of the retinal layers. Interestingly, however, the degree of anatomical thinning does not always parallel the improvement in visual acuity.

One of the most important findings of our study was the direct relationship between foveal contour restoration and both visual and structural recovery. Postoperative BCVA improvement was significantly greater in cases where the foveal pit re-formed compared to those where it remained flat. This finding is consistent with the literature. In a 43-eye series, Lim et al.[14] found that patients who achieved early foveal pit recovery within one month postoperatively had markedly greater visual improvement at one year than those without pit reformation. They also reported that these patients had a greater reduction in CMT. Similarly, Bae et al.[9] noted that visual acuity gains were faster in the early months among patients with foveal pit reformation, although the differences between groups diminished by 12 months. This suggests that even in eyes without early pit restoration, gradual structural and functional improvement may occur over time. Uzel et al.[15] emphasized that even in eyes with incomplete foveal normalization after surgery, significant visual gains can still be achieved. However, in advanced cases with permanently flattened foveal contours, final visual acuity tends to remain lower than in those with complete pit restoration.[14] In our cohort, final BCVA was lower in patients without foveal pit recovery, supporting the notion that anatomical normalization of foveal contour enhances visual prognosis.

Another dimension of macular contour change involves metamorphopsia and retinal microstructure. Restoration of the foveal pit corresponds to a reduction in preoperative irregularities and traction within the inner retinal layers. The reappearance of foveal depression has been reported to decrease the perception of visual distortion.[13] Kim et al.[11] found that postoperative metamorphopsia scores improved significantly in mild-to-moderate ERM cases, while little improvement was observed in advanced cases. Although our study did not include staging analysis, we observed that subjective complaints such as visual distortion persisted in some patients whose foveal contour did not fully recover, consistent with prior findings. Clinicians should therefore recognize that even when visual acuity is satisfactory, minimal residual metamorphopsia may persist if subtle macular surface irregularities remain.

When our findings are interpreted in light of recent classifications and prognostic factors, they reaffirm the importance of preoperative macular architecture. The ERM staging system proposed by Govetto et al.,[1] based on the presence of ectopic inner foveal layers (EIFL), has been shown to be valuable for predicting surgical outcomes. Although our series mainly included advanced-stage cases, large-scale studies have demonstrated that stage 1–2 eyes achieve better final visual acuity, whereas stage 3–4 eyes, despite lower final BCVA, show the greatest absolute visual gain after surgery. In a 46-eye OCTA-based study, Li et al.[16] found that lower-stage ERM cases had better postoperative visual function, while advanced-stage cases benefited most dramatically from surgery. They also reported a positive correlation between postoperative visual improvement and structural parameters such as preoperative EIFL thickness and central retinal thickness. Moreover, disorganization of the inner retinal layers (DRIL) and integrity of the photoreceptor layer have emerged as key prognostic biomarkers. Kunavisarut et al.[5] demonstrated in 130 patients that severe preoperative DRIL and disruption of the ellipsoid zone (EZ) band were the strongest predictors of limited postoperative visual recovery.[16] Preservation of the EZ band prior to surgery has consistently been identified as a critical determinant of visual prognosis. Although our study did not specifically analyze EZ continuity, previous literature consistently reports that patients with intact photoreceptor layers exhibit significantly better postoperative BCVA.[5] Similarly, the degree of disorganization in the inner retinal layers affects visual improvement. In one study, patients with preoperative DRIL exhibited less visual gain at 12 months and greater intraoperative difficulty with microhemorrhage during inner membrane peeling.[17] These findings suggest that in cases with advanced structural changes, the potential

visual benefit of surgery may be limited, emphasizing the importance of individualized surgical planning.

From a clinical standpoint, several implications emerge from our findings. First, as macular contour improvement correlates with better visual rehabilitation, postoperative OCT monitoring of foveal pit restoration can serve as a useful prognostic marker. Early postoperative (1–3 month) foveal deepening may predict greater long-term visual improvement. Lim et al.[14] reported that patients showing early foveal recovery within the first postoperative month had significantly higher rates of ≥2-line visual gain at 1 year. Conversely, lack of early foveal contour recovery should not be considered a poor prognostic sign; gradual normalization of foveal anatomy and parallel visual improvement can occur over time.[9,14] Indeed, a ~3-year longitudinal study reported partial recovery of the foveal pit in approximately half of advanced EIFL cases.[18] Therefore, clinicians should recognize that postoperative anatomical progression may vary among patients and should counsel them that visual rehabilitation may proceed gradually.

