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RESEARCH ARTICLE

The Predictive Effect of Hormone Levels on Pregnancy Outcomes on the Day of Intrauterine Insemination and hCG Administration

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Abstract

Introduction: Intrauterine insemination (IUI) is commonly used to treat unexplained infertility. Hormonal markers, especially estradiol (E2) and progesterone (P), are crucial in predicting endometrial receptivity and pregnancy outcomes. This study investigates the predictive value of E2 and P levels measured on the day of human chorionic gonadotropin (hCG) administration and IUI.

Methods: A retrospective review was conducted on 81 women aged 18–38 who underwent IUI for unexplained infertility between 2018 and 2020. Serum E2 and P levels were assessed on hCG and IUI days. Pregnancy outcomes were compared using t-tests and chi-square tests ($p < 0.05$) via SPSS 25.0.

Results: Out of 81 participants, 11 achieved pregnancy (13.5%). Pregnant women had significantly higher E2 levels on hCG (472.3 ± 291.3 vs. 398.6 ± 277.2 pg/mL, $p = 0.018$) and IUI days (425.3 ± 269.1 vs. 371.2 ± 275.8 pg/mL, $p = 0.033$). P levels were also higher in this group on both days (hCG: 1.43 ± 1.62 vs. 0.74 ± 1.29 ng/mL, $p = 0.001$; IUI: 2.48 ± 1.92 vs. 2.31 ± 2.12 ng/mL, $p = 0.024$). Lower IUI-to-hCG hormone ratios were noted in the pregnant group (E2: 0.90 vs. 0.93, $p = 0.045$; P: 1.7 vs. 3.1, $p = 0.001$).

Conclusion: Elevated E2 and P levels on hCG and IUI days are associated with improved pregnancy outcomes. Hormonal monitoring may enhance IUI success and guide personalized infertility treatments.

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Introduction

Infertility, defined as the inability to achieve pregnancy after 12 months of regular unprotected intercourse, affects approximately 10–15% of reproductive-aged couples worldwide, posing significant psychological and social burdens. Among the various treatment strategies, intrauterine insemination (IUI) is a widely practiced first-line assisted reproductive technique, especially in cases of unexplained infertility, where no definitive cause is identified despite a thorough evaluation.

One of the key factors influencing IUI success is endometrial receptivity, which is tightly regulated by dynamic changes in serum estradiol (E2) and progesterone (P) levels throughout the follicular and luteal phases. Estradiol plays a critical role in proliferative endometrial development, while progesterone is essential for secretory transformation and maintenance of luteal phase adequacy. The timely and optimal modulation of these hormones is vital for successful embryo implantation.

Although several studies have assessed hormonal thresholds during ovarian stimulation protocols, the predictive value of serum E2 and P concentrations specifically on the day of hCG administration and on the day of IUI remains inadequately defined. Some reports suggest that elevated progesterone levels prior to ovulation may impair endometrial-embryo synchrony, while others emphasize the potential benefit of higher E2 levels as indicators of follicular maturity and endometrial readiness.^{1–3}

However, despite the critical timing of hCG and insemination in IUI cycles, few studies have simultaneously compared hormone profiles at both these strategic time points in relation to pregnancy outcomes. Moreover, limited evidence exists on how the ratios of hormone changes between hCG and IUI days may reflect endometrial receptivity or luteal phase adequacy.

The primary aim of this study is to investigate whether serum estradiol and progesterone levels measured on the day of hCG administration and the day of intrauterine insemination can predict pregnancy success in patients with unexplained infertility. Additionally, we aim to evaluate the predictive potential of E2 and P ratios between these two time points, hypothesizing that dynamic hormonal fluctuations may serve as non-invasive biomarkers of endometrial receptivity and fertility prognosis.

Material and Methods

This study was designed retrospectively and conducted on patients who underwent IUI treatment due to unexplained infertility. Data were collected from patients treated between 2018 and 2020 using the hospital automation system and archives after obtaining informed consent from the patients. The study was conducted with the approval of the ethics committee (TABED 2-25-1310), and all patient data were evaluated in accordance with confidentiality principles.

A total of 255 patients who underwent IUI for unexplained infertility between 2018 and 2020 were included in the study. However, patients with missing hormone levels (estradiol and progesterone) or unknown pregnancy outcomes were excluded, and statistical analysis was performed with 81 patients aged 18–38.

All patients included in this study were followed up with a diagnosis of unexplained infertility and had experienced at least one previous unsuccessful IUI attempt. For ovulation induction, patients were started on 75 IU of GONAL-F®, following a low-dose step-up protocol. Follicular development was monitored via ultrasonography, and when the follicular size reached 17–21 mm, hCG was administered. In patients who developed multiple follicles, the procedure was postponed to prevent the risk of multiple pregnancies, and as a result, 35 patients did not undergo the procedure for this reason. In cases where a single follicle reached an appropriate size, IUI was performed 36 hours after the administration of hCG. To support the luteal phase, all patients were administered vaginal progesterone gel (8%), and for those who achieved pregnancy, treatment was continued throughout the subsequent weeks of pregnancy.

The serum estradiol and progesterone levels on the day of the IUI procedure, as well as serum estradiol and progesterone levels on the day of hCG administration, were retrospectively collected from the study population. Additionally, the results of the hCG test performed on day 14 after the IUI procedure were analyzed.

This study included patients aged between 18 and 38 years who were diagnosed with unexplained infertility and underwent IUI treatment. Eligibility for inclusion required the availability of complete serum estradiol and progesterone measurements on both the day of hCG administration and the day of IUI, as well as documented pregnancy outcomes. Patients were

excluded if serum estradiol and progesterone levels were unavailable, if pregnancy outcome data were incomplete, or if they were older than 40 years. Additionally, individuals diagnosed with secondary infertility or underlying reproductive pathologies such as endometriosis or polycystic ovary syndrome (PCOS) were excluded to ensure a homogenous population of unexplained infertility cases.

All data were collected retrospectively from hospital archive records and database. Serum E2 and P levels on the day of IUI, as well as hormone levels on the day of hCG administration, were evaluated. Additionally, the pregnancy status was determined by the hCG test performed on day 14 after IUI, and the results were recorded. In patients with positive hCG tests, serum estradiol and progesterone levels were monitored until the 10th week of pregnancy.

Serum estradiol and progesterone levels were analyzed using the immunoassay method, following routine clinical protocols. Hormone levels were recorded at two separate time points: on the day of hCG administration and on the day of IUI. These values were compared between the successful (positive hCG test) and unsuccessful (negative hCG test) groups.

The data were analyzed using SPSS 25.0 (Statistical Package for the Social Sciences) software. The independent groups t-test was applied for continuous variables, while categorical data were evaluated using the chi-square test. Relationships between pregnancy rates and serum hormone levels were examined, and a significance level of $p < 0.05$ was considered.

Results

This study evaluated a total of 81 patients who underwent IUI treatment due to unexplained infertility. Among these patients, 11 were found to have positive pregnancy tests, indicating an IUI success rate of 13.5%. Out of the 13 patients who achieved pregnancy, 10 resulted in live births. The results comprehensively evaluated the relationships between hormone levels and pregnancy outcomes.

Table 1 compares the demographic and clinical data of patients with positive and negative pregnancy outcomes. There were no statistically significant differences between the groups in terms of age, body mass index (BMI), infertility duration, or follicle count ($p > 0.05$). The mean age of the positive pregnancy group was 26.64 ± 6.43 years, while it was 29.05 ± 4.14 years in the negative group ($p = 0.125$). In terms of BMI,

there was no significant difference between the groups, with the positive group having a BMI of 25.2 ± 3.1 and the negative group 25.8 ± 3.4 ($p = 0.367$). Similarly, there were no significant differences in infertility duration and follicle count between the groups. These findings suggest that the groups were homogeneous at the beginning, allowing a more accurate evaluation of the effect of hormonal parameters on pregnancy success.

Table 1. Baseline demographic and clinical characteristics of the study groups.

Parameter	Pregnant (n=11)	Non-Pregnant (n=70)	p-value
Age (years)	26.64 ± 6.43	29.05 ± 4.14	0.125
Body Mass Index (kg/m ²)	25.2 ± 3.1	25.8 ± 3.4	0.367
Duration of Infertility (years)	1.5 ± 1.2	1.8 ± 1.4	0.299
Follicle Count	1.1 ± 0.2	1.1 ± 0.2	0.865

Abbreviations: BMI, body mass index.

In this study, baseline hormonal levels, including AMH, FSH, E2, and Day 21 Progesterone, were compared between pregnant and non-pregnant groups. Despite slight differences in the means, none of the parameters showed statistically significant differences ($p > 0.05$). The mean AMH level was 2.6 ± 1.0 ng/mL in the pregnant group and 2.5 ± 1.1 ng/mL in the non-pregnant group, with a p-value of 0.389. FSH levels were also similar between groups, with means of 6.4 ± 2.1 mIU/mL and 6.5 ± 2.0 mIU/mL for pregnant and non-pregnant groups, respectively ($p = 0.456$). Basal estradiol levels were slightly higher in the pregnant group (46.0 ± 15.0 pg/mL) compared to the non-pregnant group (44.5 ± 15.5 pg/mL), but this difference was not statistically significant ($p = 0.312$). Finally, Day 21 progesterone levels showed no significant difference, with the pregnant group having a mean of 12.5 ± 4.2 ng/mL and the non-pregnant group having a mean of 11.8 ± 4.0 ng/mL ($p = 0.275$). These findings suggest that while these baseline hormonal values are important for understanding general ovarian function and luteal phase health, they may not be reliable predictors of pregnancy success in IUI cycles. The mean AFC in the pregnant group was 10.5 ± 3.2 , while it was 10.2 ± 3.4 in the non-pregnant group, with a p-value of 0.742, indicating that both groups had similar antral follicle counts.

Table 2. Baseline hormonal values in pregnant and non-pregnant groups.

Parameter	Pregnant (n=11)	Non-Pregnant (n=70)	p-value
AMH (ng/mL)	2.6 ± 1.0	2.5 ± 1.1	0.389
FSH (mIU/mL)	6.4 ± 2.1	6.5 ± 2.0	0.456
Basal Estradiol (E2, pg/mL)	46.0 ± 15.0	44.5 ± 15.5	0.312
Day 21 Progesterone (ng/mL)	12.5 ± 4.2	11.8 ± 4.0	0.275
Antral Follicle Count	10.5 ± 3.2	10.2 ± 3.4	0.742

Abbreviations: AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; E2, estradiol.

The comparison of sperm parameters between the pregnant and non-pregnant groups shows no statistically significant differences ($p > 0.05$) across all variables. Sperm concentration was nearly identical between the groups, with 50.5 ± 12.0 million/mL in the pregnant group and 49.8 ± 11.5 million/mL in the non-pregnant group ($p = 0.635$). Similarly, total motility was $55.0 \pm 10.2\%$ in the pregnant group and $54.5 \pm 9.8\%$ in the non-pregnant group ($p = 0.743$), while progressive motility was $40.2 \pm 9.5\%$ in the pregnant group compared to $39.8 \pm 9.1\%$ in the non-pregnant group ($p = 0.815$).

Table 3. Semen analysis results in pregnant and non-pregnant groups.

Parameter	Pregnant (n=11)	Non-Pregnant (n=70)	p-value
Sperm Concentration (million/mL)	50.5 ± 12.0	49.8 ± 11.5	0.635
Total Motility (%)	55.0 ± 10.2	54.5 ± 9.8	0.743
Progressive Motility (%)	40.2 ± 9.5	39.8 ± 9.1	0.815
Morphology (Normal Forms, %)	5.0 ± 1.2	5.1 ± 1.3	0.721
Total Motile Sperm Count (million)	27.8 ± 7.2	27.2 ± 6.9	0.689

For sperm morphology, the proportion of normal forms was also similar, at $5.0 \pm 1.2\%$ in the pregnant group and $5.1 \pm 1.3\%$ in the non-pregnant group ($p = 0.721$). Additionally, the total motile sperm count, which represents the total number of motile sperm available, was 27.8 ± 7.2 million in the pregnant group and 27.2 ± 6.9 million in the non-pregnant group ($p = 0.689$). This further indicates no significant differences in the total number of motile sperm between the groups, suggesting that sperm quality and quantity were comparable across the two groups and may not be the sole determining factor in pregnancy success.