Limitations

This study has several limitations. First, due to its retrospective design, variations in patient selection and surgical technique could not be fully controlled, which may have influenced the homogeneity of the results. Second, the follow-up period was limited to six months, preventing assessment of long-term visual and anatomical outcomes. Third, advanced microstructural parameters such as ellipsoid zone integrity, disorganization of the retinal inner layers (DRIL), and EIFL staging were not quantitatively analyzed on optical coherence tomography (OCT); therefore, the correlation between structural alterations and functional recovery could not be fully elucidated.

CONCLUSION

In this study, significant functional and structural improvements were observed following PPV in patients with idiopathic ERM. Both best-corrected visual acuity (BCVA) and CMT demonstrated marked postoperative improvement, confirming that surgical removal of the membrane effectively reduces tractional stress and restores retinal architecture. Among the key findings, the re-establishment of a normal foveal contour was strongly associated with greater visual gains and more pronounced anatomical recovery. Patients who exhibited postoperative foveal pit restoration achieved significantly better outcomes compared with those in whom the foveal contour remained flattened.

These results highlight the importance of foveal morphology as a prognostic indicator after ERM surgery. The degree of macular contour recovery may reflect the integrity of inner and outer retinal layers, particularly the photoreceptor and ellipsoid zones, which are critical for optimal visual rehabilitation. Although functional improvement can still occur in patients without complete anatomical restoration, the process tends to be slower and less extensive.

In clinical practice, early postoperative evaluation of macular contour via optical coherence tomography (OCT) can provide valuable insight into long-term visual prognosis. Therefore, foveal pit recovery should be considered a favorable biomarker for postoperative visual outcome and a meaningful endpoint for surgical success in idiopathic ERM management.

Statement

Ethics Committee Approval: This study is derived from a medical specialty thesis completed in 2012. At the time the study was conducted, ethical committee approval was not mandatory according to national and institutional regulations. Therefore, no ethical approval number is available.

Informed Consent: Informed consent was not obtained due to the retrospective nature of the study.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Author Contributions: Concept – AM, DS; Design – AM, DS; Supervision – AM; Results – AM; Materials – AM, DS; Data Collection and/or Processing – AM; Analysis and/or Interpretation – AM, DS; Literature Search – AM, DS; Writing – AM; Critical Reviews – AM, DS.

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CASE REPORT

A specific component of familial Mediterranean fever: Menstrual attacks only

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ABSTRACT

Familial Mediterranean fever (FMF) is the prototype of monogenic autoinflammatory diseases. The disease is characterized by recurrent attacks of fever, abdominal pain, and chest pain. Menstruation can be a triggering factor for these attacks. We report two cases of FMF in which abdominal pain attacks occurred exclusively during menstrual periods. A 14-year-old female patient was diagnosed with FMF at the age of 10 after experiencing recurrent episodes of fever and abdominal pain lasting 1–3 days and recurring every 1–2 months since the age of 3. After colchicine treatment, her fever and abdominal pain attacks resolved; however, she reported severe abdominal pain lasting for 3 days during every menstrual period over the past year. The patient was considered to have FMF characterized by isolated menstrual attacks. The family acknowledged that the patient was not taking colchicine regularly. With regular colchicine therapy, a significant reduction in isolated menstrual attacks was observed. A 15-year-old female patient was referred because of recurrent abdominal pain over the past 3 years. Upon further questioning, she reported no associated fever or chest pain. It was noted that the abdominal pain occurred specifically during menstrual periods and lasted for 2–4 days. Significant elevations in C-reactive protein levels were detected during episodes of abdominal pain and menstruation. Given her typical history of isolated menstrual attacks, she has remained attack-free for 2 years while receiving colchicine therapy. Although the exact mechanism underlying the relationship between menstruation and FMF attacks remains unclear, FMF attacks typically begin immediately before the onset of menstruation. In some cases, however, the attacks begin just after menstruation starts. These patients appear to have a higher rate of dysmenorrhea and an increased frequency of attacks before and after menarche compared with patients with typical clinical presentations of FMF. Fever may not always be present during attacks; therefore, elevated acute-phase reactant levels may be useful in distinguishing menstrual FMF attacks from dysmenorrhea.