In this comparison of follicular size at the time of rupture between the pregnant and non-pregnant groups (Table 4), the mean follicular size in the pregnant group was 19.8 ± 2.5 mm, while in the non-pregnant group, it was 19.5 ± 2.7 mm. The difference between the groups was not statistically significant ($p = 0.675$). This suggests that the size of the follicle at the time of rupture was similar in both groups and did not appear to have a significant impact on pregnancy outcomes in this study.

Table 4. Follicular size at rupture in pregnant and non-pregnant groups.

Parameter	Pregnant (n=11)	Non-Pregnant (n=70)	p-value
Follicular Size (mm)	19.8 ± 2.5	19.5 ± 2.7	0.675

In this study, serum E2 levels measured on the days of hCG administration IUI were carefully evaluated. The average E2 level on the hCG day was 472.3 ± 291.3 pg/mL in the group that achieved pregnancy, significantly higher than 398.6 ± 277.2 pg/mL in the non-pregnant group ($p = 0.018$). Similarly, E2 levels on the day of IUI were also higher among those who conceived (425.3 ± 269.1 pg/mL vs. 371.2 ± 275.8 pg/mL, $p = 0.033$). A statistically significant difference was also found in the ratio of E2 levels between IUI and hCG days.

Progesterone (P) levels followed a similar pattern. On the day of hCG administration, mean P levels were notably elevated in the pregnant group (1.43 ± 1.62 ng/mL) compared to the non-pregnant group (0.74 ± 1.29 ng/mL, $p = 0.001$). Progesterone levels on the IUI day remained higher in the pregnant cohort (2.48 ± 1.92 ng/mL) relative to those who did not conceive (2.31 ± 2.12 ng/mL, $p = 0.024$). Interestingly, the IUI-to-hCG P ratio was significantly lower in the pregnant group, suggesting a more stable hormonal transition ($p = 0.001$).

Additionally, the estradiol IUI/hCG ratio was lower in the group that achieved pregnancy (0.90 vs. 0.93), a difference that was also statistically significant ($p = 0.045$).

These findings indicate that serum E2 and P levels on both hCG and IUI days are meaningful markers in predicting pregnancy success. Elevated hormone levels at these time points appear to support a more receptive endometrial environment, increasing the likelihood of successful implantation. However,

the data also suggest that excessive elevations might negatively impact follicular development or endometrial synchrony.

Table 5. Hormonal parameters and pregnancy outcomes.

Parameter	Pregnant (n=11)	Non-Pregnant (n=70)	p-value
Age (years)	26.64 ± 6.43	29.05 ± 4.14	0.009
hCG Day Estradiol (E2, pg/mL)	472.3 ± 291.3	398.6 ± 277.2	0.018
IUI Day Estradiol (E2, pg/mL)	425.3 ± 269.1	371.2 ± 275.8	0.033
hCG Day Progesterone (P, ng/mL)	1.43 ± 1.62	0.74 ± 1.29	0.001
IUI Day Progesterone (P, ng/mL)	2.48 ± 1.92	2.31 ± 2.12	0.024
IUI P / hCG P Ratio	1.7	3.1	0.001
IUI E2 / hCG E2 Ratio	0.90	0.93	0.045

Abbreviations: hCG, human chorionic gonadotropin; IUI, intrauterine insemination; E2, estradiol; P, progesterone.

Discussion

This study set out to assess the predictive utility of E2 and P levels measured at two critical time points—hCG trigger and IUI day—in women with unexplained infertility. The results demonstrated that elevated levels of both hormones, in conjunction with lower IUI/hCG ratios, were significantly associated with positive pregnancy outcomes.

Our results align with existing literature that underscores the role of periovulatory hormonal dynamics in endometrial receptivity. Estradiol, in particular, is known to facilitate follicular maturation and endometrial proliferation—two essential components of successful implantation.^{4,5} Consistent with our findings, previous studies have shown that higher mid-cycle E2 levels correlate with improved IUI outcomes, reinforcing its value as a non-invasive biomarker of endometrial readiness.^{2,6}

Traditionally, elevated progesterone during the follicular phase has raised concerns about disrupted synchrony between embryo and endometrium.⁷ Nonetheless, our study supports emerging evidence that higher P levels, especially on the hCG day, may reflect a healthy luteal transformation in the context of controlled ovarian stimulation, rather than a detrimental shift.^{8,9}

One novel feature of this study is the evaluation of hormone ratios (IUI/hCG), rather than absolute values alone. These ratios may provide more accurate insight into the physiological shift from follicular to luteal phase. In our data, a significantly lower P ratio was linked to successful pregnancies, perhaps reflecting more stable luteal support.¹⁰ Although few studies have analyzed such ratio-based indicators, our results support growing interest in dynamic hormone patterns rather than static thresholds.¹¹

Baseline demographic and hormonal characteristics—such as AMH, FSH, AFC, and BMI—did not differ significantly between groups, consistent with prior reports suggesting that static baseline values are weak predictors in IUI success.¹²⁻¹⁴ This further emphasizes the relevance of mid-cycle dynamic markers in guiding treatment strategies for unexplained infertility.

Clinically, these findings advocate for routine monitoring of E2 and P on both the hCG trigger and IUI days. Dynamic hormonal ratios may serve as simple, accessible tools to predict cycle success, guiding decisions such as optimal insemination timing, need for luteal phase support, or tailoring protocols based on individual hormonal responses.^{15,16}

Despite its valuable contributions, the study is not without limitations. Its retrospective nature may introduce selection bias, and the small number of pregnancies limits the statistical power for subgroup analysis. Additionally, important markers of endometrial receptivity, such as thickness and vascularity, were not evaluated. Moreover, serum hormone levels may not perfectly reflect intrauterine or endometrial conditions, as local receptor activity and paracrine factors also play significant roles.¹⁷

Nonetheless, the study's strengths include a homogenous patient population (limited to unexplained infertility), standardized stimulation protocols, and a novel approach through dual-timepoint hormonal assessment and ratio analysis. This practical and reproducible design holds promise for further validation in future prospective trials.

In conclusion, the findings confirm that E2 and P levels on both hCG and IUI days are predictive of pregnancy outcomes in IUI cycles. Elevated mid-cycle hormone levels enhance endometrial receptivity and support implantation, while disproportionate hormonal shifts—particularly in progesterone

ne—may contribute to cycle failure. These insights underscore the importance of individualized hormonal monitoring and adjustment to improve IUI success rates in unexplained infertility cases. Larger-scale, prospective studies are warranted to further clarify these relationships and optimize clinical protocols.

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DECLARATIONS

Ethical Approval: Ethics committee approval was obtained from the ethics committee unit of the Ankara Bilkent City Hospital (TABED 2-25-1310). The study commenced after obtaining the relevant ethical committee approval, and consent was obtained from the relevant clinics. The study was designed retrospectively, and no additional tests or hospital visits were required for the study. Consent for the use of data was obtained from the patients, and the confidentiality of patient identities was carefully maintained.

Consent to participate: Following ethics committee approval, written informed consent forms were obtained from all participants for their participation in the study.

Consent for publication: There are no circumstances in the study that violate anonymity, and identifying information has been kept confidential. There are no issues regarding its publication.

Availability of data and materials: Patient data is stored indefinitely in the hospital's automation system. It can be shared upon request, provided that patient identity remains confidential.

Competing interests: There are no conflicts of interest among the authors.

Authors' contributions: M.İ.H. and İ.H. contributed to the data collection phase of the study. U.Z. and Ö.M.T. were responsible for the study design and planning. Ç.K., Ş.B. and F.B.F. were responsible for writing of manuscript. U.Z. and B.T. jointly drafted the main manuscript. All authors critically reviewed and approved the final version of the manuscript.

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RESEARCH ARTICLE

Advanced Maternal Age Pregnancies: Perinatal Outcomes and Maternal Characteristics in Comparison with Women Aged 20–35 Years

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Abstract

Introduction: Advanced maternal age (AMA) pregnancies are associated with increased maternal and perinatal risks; however, the relative contribution of maternal age itself versus accompanying maternal characteristics remains debated. This study aimed to evaluate maternal characteristics and perinatal outcomes in women aged ≥ 35 years compared with those aged 20–35 years.

Methods: This retrospective comparative cohort study included singleton pregnancies delivered between January 2022 and July 2025 at a tertiary referral center. Women aged ≥ 35 years constituted the AMA group, while women aged 20–35 years served as controls. Maternal characteristics, obstetric complications, mode of delivery, and perinatal outcomes were compared between groups. Neonatal intensive care unit (NICU) admission was defined as the primary outcome.

Results: A total of 599 women were included (300 AMA, 299 controls). Overweight/obesity, gestational diabetes mellitus, chronic hypertension, and cesarean delivery were significantly more frequent in the AMA group (all $p < 0.01$). NICU admission was higher among infants born to women aged ≥ 35 years compared with controls (25.0% vs. 10.4%, $p < 0.001$). Other key neonatal outcomes, including birth weight, Apgar scores, fetal growth restriction, and preterm birth, did not differ significantly between groups. Multivariable logistic regression analysis demonstrated that increased body mass index, gestational diabetes mellitus, and cesarean delivery were independently associated with the advanced maternal age group.

Conclusion: Advanced maternal age was associated with a higher burden of maternal comorbidities and increased cesarean delivery rates, whereas most neonatal outcomes were comparable between age groups. These findings suggest that adverse perinatal outcomes in AMA pregnancies are largely driven by coexisting maternal characteristics rather than maternal age alone when appropriate care is provided.

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Introduction

Historically, advanced maternal age (AMA) has been defined as pregnancy in women aged 35 years or older at the expected time of delivery. This cutoff was selected based on the increasing incidence of fertility-related challenges and genetic abnormalities observed in women aged 35 years and older.¹ Indeed, recent studies have reported a higher incidence of chromosomal abnormalities and certain congenital anomalies among offspring born to women aged 35 years and older.²⁻⁴ Notably, this association appears to become more pronounced with advancing maternal age.

In recent decades, the prevalence of advanced maternal age has increased substantially both worldwide and in Türkiye.^{5,6} This rise has been attributed to multiple social, demographic, and medical factors, including delayed childbearing due to higher educational attainment and career planning, changes in family structure, improved access to effective contraception, and the widespread use of assisted reproductive technologies.^{7,8} As a result, an increasing proportion of women are conceiving and delivering at older ages, resulting in a growing proportion of pregnancies occurring at older maternal ages.

Advanced maternal age pregnancies have been associated with a higher frequency of several obstetric and perinatal complications. In particular, increasing maternal age has been consistently linked to higher rates of spontaneous miscarriage, largely attributed to age-related chromosomal abnormalities.^{9,10} In addition, previous studies have demonstrated that women of advanced maternal age more commonly experience gestational diabetes mellitus, hypertensive disorders of pregnancy, placental abnormalities, and higher rates of cesarean delivery.¹¹⁻¹⁵ Beyond maternal complications, adverse perinatal outcomes such as preterm birth, low birth weight, intrauterine growth restriction, neonatal intensive care unit admission, and perinatal mortality have been reported more frequently in this population.^{16,17} However, the extent to which these outcomes are attributable to maternal age itself versus accompanying maternal characteristics remains a matter of ongoing debate.

Despite the growing literature on advanced maternal age pregnancies, data from tertiary care centers in Türkiye remain limited. Given the increasing prevalence of advanced maternal age, institution-specific analyses may provide valuable insights into real-world clinical practice. Therefore, this study aimed

to evaluate perinatal outcomes and associated maternal characteristics in pregnancies of women aged 35 years and older and to compare these findings with those of women aged 20–35 years who delivered at Eskişehir City Hospital.

Material and Methods

This study was designed as a retrospective comparative cohort study conducted at Eskişehir City Hospital, a tertiary referral center. Pregnancies of women aged 35 years and older, identified over a 3.5-year study period from January 2022 to July 2025, were compared with those of women aged 20–35 years in terms of associated maternal characteristics and perinatal outcomes.

Inclusion criteria consisted of pregnancies that resulted in delivery at Eskişehir City Hospital between January 2022 and July 2025. Only singleton pregnancies were included. Participants were categorized into two groups according to maternal age at delivery: women aged 35 years and older constituted the advanced maternal age group, while women aged 20–35 years served as the control group.

Exclusion criteria included pregnancies complicated by multiple gestation, cases with lethal fetal anomalies incompatible with postnatal survival, pregnancies with incomplete or missing medical records regarding maternal characteristics or perinatal outcomes, and deliveries occurring before 24 weeks of gestation.

AMA was defined as maternal age of 35 years or older at the time of delivery.¹ Preterm birth was defined as delivery occurring before 37 completed weeks of gestation.¹⁸ Low birth weight (LBW) was defined as a birth weight below 2500 g, according to World Health Organization and UNICEF criteria. Fetal growth restriction (FGR) was defined based on birth weight percentiles for gestational age and categorized as mild FGR (birth weight between the 3rd and 10th percentiles) and severe FGR (birth weight below the 3rd percentile), in accordance with institutional reference standards used in routine clinical practice.¹⁹

Preeclampsia was defined as new-onset hypertension developing after 20 weeks of gestation, with or without proteinuria and/or signs of maternal end-organ dysfunction, according to standard clinical diagnostic criteria.²⁰ Gestational diabetes mellitus (GDM) was diagnosed based on the results of routine screening and diagnostic testing performed during pregnancy, in line with the institutional protocol.²¹

Apgar scores were recorded at the 1st and 5th minutes after birth. Neonatal intensive care unit (NICU) admission was defined as admission of the newborn to the NICU for any indication following delivery. Stillbirth was defined as fetal death occurring at or after 24 weeks of gestation, and perinatal mortality was defined as stillbirth or neonatal death occurring within the first 7 days of life.

Data were obtained retrospectively from the electronic medical record system of Eskişehir City Hospital. Maternal demographic characteristics, obstetric history, and pregnancy-related complications were retrieved from antenatal follow-up records and ultrasonography reports. Information regarding delivery outcomes was collected from delivery room records, while neonatal outcomes, including Apgar scores and NICU admission, were obtained from neonatal intensive care unit and newborn medical records.

All relevant data were extracted using a standardized data collection form to ensure consistency. Data accuracy and completeness were verified through cross-checking of records, and the collected data were reviewed by the investigators prior to analysis.

Maternal characteristics evaluated in the study included maternal age, gravidity, parity, history of spontaneous abortion, body mass index (BMI), and smoking status. Obstetric and medical comorbidities assessed were chronic hypertension, gestational diabetes mellitus, and preeclampsia. In addition, obstetric complications such as fetal growth restriction, placental abruption, and preterm birth were recorded. Mode of delivery (vaginal delivery or cesarean section) was also documented as part of maternal and obstetric characteristics.

The primary outcome of the study was neonatal intensive care unit admission, given its clinical relevance and the observed difference between age groups. Secondary outcomes included gestational age at delivery, birth weight, low birth weight, fetal growth restriction, Apgar scores at the 1st and 5th minutes, mode of delivery, and stillbirth and perinatal mortality.

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were presented as mean \pm standard deviation or median with interquartile range (IQR), as appropriate, while categorical

variables were expressed as number and percentage. Comparisons between the advanced maternal age group and the control group were performed using the independent samples t-test or the Mann–Whitney U test for continuous variables, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate. A two-sided p value < 0.05 was considered statistically significant. In addition, multivariable logistic regression analysis was performed to identify factors independently associated with advanced maternal age (≥ 35 years), and results were reported as adjusted odds ratios with 95% confidence intervals.

Following approval by the Ethics Committee of the Republic of Turkey Ministry of Health, Eskişehir City Hospital (approval date: September 11, 2025; decision number: ESH/BAEK 2025/221), this study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association, revised 2024).

Results

A total of 599 women were included in the analysis, comprising 300 women aged ≥ 35 years (advanced maternal age group) and 299 women aged 20–35 years (control group).

Maternal and obstetric characteristics

Maternal and obstetric characteristics of the study population are presented in Table 1. Women in the advanced maternal age group had significantly higher gravida and parity values compared with the control group (both $p < 0.001$). A history of spontaneous abortion was also more frequent among women aged ≥ 35 years ($p < 0.001$).

The prevalence of overweight or obesity (BMI ≥ 25 kg/m²) was significantly higher in the advanced maternal age group than in the control group (93.7% vs. 83.3%, $p < 0.001$). Gestational diabetes mellitus was more common among women aged ≥ 35 years (18.7% vs. 9.0%, $p = 0.001$), and chronic hypertension was observed exclusively in the advanced maternal age group (2.7% vs. 0.0%, $p = 0.004$). Smoking status and preeclampsia rates were similar between the two groups.

The distribution of fetal growth restriction categories did not differ significantly between groups ($p = 0.38$). Rates of placental abruption and preterm birth (< 37 weeks) were comparable between women aged ≥ 35 years and those aged 20–35 years. In contrast, cesarean delivery was significantly more frequent in the

advanced maternal age group compared with the control group (48.7% vs. 29.8%, $p < 0.001$).

Multivariable logistic regression analysis was

Table 1. Comparison of maternal and obstetric characteristics between the advanced maternal age and control groups

Variable	Advanced maternal age group (≥ 35 years)	Non-Pregnant (n=70)	p-value
Gravida (median, IQR)	3 (2)	2 (2)	<0.001
Parity (median, IQR)	1 (1)	1 (1)	<0.001
History of spontaneous abortion (median, IQR)	0 (1)	0 (0)	<0.001
BMI ≥ 25 kg/m ² , n (%)	281 (93.7%)	249 (83.3%)	<0.001
Smoking, n (%)	12 (4.0%)	10 (3.3%)	0.67
Chronic hypertension, n (%)	8 (2.7%)	0 (0.0%)	0.004
Gestational diabetes mellitus, n (%)	56 (18.7%)	27 (9.0%)	0.001
Preeclampsia, n (%)	13 (4.3%)	11 (3.7%)	0.68
FGR – None, n (%)	247 (82.3%)	241 (80.6%)	0.38
FGR – Mild (3rd–10th percentile), n (%)	32 (10.7%)	28 (9.4%)	
FGR – Severe (<3rd percentile), n (%)	21 (7.0%)	30 (10.0%)	
Placental abruption, n (%)	4 (1.3%)	1 (0.3%)	0.18
Preterm birth (<37 weeks), n (%)	24 (8.0%)	16 (5.4%)	0.19
Mode of delivery (cesarean), n (%)	146 (48.7%)	89 (29.8%)	<0.001

Data are presented as median (interquartile range) or number (percentage), as appropriate. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. P values for fetal growth restriction represent the overall comparison across categories. BMI: Body mass index; FGR: Fetal growth restriction; IQR: Interquartile range.

performed to evaluate factors independently associated with advanced maternal age (≥ 35 years). After adjustment, maternal body mass index ≥ 25 kg/m² (adjusted OR 2.64, 95% CI 1.50–4.63, $p = 0.001$), gestational diabetes mellitus (adjusted OR 1.83, 95% CI 1.10–3.05, $p = 0.020$), and cesarean delivery (adjusted OR 1.93, 95% CI 1.36–2.72, $p < 0.001$) remained independently associated with advanced maternal age (Table 3). Chronic hypertension was not independently associated with advanced maternal age in the multivariable model.

Table 3. Multivariable logistic regression analysis of factors associated with advanced maternal age (≥ 35 years)

Variable	Adjusted OR	95% CI	p value
BMI ≥ 25 kg/m ²	2.64	1.50–4.63	0.001
Gestational diabetes mellitus	1.83	1.10–3.05	0.020
Chronic hypertension	—	—	0.999
Cesarean delivery	1.93	1.36–2.72	<0.001

Model statistics:

Omnibus test $\chi^2 = 49.19$, $p < 0.001$; Nagelkerke $R^2 = 0.105$; Hosmer–Lemeshow test $p = 0.954$.

Footnotes:

Data are presented as adjusted odds ratios (OR) with 95% confidence intervals (CI).

Multivariable logistic regression analysis was performed including BMI ≥ 25 kg/m², gestational diabetes mellitus, chronic hypertension, and mode of delivery. Chronic hypertension could not be reliably estimated due to very low event counts in the control group.

BMI: Body mass index.

Perinatal and neonatal outcomes

Perinatal and neonatal outcomes are summarized in Table 2. Median gestational age at delivery and birth weight were similar between the two groups. The proportion of low birth weight infants did not differ significantly between women aged ≥ 35 years and controls.

No significant differences were observed in 1-minute or 5-minute Apgar scores between the groups. However, neonatal intensive care unit (NICU) admission was significantly more frequent among infants born to women aged ≥ 35 years compared with those born to younger women (25.0% vs. 10.4%, $p < 0.001$).

Fetal congenital or chromosomal anomalies were detected in a small number of cases. In the advanced maternal age group, two neonates (0.7%) were diagnosed with fetal anomalies, including one case of ventricular septal defect and one case of mild renal pelviectasis. In the control group, one neonate (0.3%) was diagnosed with a ventricular septal defect. There was no statistically significant difference between the groups regarding the presence of congenital or chromosomal anomalies ($p = 0.56$).

Rates of stillbirth were low in both groups and did not differ significantly between the advanced maternal age and control groups.

Table 2. Comparison of perinatal and neonatal outcomes between the advanced maternal age and control groups

Variable	Advanced maternal age group (≥ 35 years) (n = 300)	Control group (20–35 years) (n = 299)	P value
Gestational age at delivery (weeks), median (IQR)	38 (2)	38 (2)	0.78
Birth weight (g), median (IQR)	3225 (624)	3190 (645)	0.62
Low birth weight (LBW, <2500 g), n (%)	34 (11.3%)	23 (7.7%)	0.168
Apgar score at 1 minute, median (IQR)	9 (0)	9 (0)	0.95
Apgar score at 5 minutes, median (IQR)	10 (0)	10 (0)	0.97
NICU admission, n (%)	75 (25.0%)	31 (10.4%)	<0.001
Stillbirth, n (%)	5 (1.7%)	2 (0.7%)	0.26
Congenital /chromosomal anomaly, n (%)	2 (0.7%)	1 (0.3%)	0.56*

Data are presented as median (interquartile range) or number (percentage), as appropriate. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate.

*Fisher’s exact test was used due to low event counts. LBW: Low birth weight; NICU: Neonatal intensive care unit; IQR: Interquartile range.

Discussion

In this retrospective comparative cohort study, pregnancies in women aged 35 years and older were associated with distinct maternal and obstetric characteristics when compared with women aged 20–35 years. Advanced maternal age was associated with higher rates of gestational diabetes mellitus, increased body mass index, and cesarean delivery. In addition, neonatal intensive care unit admission was more frequent among infants born to women of advanced maternal age. However, multivariable analysis demonstrated that increased body mass index, gestational diabetes mellitus, and cesarean delivery were independently associated with the advanced maternal age group, suggesting that the observed differences are largely driven by coexisting maternal characteristics rather than maternal age alone. In contrast, key neonatal indicators reflecting immediate postnatal condition, including Apgar scores at 1 and 5 minutes, birth weight, fetal growth restriction, and preterm birth, did not differ significantly between the two age groups. These findings suggest that while pregnan-

cies at advanced maternal age are accompanied by a higher burden of maternal comorbidities and obstetric interventions, maternal age alone does not necessarily translate into widespread adverse neonatal outcomes when appropriate antenatal and perinatal care is provided.

These findings are consistent with previous literature suggesting that advanced maternal age is mainly associated with increased maternal comorbidities and higher rates of obstetric intervention, particularly cesarean delivery, rather than uniformly adverse neonatal outcomes. A recent review published in *Best Practice & Research in Clinical Obstetrics and Gynecology* emphasized that many risks attributed to advanced maternal age are mediated through coexisting maternal conditions and clinical management strategies rather than maternal age itself.¹⁴ In line with this perspective, our study demonstrated comparable Apgar scores, birth weight, fetal growth restriction, and preterm birth rates between age groups, despite a significantly higher rate of NICU admission among infants born to older women. The increased NICU admission rate may therefore reflect a more cautious neonatal management approach in the presence of maternal comorbidities and higher cesarean delivery rates, rather than an increase in immediate neonatal morbidity.¹⁴ Overall, these findings support an individualized approach to risk assessment in advanced maternal age pregnancies, rather than reliance on maternal age alone in the absence of other risk factors as a predictor of adverse perinatal outcomes.

The present study has several strengths. First, it includes a relatively large and well-defined cohort with nearly equal numbers of women in the advanced maternal age and control groups, enhancing the robustness of group comparisons. Second, all data were obtained from a single tertiary referral center, ensuring consistency in antenatal follow-up, diagnostic criteria, and perinatal management protocols. Third, comprehensive maternal, obstetric, and neonatal outcomes were evaluated with minimal missing data, allowing for a reliable assessment of perinatal outcomes associated with advanced maternal age in routine clinical practice.