Keywords: Colchicine, familial mediterranean fever, isolated menstrual attacks.

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent febrile episodes and serositis. The attacks last 1–3 days and recur every 1–2 months. The disease is most commonly observed in Mediterranean populations, especially among Turks, Jews, Arabs, and Armenians. Türkiye has the highest number of patients with FMF worldwide. Fever, abdominal pain, and chest pain are the cardinal features of the disease, and 95–98% of patients report these symptoms. Arthralgia, arthritis, and myalgia are other relatively common features that may be observed during attacks. Erysipelas-like erythema is a pathognomonic skin rash that is most commonly located around the ankles and is observed in 30–40% of patients.[1] In addition to these clinical features, patients may sometimes associate specific triggers with the onset of attacks, such as stress, cold exposure, strenuous exercise, recent infection, surgery, and menstruation.[2]

In female patients, fluctuations in estrogen levels, particularly the decline preceding menstruation, have been implicated in triggering FMF attacks.[3] Although menstruation can be a triggering factor, we report two cases of FMF in which abdominal pain attacks occurred exclusively during menstrual periods. This report aims to highlight an atypical presentation of FMF limited to menstrual attacks and to raise awareness of its clinical recognition.

CASE REPORTS

Case 1

A 10-year-old female patient who had been experiencing recurrent episodes of fever and abdominal pain lasting 1–3 days and recurring every 1–2 months since the age of 3 was referred to pediatric rheumatology. She had typical FMF attacks, and MEFV gene analysis revealed a pathogenic exon 10 mutation (homozygous V726A). While receiving colchicine regularly, the patient experienced no attacks, which led the family to reduce the colchicine dosage. However, at the age of 14, she began experiencing severe abdominal pain episodes lasting 3 days during each menstrual period over the preceding year. She did not describe any other symptoms. During emergency department visits, significant elevations in C-reactive protein (CRP) levels (CRP: 135 mg/L, 87 mg/L, and 217 mg/L; normal range: 0–5 mg/L) were detected during episodes of abdominal pain and menstruation. The patient was considered to have FMF characterized by isolated menstrual attacks. With regular colchicine use twice daily, a significant reduction in isolated menstrual attacks was observed. During follow-up, she had no active complaints, and acute-phase reactant levels were normal, with no evidence of subclinical inflammation.

Case 2

A 15-year-old female patient was referred to pediatric rheumatology because of recurrent abdominal pain over the past 3 years. Upon further questioning, it was noted that she did not have fever, chest pain, erysipelas-like erythema, arthritis, or myalgia accompanying the abdominal pain. It was learned that the abdominal pain occurred specifically during menstrual periods and lasted for 2–4 days. Laboratory tests revealed significant elevations in CRP levels (CRP: 188 mg/L and 96 mg/L) during episodes of abdominal pain and menstruation. The patient had a typical history of isolated menstrual attacks of FMF, and MEFV gene analysis revealed pathogenic compound heterozygous mutations in exon 10 (heterozygous M694V/heterozygous V726A). The patient has been followed for 2 years, and colchicine treatment twice daily has led to the resolution of abdominal pain attacks during menstruation.

DISCUSSION

Although the exact mechanism underlying the relationship between menstruation and FMF attacks is not fully understood, decreased estrogen levels are thought to trigger FMF attacks.[1] Another observation supporting this hypothesis is that patients are almost entirely in remission during pregnancy because of increased estrogen levels.[3] However, it should be noted that triggering factors in FMF may vary among individuals.

A study conducted in Türkiye by Batu et al.[4] showed that patients who experience attacks exclusively during their menstrual periods tend to have an earlier onset of symptoms and receive their diagnosis at a younger age. In addition, these patients were observed to have a higher rate of dysmenorrhea and a greater frequency of attacks both before and after menarche compared with patients with a typical clinical presentation of FMF. FMF attacks usually begin just before the onset of menstruation, whereas in some cases, they begin immediately after menstruation starts. Fever may not always be present during attacks. Therefore, elevated acute-phase reactant levels can be helpful in distinguishing a menstrual FMF attack from dysmenorrhea. Additionally, the localization of pain, such as widespread abdominal pain that may be accompanied by chest or back pain, may indicate an FMF attack and allow patients to differentiate between an attack and dysmenorrhea.[4,5]