Several limitations should be acknowledged. The retrospective design of the study inherently limits causal inference and may be subject to residual confounding. Although a multivariable logistic regressi-

on analysis was performed, the possibility of unmeasured confounders cannot be excluded. In addition, some outcomes had relatively low event rates, which may have limited the precision of effect estimates. Finally, as this was a single-center study conducted in a tertiary care setting, the findings may not be fully generalizable to other populations or healthcare systems.

Conclusion

Advanced maternal age was associated with a higher prevalence of maternal comorbidities and an increased rate of cesarean delivery. Although neonatal intensive care unit admission was more frequent among women aged 35 years and older, other key neonatal outcomes—including Apgar scores, birth weight, fetal growth restriction, and preterm birth—were comparable between advanced maternal age pregnancies and those of younger women. These findings suggest that advanced maternal age alone does not inevitably result in adverse neonatal outcomes when appropriate antenatal and perinatal care is provided. Therefore, individualized risk assessment based on accompanying maternal characteristics, rather than maternal age alone, should guide clinical management in advanced maternal age pregnancies.

Ethics Committee Approval

This study was approved by the Ethics Committee of the Republic of Turkey Ministry of Health, Eskişehir City Hospital (approval date: September 11, 2025; decision number: ESH/BAEK 2025/221) and was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

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RESEARCH ARTICLE

Obstetric and Neonatal Outcomes in Epilepsy-Complicated Pregnancies: The Impact of Levetiracetam Monotherapy

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Abstract

Introduction: To evaluate the impact of levetiracetam monotherapy on obstetric and neonatal outcomes in pregnant women with epilepsy.

Methods: The present retrospective cohort study included pregnant women with epilepsy followed at our center from the first trimester onward. Patients with seizures during pregnancy, polytherapy use, and multiple gestations were excluded. Patients were divided into a non-medicated group and a levetiracetam monotherapy group. Demographic, obstetric, delivery, and neonatal outcomes were compared.

Results: A total of 74 patients were included in the study; 22 (29.7%) were assigned to the non-medicated group, and 52 (70.3%) were included in the levetiracetam group. No statistically significant differences were observed between the groups in maternal age, obstetric history, duration of epilepsy, gestational age at delivery, and APGAR scores. Neonatal birth weight was significantly lower ($p = 0.042$) and neonatal intensive care unit (NICU) admission rates were significantly higher in the levetiracetam group ($p = 0.047$).

Conclusion: Levetiracetam monotherapy was associated with lower neonatal birth weight and higher NICU admission rates, without significant differences in other major perinatal outcomes. These findings suggest that levetiracetam may represent a relatively safe treatment option during pregnancy with appropriate patient selection and close monitoring; however, larger prospective studies are needed.

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Introduction

Epilepsy represents a common neurological disorder in reproductive-aged women and complicates approximately 0.3–0.5% of pregnancies.¹ Due to both the disease itself and the potential maternal and fetal effects of antiepileptic drug use, epilepsy is considered a high-risk condition during pregnancy. Therefore, the management of epilepsy throughout pregnancy requires a careful balance between seizure control and fetal safety.^{1,2}

During pregnancy, epileptic seizures are associated not only with seizure-related maternal trauma and an increased risk of hypoxia, but also with adverse perinatal outcomes in the fetal compartment, including placental abruption, fetal hypoxia, spontaneous abortion, and preterm labor.^{1–4} In addition, the use of antiepileptic drugs during pregnancy, particularly in the early gestational period, has been associated with an increased risk of major congenital anomalies and adverse neonatal outcomes.^{5–7} These reported risks are known to vary depending on the type and dosage of the antiepileptic drug used, as well as whether monotherapy or polytherapy is administered.^{7–9}

Recently, clinical practice has shifted from older antiepileptic drugs toward newer options, particularly levetiracetam and lamotrigine, which are considered to have more favorable safety profiles.^{6,7,9} Levetiracetam, one of the most commonly used antiepileptic drugs, has been shown to be better tolerated by patients and to have a relatively low risk profile with respect to major congenital malformations.^{10,11} However, data regarding prenatal exposure to levetiracetam remain limited.^{12–15} In the present study, we aimed to evaluate the impact of levetiracetam use on perinatal outcomes in pregnancies complicated by epilepsy, beyond the risks associated with the disease itself.

Material and Methods

This single-center study employed a retrospective cohort design. The study population comprised pregnant women with a diagnosis of epilepsy who were followed at the Perinatology Clinic of Ankara Bilkent City Hospital between March 2025 and December 2025 and who delivered at the same center. The patient data were retrospectively collected using the hospital's electronic medical record system and archived files. The study protocol was reviewed and approved by the relevant institutional ethics committee prior to the initiation of the study (approval number: 2-26-1983). All study procedures were performed

in compliance with the ethical standards outlined in the Declaration of Helsinki.

Singleton pregnancies in women aged 18–45 years whose antenatal follow-up and delivery were both conducted at our center and who were evaluated by the neurology clinic during pregnancy were included in the study. A confirmed diagnosis of epilepsy established by a neurologist prior to pregnancy, along with the availability of relevant medical records, was required for inclusion. Only patients who had been receiving levetiracetam from the preconceptional period onward and whose pregnancy follow-up was entirely carried out at our center were included in the analysis. Patients' antiepileptic therapies were managed and adjusted by neurologists. The principal criteria required for discontinuation of antiepileptic drug (AED) therapy were a seizure-free period of at least two years, absence of epileptiform activity on electroencephalography (EEG), and no evidence of structural cerebral lesions. In patients who did not meet these criteria, antiepileptic treatment was continued during pregnancy.

Patients who received polytherapy or had multiple gestations were excluded to avoid potential confounding effects on fetal outcomes. In addition, patients with a history of epileptic seizures during pregnancy were not included in the analysis to avoid potential confounding effects of seizures on fetal outcomes. The administered doses of levetiracetam ranged from 500 to 1500 mg and were within the optimal therapeutic range in all patients.

Patients were divided into two groups based on antiepileptic drug use during pregnancy: those who did not use antiepileptic medication (non-medicated group) and those who used antiepileptic medication (levetiracetam group). Demographic characteristics, obstetric history (gravidity, parity, number of abortions, and number of living children), duration of epilepsy, and pregnancy and delivery-related data (gestational age at delivery, birth weight, mode of delivery, and APGAR scores) were recorded for both groups. Neonatal outcomes included admission to the neonatal intensive care unit (NICU), preterm birth, low birth weight (defined as a birth weight <2500 g), and a first- or fifth-minute APGAR score <7.

Data analysis was performed using IBM SPSS Statistics software, version 29.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was applied to examine the distribution of continuous variables. Continuous variables that did not follow a nor-

mal distribution were presented as the median and interquartile range (IQR), and comparisons between groups were performed using the Mann–Whitney U test. Categorical variables were expressed as numbers and percentages, and comparisons between groups were conducted using the chi-square test or Fisher’s exact test when the expected cell count was less than five. A p -value <0.05 was considered statistically significant in all analyses.

Results

During the study period, a total of 132 deliveries occurred among pregnant women with a diagnosis of epilepsy at our center. Of these, 52 were excluded due to the occurrence of at least one epileptic seizure during pregnancy, and six were excluded because of polytherapy use. Consequently, a total of 74 patients were included in the analysis. Among these, 22 patients (29.7%) were assigned to the non-medicated group, while 52 patients (70.3%) were included in the levetiracetam group.

When the non-medicated and levetiracetam groups were compared, no statistically significant differences were observed in terms of maternal age, gravidity, parity, history of abortions, number of living children, duration of epilepsy, gestational age at delivery, or first- and fifth-minute APGAR scores. However, birth weight was significantly lower in the levetiracetam group (median: 2910 grams) compared with the non-medicated group (median: 3312.5 grams) ($p = 0.042$) (Table 1).

Table 1. Clinical and obstetric characteristics of epileptic patients according to antiepileptic drug use

Variable	Non-medicated group (n = 22) Median (IQR)	Levetiracetam group (n = 52) Median (IQR)	p value
Age (years)	27 (8)	29 (8)	0.061
Gravidity	1.5 (2)	2 (2)	0.980
Parity	0 (1)	0 (1)	0.422
History of abortion	0 (1)	0 (1)	0.538
Number of living children	0 (1)	0 (1)	0.501
Duration of epilepsy (years)	10 (6)	14.5 (11.75)	0.148
Gestational age at birth (weeks)	39 (2)	38 (3)	0.293
Birth weight (g)	3312.5 (750)	2910 (505)	0.042
APGAR score at 1 minute	7 (0)	7 (1)	0.131
APGAR score at 5 minutes	9 (1)	9 (1)	0.604

Data are presented as median (interquartile range).

Comparisons between groups were performed using the Mann–Whitney U test.

A p value <0.05 was considered statistically significant.

When obstetric and neonatal outcomes were evaluated, no significant difference was observed between the groups with respect to mode of delivery ($p = 0.202$). There were also no statistically significant differences between the groups in terms of preterm birth, low birth weight, or a first-minute APGAR score below 7 (all $p > 0.05$). All neonates had fifth-minute APGAR scores of 7 or higher. However, the rate of admission to the neonatal intensive care unit (NICU) was significantly higher in the levetiracetam group compared with the non-medicated group (30.7% vs. 9.1%; $p = 0.047$). These obstetric and neonatal outcomes are summarized in Table 2.

Table 2. Comparison of obstetric and neonatal outcomes between non-medicated and levetiracetam groups

Variable	Non-medicated group (n = 22) n (%)	Levetiracetam group (n=52) n (%)	p value
Mode of delivery			0.202
Vaginal delivery	12 (54.5)	20 (38.5)	
Cesarean section	10 (45.5)	32 (61.5)	
NICU admission	2 (9.1)	16 (30.7)	0.047
Preterm birth	4 (18.2)	14 (26.9)	0.423
Low birth weight	1 (4.5)	6 (11.5)	0.666 ^a
APGAR score at 1 minute < 7	4 (18.2)	7 (13.5)	0.602

NICU: neonatal intensive care unit.

Comparisons between groups were performed using the Pearson chi-square test.

^a Fisher’s exact test was used when the expected cell count was <5 .

A p value <0.05 was considered statistically significant.

Discussion

The current study evaluated the effects of levetiracetam use in pregnant women with epilepsy on obstetric and neonatal outcomes. The findings demonstrated that neonatal birth weight was significantly lower and NICU admission rates were higher among pregnant women using levetiracetam. In contrast, no statistically significant differences were observed between the groups in terms of gestational age at delivery, mode of delivery, first- and fifth-minute APGAR scores, low birth weight, or preterm birth rates.

Although many pregnancies complicated by epilepsy result in favorable outcomes without major complications, these pregnancies are considered high-risk pregnancies due to an increased likelihood of obstetric and fetal complications. The occurrence of

convulsions during pregnancy not only increases the risk of maternal trauma but may also adversely affect the fetus through hypoxemia and asphyxia. In addition, higher rates of cesarean delivery and an increased risk of hypertensive disorders during pregnancy have been reported among women with epilepsy.^{1,3,16} Furthermore, these pregnancies have been shown to be associated with spontaneous abortion, stillbirth, preterm birth, small-for-gestational-age neonates, low fifth-minute APGAR scores, and neonatal respiratory distress syndrome.^{3,5,17}

Several studies have reported higher rates of spontaneous or iatrogenic preterm birth among pregnancies complicated by epilepsy.¹⁸ In women with epilepsy, the risk of preterm birth has been shown to be associated with antiepileptic drug exposure and, in particular, with uncontrolled seizure activity.^{3,5,17,19} In the present study, however, no significant difference in preterm birth rates was observed between women who were exposed to antiepileptic medication throughout pregnancy and those who were not. This finding may be explained by the inclusion of a highly selected population consisting only of patients who remained seizure-free during pregnancy and received monotherapy.

Levetiracetam is a widely used antiepileptic drug that is well tolerated during pregnancy and is primarily eliminated via the renal route.²⁰ Owing to its low teratogenic potential, its ability to provide effective seizure control throughout pregnancy, and the lack of evidence indicating significant adverse effects on long-term cognitive performance in children, levetiracetam has been increasingly preferred in pregnancies complicated by epilepsy.^{10,21,22} It is well established that antiepileptic drugs cross the placenta and may pose potential risks to fetal development.²³ Compared with healthy pregnancies, women with epilepsy have been reported to have an approximately threefold increased risk of congenital malformations, largely attributable to antiepileptic drug exposure.²¹ However, this increased risk has been shown to be mainly associated with exposure to carbamazepine, phenobarbital, phenytoin, and valproate.^{19,21} In contrast, the lowest risk of major congenital malformations has been reported in pregnancies exposed to lamotrigine and levetiracetam.²¹ In a study evaluating levetiracetam monotherapy, the rate of congenital malformations was higher than that in the control group, although the difference did not reach statistical significance, and the observed anomalies were pre-

dominantly isolated cardiac defects.²⁴ In the present study, no congenital malformations were observed; however, this finding may be attributable to the relatively small sample size and the limited ability of the study to detect rare outcomes.

Previous studies have demonstrated that exposure to antiepileptic drugs is associated with an increased risk of low birth weight, admission to the NICU, and a fifth-minute APGAR score below 7.^{3,19,25} In particular, adverse outcomes related to low birth weight have been reported in pregnancies complicated by epilepsy with levetiracetam exposure.^{24,26} Consistent with these findings, this study demonstrated that neonates exposed to levetiracetam had lower birth weights and higher rates of NICU admission. Although the neonatal birth weight in the levetiracetam group was lower than that of the non-medicated group, the median value remained above 2500 g, which is the accepted threshold for low birth weight. Furthermore, no statistically significant difference was observed between the two groups in terms of the proportion of neonates with low birth weight. These findings may suggest that levetiracetam has a relatively favorable safety profile regarding neonatal birth weight. However, definitive conclusions cannot be drawn based on the present study alone, and further studies are required to substantiate these results. No statistically significant differences were observed between the groups with respect to common indications for NICU admission, including preterm delivery, low birth weight, low first- or fifth-minute APGAR scores, and the overall rate of preterm birth. Although congenital anomalies were not defined as exclusion criteria, no major structural or chromosomal congenital anomalies were detected in either group. A substantial proportion of neonates in the medication-treated group were admitted to the NICU primarily for clinical observation and precautionary monitoring. The higher NICU admission rate in the medication-treated group may therefore reflect a more cautious neonatal management approach and a lower threshold for observation in pregnancies exposed to antiepileptic drugs, rather than an increase in overt perinatal morbidity. In the present study, no significant associations were found between antiepileptic drug use and maternal age, parity, duration of epilepsy, or gestational age at delivery. This finding suggests that baseline maternal and gestational characteristics were comparable between the groups and are unlikely to account for the observed neonatal differences.

One of the main strengths of this study is the evaluation of a homogeneous patient population consisting exclusively of women who received levetiracetam monotherapy and remained seizure-free throughout pregnancy. This approach allowed for a clearer assessment of the effects of levetiracetam exposure on perinatal outcomes by minimizing the potential confounding effects of seizure activity and polytherapy. In addition, the fact that all antenatal follow-up and deliveries were conducted at a single center ensured data integrity and standardized obstetric assessments. The findings should be interpreted in light of several constraints, most notably the retrospective design, which limits causal interpretation. The limited sample size may have made it difficult to evaluate outcomes such as rare congenital anomalies. In addition, classification according to epilepsy types could not be performed. Furthermore, the association between maternal serum levetiracetam levels and perinatal outcomes could not be evaluated due to the limited sample size. Therefore, the findings of this study should be supported by larger, prospective studies.

Conclusion

The present study demonstrated that neonatal birth weight was lower and the rate of NICU admission was higher in pregnant women with epilepsy who used levetiracetam monotherapy. No congenital malformations were observed in either group, and no significant differences were found between the groups with respect to preterm birth, low birth weight, or APGAR scores. Levetiracetam is widely used during pregnancy and is generally considered safe; however, further investigation may be warranted regarding the decrease in neonatal birth weight and the increased rates of NICU admission observed in the present study, as well as in some previous reports. Confirmation of these findings will require well-designed prospective studies with larger sample sizes.

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Conflict of Interest Statement

The authors have no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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RESEARCH ARTICLE

Imaging Spectrum of Donor Biliary Complications After Living Liver Donation: An MRCP-Based Analysis

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Abstract

Introduction: To evaluate the imaging spectrum of biliary complications in living liver donors using magnetic resonance cholangiopancreatography (MRCP) and to investigate the relationship between postoperative biliary complications and biliary anatomy.

Methods: In this retrospective single-center study, adult living liver donors who underwent transplantation between January 2017 and January 2025 were reviewed. Donors were followed clinically and with imaging according to institutional protocols, and MRCP was performed when biliary complications were suspected. Preoperative MRCP examinations were analyzed to classify biliary anatomy and obtain morphometric measurements. Imaging characteristics were compared between donors with and without biliary complications.

Results: A total of 181 donors were included, and radiologic biliary complications were identified in 16 donors (8.8%). Early bile leakage and biloma formation constituted the predominant imaging phenotype (68.8%), whereas biliary strictures were less frequent, presenting as common hepatic duct narrowing within the first month in three donors and as later strictures detected at 5.5 and 8 months in two donors. Variant biliary anatomy appeared numerically more frequent among donors with complications but was not significantly associated with complication development ($p=0.282$). Hepatocyte-specific contrast-enhanced MRI confirmed active bile leakage in selected cases. Three donors demonstrated biochemical cholestasis despite normal MRCP findings, highlighting the role of imaging in avoiding unnecessary invasive procedures.

Conclusion: MRCP provides a comprehensive, noninvasive framework for detecting biliary complications in living liver donors. Early imaging should focus on bile leak, while later surveillance is important for identifying biliary strictures, supporting a time-oriented radiologic approach to donor follow-up.

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Introduction

Biliary complications represent an important source of postoperative morbidity following living donor liver transplantation and require accurate radiologic evaluation for timely diagnosis and management.¹ In living donors, who constitute an otherwise healthy population, familiarity with the radiologic spectrum of donor-specific biliary alterations and accurate interpretation of postoperative biliary findings are particularly important for avoiding unnecessary interventions while ensuring timely detection of clinically relevant complications.²

Radiologic imaging, particularly magnetic resonance cholangiopancreatography (MRCP), plays a central role in the evaluation of the biliary tree in transplant settings: preoperatively, to delineate biliary anatomy and identify anatomic variants that may influence surgical planning and potential postoperative risks, and postoperatively, to assess suspected biliary complications following living donor hepatectomy.²⁻⁴ Despite the established role of MRCP in both pre- and postoperative assessment, biliary complications in living liver donors have been comparatively less explored from a radiologic perspective than those in recipients, underscoring the need for dedicated imaging-based studies to enhance radiologic awareness in this population.⁵⁻⁷

The primary aim of this study was to investigate the imaging features of biliary complications and their relationship with biliary tree anatomic variants in living liver donors. As a secondary objective, we briefly describe the observed incidence of biliary complications and the frequency of biliary interventions based on the experience of a tertiary referral center.

Material and Methods

This retrospective imaging study was conducted at a tertiary referral center after institutional ethics committee approval was obtained (Approval number: I01-105-26). Adult living liver donors who underwent liver transplantation between January 2017 and January 2025 were retrospectively reviewed.

Definition and Imaging Criteria for Biliary Complications

Following living donor liver transplantation, donors were routinely followed with clinical assessment, laboratory testing including liver function parameters, and ultrasonography according to the institutional follow-up protocol. Additional imaging

studies were performed when biliary complication was clinically suspected based on biochemical cholestasis, persistent abdominal symptoms, or abnormal ultrasonographic findings.

Biliary complications were defined as bile leakage with or without biloma formation and biliary stricture detected on postoperative imaging. Donors without imaging evidence of these findings, who had at least one year of clinical and radiologic follow-up, were classified as the non-complication group. Donors lacking adequate follow-up data or those with vascular complications were excluded from the study.

In donors demonstrating perihepatic fluid collections suspicious for bile leakage with or without biloma formation on ultrasonography and/or computed tomography, the diagnosis was established when bile-containing fluid exceeding 100 mL/day was detected from surgically placed drains or when percutaneous aspiration confirmed the presence of bile. On magnetic resonance imaging (MRI), perihepatic collections appearing hypointense on T1-weighted and hyperintense on T2-weighted sequences, particularly when communication with the biliary tree was demonstrated on MRCP, were considered compatible with biloma (Figure 1). In addition, hepatobiliary phase MR imaging with hepatocyte-specific contrast agents was evaluated, and delayed-phase contrast extravasation into adjacent collections was regarded as indicative of active biliary leakage (Figures 2-3).

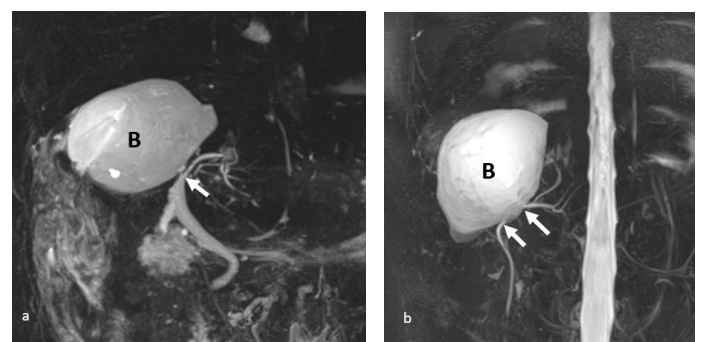


Figure 1. Coronal maximum-intensity-projection MRCP images obtained in two different donors (a, b) demonstrate well-demarcated perihepatic fluid collections compatible with biloma (B), showing direct communication with the biliary tree (arrows).

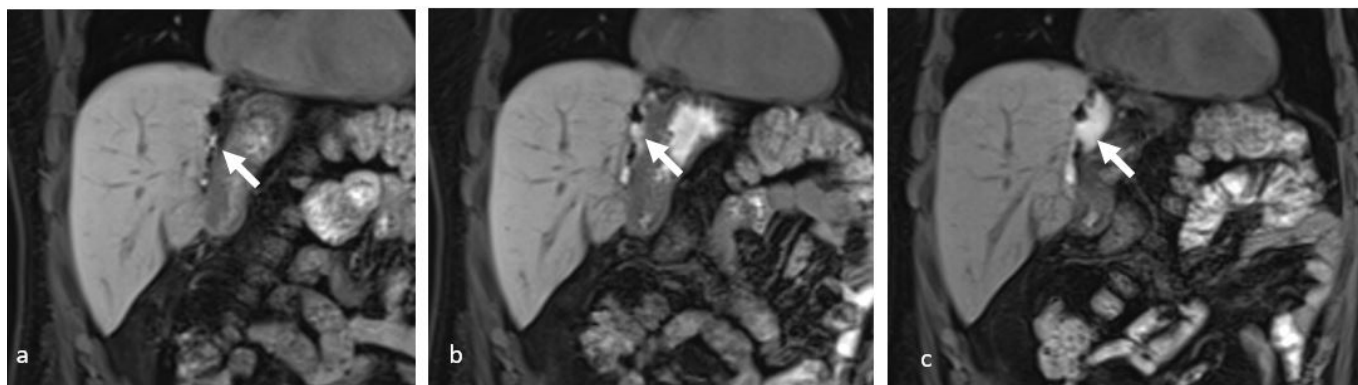


Figure 2. Coronal T1-weighted MR images in a left-lobe donor demonstrate progressive contrast extravasation along the hepatic resection margin on delayed imaging at 30 minutes (a), 60 minutes (b), and 6 hours (c) after administration of a hepatocyte-specific contrast agent, compatible with active biliary leakage (arrows).