In another study conducted in Türkiye in 2024, Demirkıran et al.[5] suggested that 76% of adolescent patients with FMF could distinguish between an FMF attack and dysmenorrhea and that 37% of patients experienced FMF attacks simultaneously with menstruation. In addition, they found no difference in the incidence of dysmenorrhea between adolescents with and without menstruation-only FMF attacks. Symptoms associated with dysmenorrhea, including fever, arthralgia, abdominal distention, sleep disturbance, headache, nausea, vomiting, and breast swelling, were more frequent in menstruation-associated FMF attacks. Several triggering factors for FMF attacks have been identified in women, with menstruation being the most frequent, followed by psychological stress, fatigue, anxiety, and environmental changes.[6]

It is well known that patients with FMF benefit from colchicine as first-line treatment. In particular, when the frequency of attacks increases, patients may benefit from an increased dose of colchicine.[4] However, treatment plans should be individualized according to each patient's clinical presentation. In patients with poor medication adherence, improving adherence has been shown to reduce the frequency of attacks. It should be particularly noted that adolescent patients may experience adherence problems because of their developmental stage, which can affect treatment continuity. Close monitoring of these patients is therefore crucial.[7,8] In the first case, symptomatic remission led the family to reduce the colchicine

dosage, which resulted in an increased frequency of FMF attacks. Adherence to the appropriate colchicine dosage significantly reduced the frequency of attacks.

If a patient with good medication adherence continues to experience attacks while receiving colchicine therapy, anti-interleukin-1 drugs should be considered.[4] Although some studies suggest that intermittent colchicine therapy may provide symptomatic relief, daily colchicine therapy should be continued in all patients because of the possibility of subclinical inflammation during the course of FMF.[8–11]

CONCLUSION

Although the exact mechanism underlying the relationship between menstruation and FMF attacks remains unclear, FMF attacks in some female patients begin just before the onset of menstruation or shortly after menstruation begins. These patients tend to experience higher rates of dysmenorrhea and an increased frequency of attacks both before and after menarche compared with those with typical FMF presentations. Fever may not always accompany these attacks; therefore, monitoring acute-phase reactant levels can assist in differentiating FMF attacks from dysmenorrhea. Recognizing this overlap is important for avoiding misdiagnosis and preventing unnecessary interventions. The association between menstrual cycles and FMF attack frequency highlights the importance of systematically assessing symptom patterns in female patients. Regular evaluation of menstrual history should therefore be incorporated into the clinical assessment of adolescent female patients with FMF. Maintaining an appropriate colchicine dosage and ensuring adherence to therapy remain essential for effective disease management. Ultimately, awareness of the menstrual cycle as a potential modifier of FMF disease expression is key to optimizing patient care and improving the quality of life of affected female patients.

Statement

Ethics Committee Approval: This is a case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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CASE REPORT

Single-stage treatment of rectal atresia by transanal approach: No need for stoma

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ABSTRACT

Rectal atresia is an extremely rare condition among anorectal anomalies. Rectal atresia and associated congenital anomalies have been reported previously; however, rectal atresia with left renal agenesis and hypospadias has not been previously reported in the English literature. We report the successful treatment of rectal atresia in a neonate with left renal agenesis and hypospadias using a single-stage endoanal approach without stoma. A one-day-old male neonate was transferred to our department because a firm tube could not be passed into the rectum. On inspection of the perineum, the anal opening was normal, and the external genitalia showed hypospadias with hooded prepuce. During the operation, a cross-shaped incision was made in the most proximal mucosa of the anal canal, which ended blindly above the dentate line, and the rectal canal was reached by dissection. The proximal rectal mucosa and distal dentate line mucosa were anastomosed. Thus, type II rectal atresia was repaired primarily and successfully without stoma using a single-stage transanal approach. Follow-up was uneventful for four years. Transanal anorectal anastomosis without stoma offers a safe, effective, and comfortable technique for the treatment of rectal atresia and decreases the risk of injury.

Keywords: Anorectal anomalies, newborn, rectal atresia, rectal stenosis, surgery.

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INTRODUCTION

Rectal atresia is an extremely rare condition among anorectal anomalies, and it is predominantly seen in males.[1,2] The anal opening is normal, the external and internal sphincters are well developed, and there is an atretic rectal segment between the anal canal and rectum. The classification of rectal atresia is divided into five types.[1] Complete fibrous membrane or severe stenosis between the distal rectum and anal canal are the prevalent types.[3] Typically, rectal atresia is diagnosed when a firm tube fails to pass into the rectum. Diagnosis can be delayed in cases of rectal stenosis because meconium may pass.