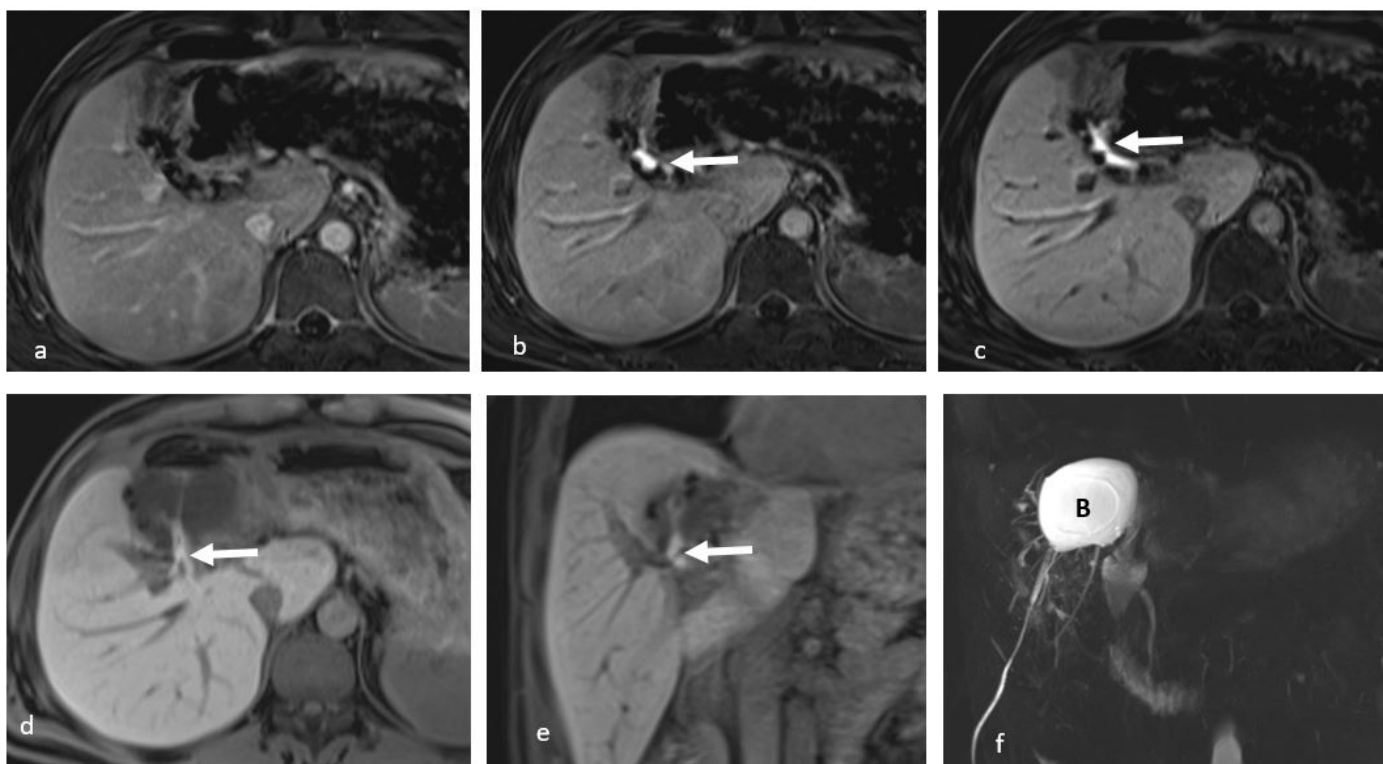


Figure 3. T1-weighted MR images obtained after administration of a hepatocyte-specific contrast agent in a left-lobe donor demonstrate progressive contrast extravasation compatible with active biliary leakage. (a) Equilibrium phase image, (b) 10-minute hepatobiliary phase image, and (c) 30-minute hepatobiliary phase image show increasing contrast accumulation (arrows) adjacent to the hepatic resection margin. (d) Axial and (e) coronal extended delayed hepatobiliary phase images at 120 minutes further confirm contrast leakage (arrows). (f) Coronal maximum-intensity-projection MRCP image demonstrates the corresponding biloma (B) formation and leakage site.

Biliary stricture was defined on MRCP as a focal or segmental luminal narrowing in bile duct caliber associated with upstream ductal dilatation or caliber change (Figure 4). MRCP evaluation also included assessment of concomitant intrahepatic bile duct dilatation.

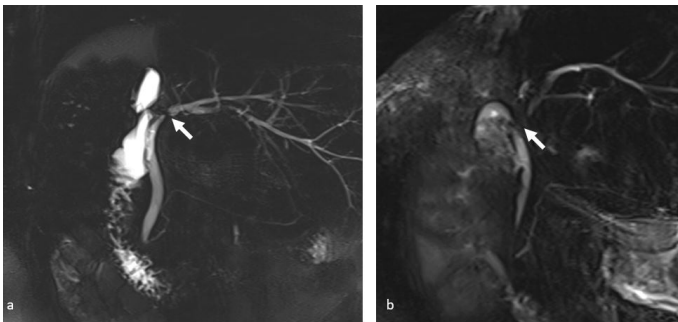


Figure 4. Coronal thick-slab MRCP images obtained in two different right-lobe donors (a, b) demonstrate focal luminal signal loss at the hepatic confluence (arrows), compatible with biliary stricture, accompanied by upstream intrahepatic biliary dilatation.

Medical records were retrospectively reviewed to obtain demographic data, graft type, postoperative clinical course, time interval between transplantation and detection of biliary complications, and information regarding endoscopic or percutaneous interventions. These biliary interventions were documented for descriptive purposes only, as the primary aim of the study was radiologic characterization of biliary complications in living liver donors rather than assessment of treatment outcomes.

Preoperative MRCP-Based Evaluation of Biliary Anatomy

All MRCP examinations were retrospectively reviewed in consensus by two radiologists, one with more than 10 years of experience in abdominal radiology and the other with 6 years of experience in general radiology. Image analysis focused on postoperative biliary findings as well as the anatomic configuration of the biliary tree. Biliary anatomy was classified according to established MRCP-based branching patterns.⁸ In type 1 (classic anatomy), the right posterior hepatic duct joins the right anterior hepatic duct to form the right hepatic duct, which subsequently merges with the left hepatic duct to create the common hepatic duct. Type 2 anatomy represents trifurcation of the right anterior, right posterior, and left hepatic ducts.

In type 3a, the right posterior hepatic duct drains into the left hepatic duct, whereas in type 3b it drains directly into the common hepatic duct below the biliary bifurcation. Type 3c describes drainage of the right posterior hepatic duct into the cystic duct, type 4 refers to aberrant drainage of right hepatic duct into the cystic duct, and type 5 anatomy refers to the presence of an accessory hepatic duct draining into the right hepatic duct. In addition, the distance between the right posterior hepatic duct and the biliary bifurcation was measured on thick-slab coronal-oblique MRCP images for morphometric analysis.

MRCP Acquisition

MR imaging was performed on 1.5-T (Optima 450w; GE Healthcare, Milwaukee, WI) and 3.0-T (MAGNETOM® Verio; Siemens Healthineers, Erlangen, Germany) systems using phased-array body coils, with patients positioned supine. Baseline imaging included heavily T2-weighted single-shot MR cholangiographic sequences, respiratory-triggered axial T2-weighted fast spin-echo acquisitions, and fat-suppressed three-dimensional gradient-echo T1-weighted sequences obtained before and after contrast administration. Detailed evaluation of the biliary tree primarily relied on heavily T2-weighted MRCP images, including thick-slab coronal-oblique projections and three-dimensional thin-slice acquisitions. Dynamic contrast-enhanced imaging with the hepatocyte-specific contrast agent gadoteric acid disodium (Gd-EOB-DTPA, Primovist) was performed following intravenous administration of 0.1–0.2 mmol/kg at an injection rate of 2–3 mL/s. Dynamic images including pre-contrast, arterial, portal venous, and equilibrium phases were acquired in the axial plane, followed by hepatobiliary phase imaging at approximately 10–30 minutes in axial and coronal planes. If biliary opacification was insufficient on hepatobiliary phase images, additional delayed acquisitions at approximately 120–150 minutes were obtained using the same pulse sequence. In cases with persistent clinical or biochemical suspicion of bile leakage despite negative initial hepatobiliary phase findings, further delayed imaging at extended intervals was performed to improve detection of contrast extravasation. Imaging was terminated when bile leakage was demonstrated or when adequate biliary excretion was achieved without evidence of leakage.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Comparisons were performed between donors with and without biliary complications based on demographic characteristics, graft type, biliary anatomy, and MRCP-derived measurements. Normality of data distribution was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean \pm standard deviation or median (range), as appropriate. The independent samples t-test was used for normally distributed variables, whereas the Mann–Whitney U test was applied for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate. A two-sided p value of < 0.05 was considered statistically significant.

Results

Donor Demographics and MRCP Findings Across Groups

A total of 181 living liver donors were included in the study. Of these, 77 donors (42.5%) were female and 104 (57.5%) were male. Right-lobe grafts were used in 124 donors (68.5%), while 57 donors (31.5%) donated a left-lobe graft. The mean donor age was 32.99 ± 8.82 years. During postoperative follow-up, 19 donors underwent MRCP due to suspected biliary complications. Radiologic biliary complications were identified in 16 donors (8.8%), whereas 3 donors demonstrated biochemical cholestasis despite normal MRCP findings.

Donor age was comparable between the biliary complication and non-complication groups (32.38 ± 8.69 vs. 33.05 ± 8.86 years, $p = 0.708$). Male donors were more frequent in both the biliary complication and non-complication groups, accounting for 12 of 16 donors (75.0%) and 92 of 165 donors (55.8%), respectively, with no significant difference in sex distribution between groups ($p = 0.137$). Similarly, right-lobe graft donation predominated in both groups, observed in 12 of 16 donors (75.0%) with complications and in 112 of 165 donors (67.9%) in the non-complication group, showing no statistically significant difference ($p = 0.558$).

Type 1 anatomy was the most common biliary configuration, observed in 69.6% of donors, followed by the type 3a variant in 15.5%. Type 2 and type 3b variants accounted for 5.5% and 5.0% of donors, res-

pectively, whereas type 5 and type 3c variants were identified in 3.9% and 0.6% of cases. When stratified by complication status, type 1 anatomy was present in 9 of 16 donors (56.3%) with biliary complications and in 117 of 165 donors (70.9%) without complications. Variant biliary anatomies appeared relatively more frequent among donors with complications, including type 2 anatomy in 4 donors (25.0%), type 3a in 2 donors (12.5%), and type 3b in 1 donor (6.3%), while no type 5 or type 3c variants were observed in this group. Despite these distributional differences, biliary anatomy variants were not significantly associated with biliary complications ($p = 0.282$) (Table 1).

Table 1. Baseline demographic and preoperative MRCP imaging parameters in donors

	Biliary complication (+) (n=16)	Biliary complication (-) (n=165)	Total (n=181)	p value
Age (years)	32.38 ± 8.69 31 (21–55)	33.05 ± 8.86 32 (17–59)	32.99 ± 8.82 32 (17–59)	0.708
Sex	4 female (25.0%) 12 male (75.0%)	73 female (44.2%) 92 male (55.8%)	77 female (42.5%) 104 male (57.5%)	0.137
Graft type	12 right (75.0%) 4 left (25.0%)	112 right (67.9%) 53 left (32.1%)	124 right (68.5%) 57 left (31.5%)	0.558
Bile duct anatomy variants				0.282
Type 1	9 (56.3%)	117 (70.9%)	126 (69.6%)	
Type 2	4 (25%)	6 (3.6%)	10 (5.5%)	
Type 3a	2 (12.5%)	26 (15.8%)	28 (15.5%)	
Type 3b	1 (6.3%)	8 (4.8%)	9 (5%)	
Type 3c	0 (0%)	1 (0.6%)	1 (0.6%)	
Type 5	0 (0%)	7 (4.2%)	7 (3.9%)	
Right posterior duct–biliary bifurcation distance (mm)	9.06 ± 5.79 7.1 (3.6–22.0)	7.23 ± 5.30 5.2 (1.5–23.3)	7.63 ± 5.41 5.4 (1.5–23.3)	0.154

Continuous variables are presented as mean \pm standard deviation and median (range).

Percentages are calculated within each biliary complication group.

The median distance from the right posterior sectoral duct to the biliary bifurcation was 7.1 mm (range, 3.6–22.0) in donors with biliary complications and 5.2 mm (range, 1.5–23.3) in donors without complications, and this parameter did not differ significantly between groups ($p = 0.154$).

Spectrum of Postoperative Biliary Complications and Interventions

Bile leakage and biloma formation were the most frequent imaging findings, observed in 11 of 16 donors (68.8%), predominantly during the early postoperative period. Imaging typically demonstrated fluid collections adjacent to the hepatic resection margin, consistent with biloma, and in two donors active biliary leakage was demonstrated on delayed hepatobiliary phase imaging performed with hepatocyte-specific contrast agents (Figures 2-3). Intrahepatic bile duct dilatation was observed in three patients, all of whom required interventional management: two were treated with ultrasound-guided percutaneous drainage, and one underwent combined percutaneous drainage and ERCP with biliary stent placement. In one patient, regional parenchymal perfusional changes were noted on imaging in association with biloma formation. Overall, six patients were managed conservatively, four underwent ultrasound-guided percutaneous drainage (including one patient who required repeated drainage), and one patient required combined percutaneous drainage and ERCP with biliary stent placement after bile leakage was confirmed.

Overall, biliary stricture developed in five donors during follow-up. Within the first postoperative month, three donors developed biliary narrowing at the level of the common hepatic duct with upstream bile duct dilatation, occasionally accompanied by perfusional alterations. Only one patient required combined percutaneous transhepatic biliary drainage and ERCP with stent placement, whereas the remaining two patients were managed conservatively without intervention. During later follow-up, two additional donors developed biliary strictures detected at 5.5 and 8 months postoperatively, respectively. Imaging demonstrated biliary narrowing with associated ductal dilatation. One patient underwent ERCP with sphincterotomy, while the other was managed conservatively (Table 2).

Three donors presented with elevated liver function tests and cholestatic parameters at 6 months, 14 months, and 2 years after transplantation. In all three cases, MRCP demonstrated normal biliary anatomy without evidence of stricture, dilatation, or bile leakage (Figure 5).

Table 2. Postoperative MRCP findings and management of biliary complications in living liver donors

Imaging finding / Complication type	No. of donors (%)	Typical MRCP findings	Timing after transplantation	Management
Bile leak ± biloma	11 (68.8%)	Perihepatic fluid collections adjacent to the resection margin; intrahepatic bile duct dilatation in 3 patients; regional perfusional change in 1 patient	Postoperative 1 week–1.5 months	Conservative follow-up (n=6); US-guided drainage (n=4, including 1 repeated); Percutaneous drainage and ERCP-assisted biliary stenting (n=1)
Biliary stricture	5 (31.2%)	Focal and segmental luminal narrowing of the bile duct with upstream dilatation	Postoperative 1 week–1 month (n = 3); later follow-up at 5.5 and 8 months (n = 2)	Combined percutaneous transhepatic biliary drainage and ERCP-guided stent placement (n = 1); ERCP-guided sphincterotomy (n=1); conservative follow-up (n = 3).
Biochemical cholestasis with normal MRCP	3	Normal biliary anatomy without stricture, dilatation, or bile leak	6 months, 14 months, and 2 years	Clinical follow-up

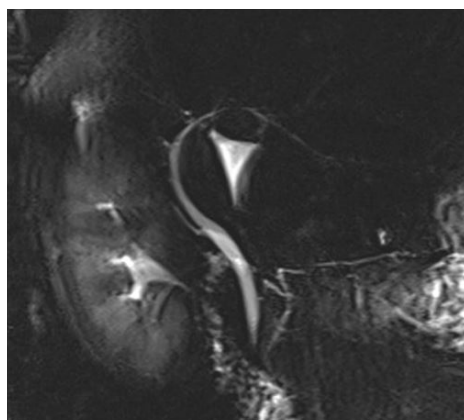


Figure 5. Coronal thick-slab MRCP image obtained in a right-lobe donor demonstrates normal biliary anatomy without evidence of bile leakage, biliary stricture, or intrahepatic duct dilatation despite clinical and laboratory findings suggestive despite biochemical cholestasis prompting MRCP evaluation.

Discussion

In this MRCP-based donor cohort, radiologic biliary complications were detected in 8.8% of living liver donors, with bile leakage and biloma formation constituting the predominant imaging phenotype (68.8%), whereas biliary strictures were less frequent, occurring as early biliary narrowing within the first postoperative month in three donors and as later-developing strictures in two donors during follow-up. Neither MRCP-defined biliary branching patterns nor MRCP-derived morphometric parameters demonstrated a statistically significant association with postoperative biliary complications. A small subgroup demonstrated biochemical cholestasis despite a normal MRCP, emphasizing that abnormal liver enzymes are not synonymous with structural biliary pathology in donors and that imaging–laboratory discordance is clinically relevant for avoiding over-intervention.

From a radiologic perspective, the predominance of bile leak/biloma aligns with the expected imaging spectrum after donor hepatectomy, where peripheral ductal injury at the transection plane results in perihepatic fluid collections. Importantly, our experience supports the incremental value of hepatocyte-specific contrast-enhanced delayed imaging in selected cases—when conventional MRCP is non-diagnostic yet clinical suspicion persists—because demonstration of contrast extravasation into a collection upgrades “postoperative fluid” into active bile leak with actionable implications.^{5,9} For biliary strictures, early biliary narrowing with upstream dilatation may be observed in association with intraoperative technical factors, whereas later strictures may reflect evolving fibrotic or ischemia-related changes; however, definitive etiologic attribution remains limited.¹⁰ MRCP continues to serve as a key noninvasive modality for evaluating duct caliber changes and biliary dilatation patterns. The lack of association between branching variants and complications suggests that, in the modern era of high-resolution MRCP and meticulous surgical planning, radiologic anatomy alone may not represent a strong predictor of donor morbidity, consistent with the existing literature.^{11,12}

Our observed donor biliary-complication rate of 8.8% falls within the broad spectrum reported in living donor hepatectomy literature, where incidences vary widely depending on study design, definitions, and follow-up strategies, generally ranging from approximately 2% to 18%.^{1,9,13,14} Large donor series have reported lower bile-leak rates with minimal or

absent strictures, whereas right-lobe–dominant cohorts tend to demonstrate slightly higher complication frequencies, likely reflecting increased technical complexity at ductal transection.^{1,12,15} Across studies, bile leakage consistently represents the most common early postoperative event, while strictures emerge later during follow-up, mirroring the temporal imaging pattern observed in our MRCP cohort.^{15,16} Emerging evidence also suggests that surgical factors such as the number of bile duct orifices may better explain leakage risk than classical MRCP-based branching classifications alone, highlighting the limitations of relying solely on morphologic anatomy for radiologic risk stratification.^{15,17} Within this context, donor biliary complication rates appear heterogeneous yet broadly consistent with our findings, supporting a radiologic paradigm in which MRCP primarily functions as a problem-solving and triage tool—guiding timely intervention while avoiding unnecessary invasive procedures in an otherwise low-risk donor population.

From a clinical imaging perspective, our findings highlight several practical implications for radiologists involved in donor follow-up. Consistent with prior reports, our experience underscores the added value of hepatocyte-specific contrast-enhanced MRI in differentiating true bile leakage from nonspecific postoperative collections. In the early postoperative period, perihepatic fluid is common and may mimic biloma on conventional sequences; however, visualization of delayed hepatobiliary phase contrast extravasation enables functional confirmation of active leakage, thereby reducing both overdiagnosis and delayed intervention.^{5,18} The temporal distribution of complications observed in our cohort further supports a phase-oriented imaging strategy: early imaging should focus on detection of bile leakage, whereas later surveillance should prioritize identification of biliary strictures. This time-dependent imaging pattern reinforces the importance of adapting radiologic interpretation to the postoperative interval rather than applying a uniform diagnostic framework across all time points. Finally, our results reinforce that MRCP should be considered not only an anatomic modality but also a clinical decision-support tool. In donors presenting with cholestatic laboratory abnormalities but normal MRCP findings, clear radiologic reporting is essential to avoid unnecessary invasive procedures by emphasizing the absence of imaging evidence for leak or stricture and suggesting alternative, non-biliary causes for biochemical alterations.

This study has several limitations that should be acknowledged. First, its retrospective single-center design and the relatively small number of biliary complications may have limited statistical power to detect subtle associations between MRCP-derived anatomic features and clinical outcomes. Second, MRCP examinations were performed based on clinical suspicion rather than standardized postoperative surveillance, which may have introduced selection bias and variability in imaging timing. In addition, imaging findings could not be systematically correlated with detailed operative parameters or interventional outcomes, such as duct division technique or the number of bile duct orifices, which may represent stronger determinants of leakage risk than morphologic anatomy alone. Future research should therefore focus on larger, multidisciplinary prospective studies integrating radiologic, surgical, and interventional datasets with longitudinal outcome tracking to better define imaging-based risk stratification and optimize postoperative management strategies in living liver donors.

Conclusion

In conclusion, MRCP-based evaluation demonstrated that biliary complications in living liver donors occur infrequently, with early leak/biloma as the dominant imaging phenotype and a smaller burden of biliary strictures. Preoperative MRCP-defined biliary branching variants were not significantly associated with donor biliary complications, suggesting that modern imaging-based anatomic characterization alone may not adequately stratify donor risk. For radiologists, MRCP — particularly when combined with hepatocyte-specific delayed imaging — provides a comprehensive, noninvasive framework for accurately detecting clinically relevant complications, guiding time-adapted surveillance, and preventing unnecessary invasive interventions in this low-risk donor population.

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RESEARCH ARTICLE

The Effect of Single/Multiple Abnormal Values in the 75 g OGTT on Maternal and Neonatal Outcomes in GDM Diagnosis

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Abstract

Introduction: Although early diagnosis and management of GDM aims to reduce adverse outcomes for the mother and newborn, the prognostic value of the number of abnormal values in the 75 g OGTT remains unclear. This study investigates whether single, double, or triple abnormal values in the 75 g OGTT are associated with maternal and neonatal outcomes in women diagnosed with GDM

Methods: This retrospective, single-center study included 120 pregnant women diagnosed with GDM according to IADPSG criteria based on a 75 g OGTT after an 8-hour fast between April 2024 and December 2025 .Groups were defined by the number of abnormal values in the 75g OGTT (fasting ≥ 92 mg/dL, 1-hour ≥ 180 mg/dL, 2-hour ≥ 153 mg/dL): single (one abnormal), double (two), or triple (all three).The data collected included age, number of pregnancies, number of births, gestational age at delivery, HbA1c, treatment method, birth weight, Apgar scores, NICU admission, neonatal hypoglycemia, hyperbilirubinemia, and macrosomia.

Results: HbA1c was higher in Group 3 (mean difference vs. Group 1: 1.82 ± 0.32 , $p < 0.001$); cesarean rates were 95% in Group 1 vs. 60% in Group 3 (absolute difference: 35%, $p = 0.024$).Macrosomia, Apgar scores at 1 and 5 minutes, admission to the NICU, neonatal hypoglycemia, and hyperbilirubinemia, among other neonatal outcomes, did not differ significantly between groups.

Conclusion: Among pregnant women diagnosed with GDM using a 75 g OGTT, increased abnormal values were associated with higher maternal HbA1c and increased likelihood of cesarean delivery, but this did not lead to consistent differences in neonatal morbidity.

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Introduction

Traditionally, gestational diabetes mellitus (GDM) is defined as the first detection of abnormal glucose tolerance during pregnancy at any time ¹ and its global prevalence has been reported to be 14.7% (based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria).² The recognition and management of GDM is important because it carries a potential risk for postpartum diabetes and increases the incidence of adverse maternal and fetal outcomes.³ The tests used for GDM diagnosis and screening are the 50g (screening), 75g OGTT, and 100g OGTT, and there are multiple recommended sets of glycemic criteria for evaluating these tests (Table 1).⁴

Table 1: International consensus cut-offs for diagnosing gestational diabetes mellitus

	ADA/IADPSG	WHO
Fasting glucose, mg/dL	92	126
1-hour glucose,mg/dL	180	-
2- hour glucose,mg/dL	153	>140
3- hour glucose,mg/dL	-	-
Required for Diagnosis	At least 1 abnormal value	At least 1abnormal value

Citations ADA 2020; I ADPSG2010 WHO 2013

The cut-off values for these sets have changed over the years.⁵ Numerous studies have examined the potential of different cut-off values and multiple abnormal values to predict adverse maternal and fetal outcomes.⁶ While various OGTT protocols (e.g., 50 g screening, 75 g, and 100 g) and diagnostic criteria exist, this study specifically focuses on the 75 g OGTT using IADPSG criteria due to its widespread adoption in international guidelines, its alignment with global prevalence estimates (e.g., 14.7% reported prevalence), and its balance of sensitivity and feasibility in routine prenatal screening.^{2,4} Furthermore, evaluating outcomes based on the number of abnormal values (single, double, or triple) addresses a gap in the literature, as prior research has more commonly explored threshold variations rather than the cumulative impact of multiple abnormalities within the 75 g test, which may better reflect the severity of glucose dysregulation and its prognostic implications for maternal and neonatal risks.⁷

The aim of this study is to observe the effect of single, double, or triple abnormal values on maternal and fetal adverse outcomes in pregnant women diagnosed with GDM using the 75g OGTT.