Various operative procedures for the treatment of rectal atresia have been reported. Most cases have been managed with a staged procedure with covering sigmoid colostomy.[1,2,4,5] Performing a colostomy in rectal atresia ensures fecal discharge and anastomotic safety during the repair of rectal atresia. The cases reported so far have generally been treated by performing a colostomy.

Here, the successful treatment of rectal atresia in a neonate with left renal agenesis and hypospadias using a single-stage endoanal approach without stoma is reported.

CASE REPORT

A one-day-old male neonate who was born at 39 gestational weeks with a birth weight of 2770 g was transferred to our department because a firm tube could not be passed into the rectum during the routine examination of the baby. On inspection of the perineum, the anal opening was normal, and the external genitalia showed hypospadias with hooded prepuce (Fig. 1a).

On rectal examination, the anal opening was normal, and there was no meconium. However, a firm catheter could not be passed more than 25 mm into the anal canal. Abdominal X-ray showed massively dilated bowel loops. The distance between the anus and the blind rectal pouch was measured as 5 mm at the 24th postnatal hour by cross-table lateral X-ray (Fig. 1b). Urinary ultrasound revealed left renal agenesis, and there was no presacral mass on spinal ultrasound. Echocardiography was normal. There was no meconium in the urine.

At the beginning of the operation, good muscle contractions around the anus were observed in four quadrants using a muscle stimulator. The tip of the anus was demonstrated with baby retractors, and a cross-shaped incision was made with needle cautery in the most proximal mucosa of the anal canal, which ended blindly above the dentate line, and the rectal canal was reached by dissection. The proximal rectal mucosa and distal dentate line mucosa were anastomosed with 4/0 absorbable sutures (Fig. 2). A number 11 Hegar dilator was passed into the rectum. Thus, type II rectal atresia was repaired primarily and successfully without stoma using a single-stage transanal approach.

On the 7th day, the patient was discharged with normal gastrointestinal passage. The first rectal examination with a number 11 Hegar dilator was performed on the 21st postnatal day; monthly follow-ups were uneventful for four years.

DISCUSSION

Rectal atresia is a very rare condition, with an incidence of 1–2% among all anorectal anomalies.[1,2] The anal opening and anal canal are normal and end blindly 1.5–3 cm from the anal verge. The external and internal sphincters are well developed, and there is atresia at the junction of the anus and rectum.

The embryogenesis of rectal atresia is unknown. However, some theories have been postulated, including the embryological theory (vascular accident between the 13th and 14th gestational weeks), genetic theory (especially high incidence in Southern India), and infective theory (intrauterine infection causing thrombosis of the vessels and atresia).[1]

In rectal atresia, the lumen is interrupted by a thin membrane or dense fibrous tissue. The classification of rectal atresia is divided into five types (Fig. 3).[1]

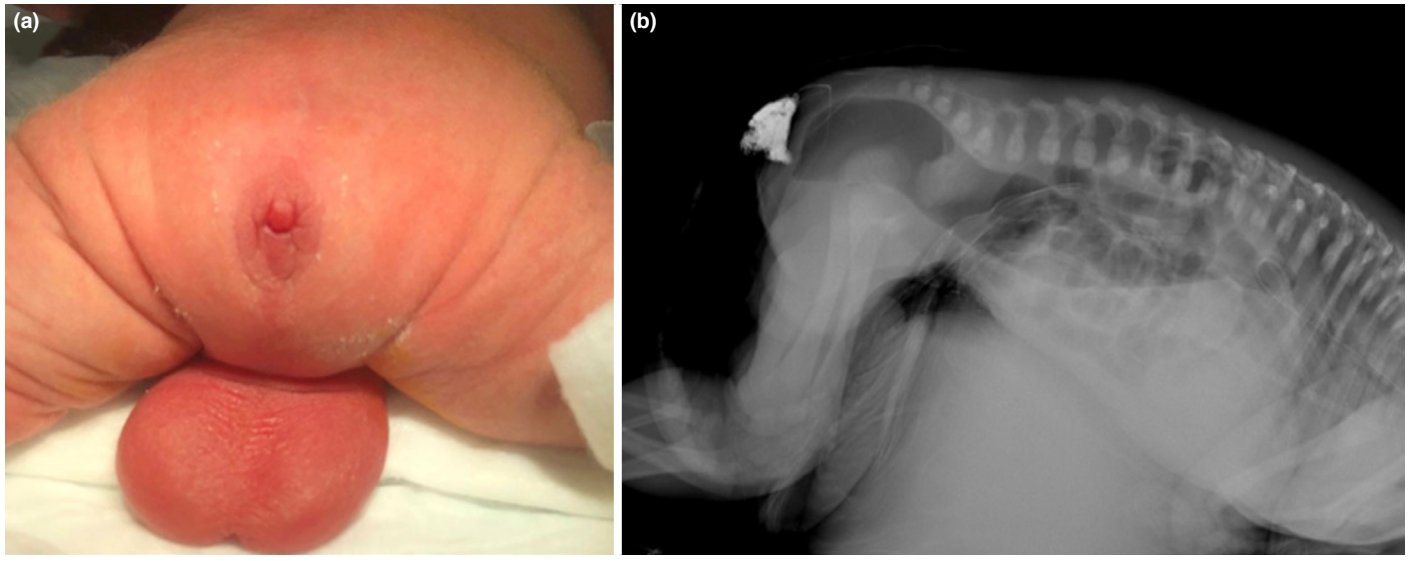

Figure 1: (a) Perineum, **(b)** An invertogram after 24 hours of birth.

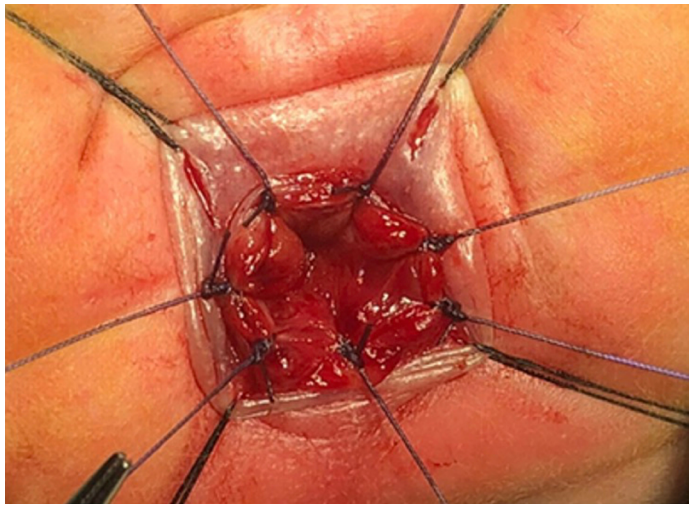

Figure 2: Trans-anal anorectal anastomosis.

Type I: Rectal stenosis: intramural (A) or web with a hole (B)

Type II: Rectal atresia with a septal defect

Type III: Rectal atresia with a fibrous cord between two atretic ends

Type IV: Rectal atresia with a gap

Type V: Multiple; (A) rectal atresia with stenosis, (B) multiple rectal atresia, and (C) thickened Houston valves/multiple rectal stenosis (modified from Gupta and Shilpa).

Clinical presentations in rectal atresia include failure to pass meconium, inability to insert a firm rectal tube or thermometer into the anal verge, and, when the diagnosis is delayed, abdominal distention or bilious vomiting. Rectal atresia is usually diagnosed when a firm tube fails to pass into the rectum after routine control at birth. Diagnosis can be delayed in cases of rectal stenosis because meconium may pass. In our hospital, all newborns are screened by placing a wide nasogastric tube into the anal canal to confirm patency. Therefore, all congenital anorectal malformations, including rectal atresia, are noticed during the first examination.

Imaging is important for planning surgery, confirming the exact anatomy, and investigating associated anomalies. Plain X-ray and cross-table X-ray (invertogram), abdominal and pelvic ultrasound, cranial and spinal ultrasound, echocardiography, and MRI have been used for preoperative scanning.[6] Because of the possibility of an associated presacral mass (29% of patients in Peña's series),[7] some authors have suggested spinal ultrasound and/or pelvic MRI in the newborn period. An invertogram after 18 hours of birth with a radiopaque marker placed in the anal canal may help determine the distance between the pouches.[4] The gap between the pouches in our case was measured as 5 mm by an invertogram at the 24th postnatal hour.

Associations with congenital cardiac and urogenital anomalies, skeletal anomalies, and presacral masses in cases with rectal atresia have been reported in the literature.[1,2,5–8] Glanular hypospadias was reported in one case with combined VSD.[8] More than 50% of patients with anorectal malformations have other concurrent congenital anomalies.[2,9] In our case, left renal agenesis was detected on abdominal US, cranial and spinal ultrasound findings were normal, and echocardiography was normal. In addition, he had hypospadias with hooded prepuce.

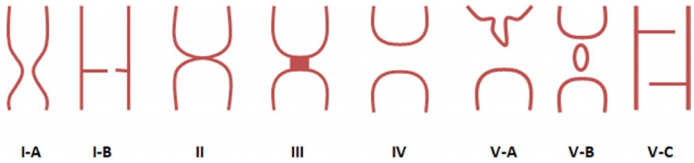

Figure 3: The classification of rectal atresia.

Many operative approaches have been described for the treatment of rectal atresia, but there is no clear consensus on the best management. Operative techniques include posterior sagittal anorectoplasty, transanal endorectal pull-through, transanal end-to-end rectorectal anastomosis, Y-V anorectoplasty, abdominoperineal pull-through, single-stage sacral approach, magnamosis, transanal membranotomy, endoscopic transanal approach, Soave pull-through, and Duhamel's procedure.[1–3,5,9,10] Each surgical technique has its own advantages and disadvantages. The main objective of surgical repair in rectal atresia is to preserve the sphincter complex, anal canal, and dentate line for good continence. Total mobilization and resection of the anal canal should be avoided in order not to disrupt the sphincter mechanism. Preservation of the anal canal offers a safe, easy, and effective technique for rectal atresia and decreases the risk of injury. In addition, depending on the type of rectal atresia and associated anomalies, opening a stoma may generally be advised. Colostomy may not be required in the first four types of rectal atresia; however, performing a colostomy in type V atresia ensures fecal discharge and anastomotic safety during the repair of rectal atresia. Colostomy was not initially considered in our case because the gap length was very short, at 5 mm, and type II rectal atresia was present; therefore, it was decided to start the surgery with the primary transanal approach.

CONCLUSION

In conclusion, rectal atresia is an extremely rare condition, and it is usually associated with other anomalies. The association of renal agenesis, glanular hypospadias, and rectal atresia has not been previously reported in the English literature. Transanal anorectal anastomosis without stoma offers a safe, effective, and comfortable technique for the treatment of rectal atresia, especially types I, II, III, and IV, and decreases the risk of injury.

Statement

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: We declared taking informed written consent for the publication of clinical photographs/material, from the legal guardian of the patient with an understanding that every effort will be made to conceal the identity of the patient, however it cannot be guaranteed.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Author Contributions: Concept – MHÇ, AC; Design – MHÇ, AC; Supervision – MHÇ, AC, ODA, SC; Results – AC; Materials – MHÇ, AC, ODA, SC; Data Collection and/or Processing – MHÇ, AC, ODA, SC; Analysis and/or Interpretation – MHÇ, AC; Literature Search – MHÇ, AC; Writing – MHÇ, AC; Critical Reviews – MHÇ, AC, ODA, SC.

Peer-review: Externally peer-reviewed.

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LETTER TO THE EDITOR

Reevaluating the clinical role of transcutaneous tibial nerve stimulation in the management of overactive bladder

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To the Editor,

I read with great interest the study by Şen et al.,[1] entitled "Efficacy of transcutaneous posterior tibial nerve stimulation in women with idiopathic overactive bladder." In this prospective study, the authors investigated the effects of transcutaneous posterior tibial nerve stimulation (TTNS) in women with idiopathic overactive bladder (OAB) who were unresponsive to anticholinergic therapy. The findings demonstrated meaningful clinical improvements in urinary symptoms, including reductions in urinary frequency and urge incontinence episodes, accompanied by enhanced pelvic floor muscle strength. The absence of reported adverse events highlights the favorable safety and tolerability of TTNS as a noninvasive neuromodulation technique. A notable strength of this study is its structured treatment protocol, combined with behavioral and pelvic floor interventions, reflecting a comprehensive clinical approach. However, certain limitations, including the relatively small sample size, lack of a control group, and short follow-up period, should be considered when interpreting these results. Despite these limitations, the study provides valuable evidence supporting TTNS as a promising therapeutic option for patients with refractory OAB. Emerging evidence and updated guideline algorithms published following the original study have expanded the role of TTNS in the management of overactive bladder, and this letter aims to interpret the study's findings within this contemporary clinical framework.

The noninvasive nature of TTNS, together with its favorable safety profile, makes it an attractive option for clinical practice. Neuromodulation through the activation of somatic afferent fibers in the tibial nerve has been shown to influence bladder function through the indirect modulation of efferent pathways. Compared with sacral neuromodulation, tibial nerve stimulation offers several practical advantages, including easier accessibility and a lower incidence of adverse effects and complications.[2] These characteristics are particularly relevant in the long-term management of OAB, in which treatment tolerability and adherence are essential.

Clinical evidence consistently demonstrates that tibial nerve stimulation improves key OAB symptoms, including urgency, urinary frequency, nocturia, and urge incontinence.[3] In addition, its therapeutic effects may persist beyond the stimulation period, suggesting a sustained neuromodulatory influence rather than a purely transient response.[4] Advances in stimulation techniques have further expanded their applicability in the field. While percutaneous tibial nerve stimulation (PTNS) requires repeated outpatient procedures, TTNS provides a noninvasive alternative that is easier to implement in routine practice. Comparative studies have reported similar efficacy between TTNS and PTNS, with TTNS offering advantages in terms of patient comfort and acceptability.[5] Emerging technologies,

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including implantable and wireless systems, further support the evolution of more patient-centered neuromodulation strategies.

Although the mechanisms remain incompletely understood, experimental studies indicate that the effects of tibial nerve stimulation are frequency-dependent and involve both spinal and supraspinal pathways.[6] Coactivation of adjacent neural structures, such as the saphenous nerve, may also contribute to the inhibition of bladder activity, supporting the biological plausibility of this approach.[7]

Randomized studies comparing tibial nerve stimulation (TNS) with no active treatment have demonstrated improvements in urinary frequency, urgency, nocturia, and UUI episodes, along with reductions in symptom-related discomfort, without serious adverse events.[8] Although cure rates remain unclear, these results indicate meaningful symptom relief and improved quality of life. Notably, transcutaneous and percutaneous TNS yield comparable clinical outcomes, with no consistent evidence favoring one modality over the other.[9] Variations in stimulation intensity also appear to have minimal effects on outcomes, while transcutaneous TNS is generally associated with fewer adverse effects than percutaneous techniques.[8,9]

TNS has also demonstrated comparable and, in some cases, superior effectiveness relative to both pharmacological and nonpharmacological treatments. Studies comparing TNS with antimuscarinic agents, including oxybutynin, solifenacin, and tolterodine, have reported similar improvements in urinary symptoms, with some evidence favoring TTNS in the short term.[9] When used in combination with pharmacological or behavioral therapies, TNS may provide additional and more sustained improvements in selected patients, although this benefit has not been consistently observed across all studies, particularly when combined with other electrical stimulation modalities.[3]

Current evidence-based recommendations suggest that both transcutaneous and percutaneous TNS may be considered for symptom control in women with UUI or OAB, either as standalone or combination therapies. However, further high-quality studies are needed to better define their role within treatment algorithms.

In clinical practice at our hospital, TTNS has been increasingly employed in patients with OAB who do not sufficiently benefit from behavioral therapy, bladder retraining, or pharmacological treatment. Patients wishing to avoid invasive interventions, such as intravesical botulinum toxin injections, often prefer this treatment. In this population, TTNS appears to be well tolerated and promising, with encouraging outcomes in terms of symptom control and patient satisfaction. Although these observations are derived from clinical experience rather than controlled trials, they align with previously reported findings.

Collectively, the findings of Şen et al.[1] and the expanding body of evidence suggest that TTNS plays a broader role in OAB management than previously recognized. Given its safety, accessibility, and patient acceptability, TTNS may be considered not only for refractory cases but also earlier in the treatment pathway for appropriately selected patients.

In conclusion, the study by Şen et al.[1] contributes valuable evidence to the field and aligns with the evolving role of neuromodulation in the treatment of OAB. Further well-designed studies are warranted to clarify its long-term efficacy and optimize treatment strategies.

Statement

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