Material and Methods

2.1. Study Population.

This study was retrospective, single-center, and conducted at a tertiary care hospital. During the study period (April 2024 to December 2025), a total of 456 pregnant women were screened for GDM via 75-gram OGTT at the Perinatology Department of Ankara City Hospital between 24 and 28 weeks of gestation. Of these, 312 met the initial IADPSG diagnostic criteria for GDM. After applying exclusion criteria (multiple pregnancies: n=48; hypertensive patients: n=32; pre-existing Type 1 or Type 2 diabetes: n=24; major fetal anomalies: n=16; missing/inaccessible data: n=32), 160 patients remained eligible. To ensure balanced group comparisons and sufficient statistical power for detecting differences in outcomes, we randomly selected 40 patients from each subgroup based on the number of abnormal values (single, double, or triple) using stratified sampling via SPSS software, resulting in equal group sizes (n=40 per group) (figure 1). Patients diagnosed with gestational diabetes after a 75-gram OGTT performed between April 2024 and December 2025 at the Perinatology Department of Ankara City Hospital between 24 and 28 weeks of gestation were included in this study. Approval was obtained from the Ankara City Hospital Ethics Committee for this study (TABED 2-24-123). The Helsinki Declaration guidelines were followed at every stage of the study.

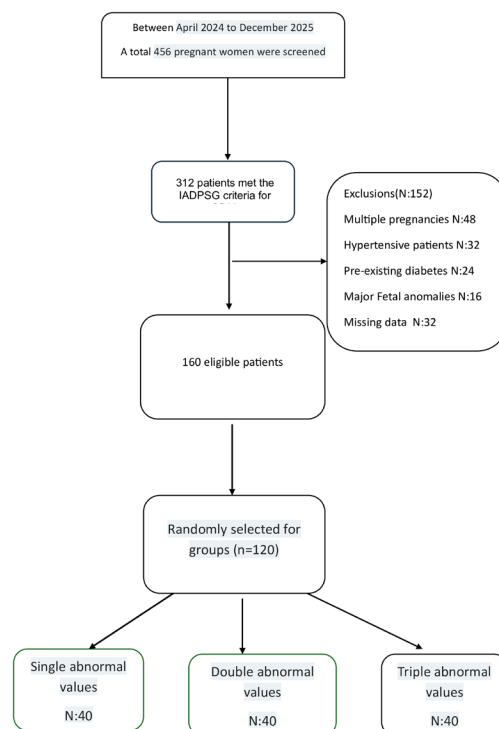


Figure 1: Study flowchart

For each patient included in this study, clinical and demographic information, age, parity, gravida, gestational age, hemoglobin A1c (HbA1c) levels measured at the time of GDM diagnosis (24–28 weeks of gestation), type of treatment received, gestational age at delivery, birth weight, Apgar scores at 1 and 5 minutes, need for neonatal intensive care (NICU), presence of hypoglycemia and hyperbilirubinemia in the newborn, and umbilical cord blood gas parameters (pH and base deficit) at birth were recorded. Newborns weighing over 4500 g were classified as macrosomic and recorded.⁸ Neonatal hypoglycemia was defined as blood glucose <45 mg/dL within the first 24 hours, based on laboratory values requiring treatment (e.g., oral glucose or IV dextrose). Hyperbilirubinemia was defined as total bilirubin >12 mg/dL requiring phototherapy. NICU admission was defined as any admission lasting >24 hours, with primary reasons recorded (e.g., respiratory distress, infection). Macrosomia threshold (>4500 g) is now consistently stated throughout.

This study included patients diagnosed with GDM who underwent a 75-gram OGTT after an 8-hour fast at 24–28 weeks of gestation.⁹ Diagnosis was based on the IADPSG criteria.² For patients with single or double abnormal values, these were identified across the fasting (≥ 92 mg/dL), 1-hour (≥ 180 mg/dL), and/or 2-hour (≥ 153 mg/dL) plasma glucose measurements following the 75g glucose load; postprandial status was thus inherently assessed via the 1- and 2-hour values, while fasting status was evaluated at baseline. No additional separate fasting or postprandial assessments beyond the OGTT were performed for grouping purposes.

Institutional GDM management followed ACOG guidelines: All patients received diet counseling and self-monitoring of blood glucose (targets: fasting <95 mg/dL, 1-hour postprandial <140 mg/dL, 2-hour <120 mg/dL). Insulin was initiated if >50% of values exceeded targets despite diet, or if HbA1c >6.5% at diagnosis.

In this study, patients with multiple pregnancies, hypertensive patients, pregnant women with Type 1 or Type 2 diabetes, patients with known major fetal chromosomal and cardiac anomalies, and patients with missing or inaccessible data were excluded.

2.2. Statistical Analysis.

SPSS 22.0 (SPSS Inc., Chicago, IL, USA) statistical software was used for data analysis. The Kolmogorov–Smirnov test and Shapiro–Wilk test

was used to analyze the normality of the data distribution. For continuous variables, one-way ANOVA was applied to compare normally distributed data across groups, while the Kruskal-Wallis test was used for non-normally distributed variables. Descriptive analyses used the mean (\pm SD) for variables. The chi-square test was used to compare categorical variables. Post-hoc pairwise comparisons were performed using Tukey's HSD for ANOVA or Dunn's test for Kruskal-Wallis, with $p < 0.05$ considered significant. To evaluate independent predictors of cesarean delivery, a multivariable logistic regression analysis adjusted for age, body mass index (BMI), parity, history of previous cesarean delivery, HbA1c levels, and study group (Group 1 as the reference category) was performed. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results

A total of 120 patients were included in this study based on the results of the 75-gram OGTT test: 40 patients with 1 positive value, 40 patients with 2 abnormal values, and 40 patients with 3 abnormal values. Various obstetric and neonatal outcomes were compared between the three groups and are presented in Table 2.

There was no significant difference in the mean ages between the groups (Group 1: 32.25 ± 5.72 years; Group 2: 29.50 ± 6.35 years; Group 3: 34.80 ± 6.01 years; $p = 0.182$).

There was no significant difference in Gravida values between groups (Group 1: 4.0 ± 3.0 ; Group 2: 2.0 ± 2.0 ; Group 3: 2.0 ± 1.0 ; $p = 0.557$).

No statistically significant difference was found between the groups in terms of parity (Group 1: 1.0 ± 1.0 ; Group 2: 1.0 ± 1.0 ; Group 3: 1.0 ± 1.0 ; $p = 0.401$).

Insulin use differed significantly between groups (Group 1: 95%, Group 2: 70%, Group 3: 30%; $p < 0.001$).

A significant difference was found in HbA1c levels; the HbA1c value was significantly higher in Group 3 (Group 1: 5.26 ± 0.44 ; Group 2: 5.58 ± 0.40 ; Group 3: 7.08 ± 1.21 ; $p < 0.001$). In the post-hoc test, there was no difference between Group 1 and Group 2, but a significant difference was observed between Group 1 and Group 3 ($p < 0.001$). A significant difference was observed between Group 2 and Group 3 ($p = 0.005$).

There was no difference between the groups in terms of gestational age (Group 1: 37 ± 2.13 ; Group 2: 36.3 ± 3.1 ; Group 3: 36.0 ± 2.9 ; $p = 0.673$).

Table 2: Patient clinicodemographic data and newborn outcomes

Variables	Group 1 N:40	Group 2 N:40	Group 3 N:40	P value
Age(years)	32.25 ± 5.72	29.5±6.35	34.8±6.01	0.182
Gravida	4.0± 3.0	2.0±2.0	2.0±1.0	0.557
Parity	1.0± 1.0	1.0±1.0	1.0±1.0	0.401
Use of insulin(%)	38(%95)	28(%70)	12(%30)	<0.001
HbA1c(%)	5.26± 0.44 ^a	5.58±0.40 ^a	7.08±1.21 ^b	<0.001
BMI(kg/m2)	28.5±4.2	29.1±3.8	30.2±4.5	0.312
Prior Cesarean History(%)	%45	%35	%40	0.567
Neonatal Outcome				
Birth week	37±2.13	36.3±3.1	36.0±2.9	0.673
Birth weight(g)	2966±643	3011±818	2589±753	0.673*
Macrosomia(%)	%15	%10	%15	0.857
Cesarean delivery(%)	38(%95) ^a	26(%65) ^b	24(%60) ^b	0.024
Apgar 1min	7.25±1.0	7.5±0.92	7.0±0.7	0.537
Apgar 5 min	8.5±0.5	8.8±0.6	8.4±0.5	0.064
Cord Ph	7.3±0.06	7.3±0.05	7.2±0.08	0.060
Base deficit(mmol/L)	5.72±3.1	3.51±2.1	3.5±3.19	0.397
NICU Admission(%)	%10	%30	%25	0.328
Neonatal hypoglycemia(%)	%5	%25	%15	0.244
Neonatal jaundice(%)	16(%40)	14(%35)	16(%45)	0.921

Hb:Hemoglobin ,NICU: neonatal intensive care unit- The chi-square test was used to compare categorical variables. ANOVA and post-hoc Tukey tests were applied for parametric variables.

* Kruskal-Walli's test was used for non-normally distributed variables. Post-hoc Dunn's test tests were applied for nonparametric variables. $p < 0.05$ statistically significant

Birth weights did not show a significant difference between the three groups. (Group 1: 2966±643 g; Group 2: 3011±818 g; Group 3: 2589±753 g; $p=0.673$).

Macrosomia rates did not differ significantly between groups. (Group 1: 6/40 (15%); Group 2: 4/40(10%); Group 3: 6/40 15%; $p=0.857$).

A significant difference was found in HbA1c levels measured at diagnosis (24-28 weeks); the HbA1c value was significantly higher in Group 3 ($p < 0.001$).

The cesarean section rate was significantly higher between groups; the highest rate was observed in Group 1 (Group 1: 38/40 (95%); Group 2: 26/40 (65%); Group 3: 24/40 (60%); $p=0.024$). Cesarean delivery rates were similar between Group 2 and Group 3, while this rate was higher in Group 1 ($P=0.031$). The indications for cesarean section for all patients are shown in Table 3.

Table 3: Cesarean Indications

Indication	Percentage
Fetal Distress	% 25
Prior Cesarean	%40
Malpresentation	%15
Other	%20

No statistically significant difference was found between Apgar 1 and Apgar 5 scores (Apgar 1: $p=0.537$; Apgar 5: $p=0.064$).

The difference in cord pH values was not found to be significant ($p=0.060$).

No significant difference was detected in base deficit between groups ($p=0.397$).

NICU admission rates were not significantly different between groups (Group 1: 10%; Group 2: 30%; Group 3: 25%; $p=0.328$).

No significant difference was detected in the rates of neonatal hypoglycemia between the groups (Group 1: 5%; Group 2: 25%; Group 3: 15%; $p=0.244$).

Neonatal jaundice: No significant difference was found in neonatal jaundice rates (Group 1: 40%; Group 2: 35%; Group 3: 45%; $p=0.921$).

Multivariable logistic regression analysis was performed to assess the independent predictors of cesarean delivery, adjusting for age, BMI, parity, prior cesarean, HbA1c, and study group (with Group 1 as the reference). The results are summarized in Table 4. Age was associated with an increased risk (adjusted OR 1.1072, 95% CI 1.0478-1.1699, $p < 0.001$), as was parity (adjusted OR 1.3611, 95% CI 1.0703-1.7308, $p = 0.011$) and prior cesarean history (adjusted OR 1.8975, 95% CI 1.1381-3.1636, $p = 0.014$). HbA1c showed a trend toward significance (adjusted OR 1.5404, 95% CI 0.9322-2.5454, $p = 0.091$), while BMI was not significantly associated (adjusted OR 0.0370, 95% CI 0.9705-1.1081, $p = 0.282$). Compared to Group 1, both Group 2 (adjusted OR 0.2492, 95% CI 0.1344-0.4621, $p < 0.001$) and Group 3 (adjusted OR 0.1750, 95% CI 0.0917-0.3341, $p < 0.001$) had significantly lower odds of cesarean delivery, indicating a higher independent risk in Group 1.

Tablo 4: Multivariable Logistic Regression Result

Variables	Adjusted Odds Ratio (OR)	%95 CI Lower	%95 CI Upper	P value
Age	1.1072	1.0478	1.1699	<0.001
BMI	1.0370	0.9705	1.1081	0.282
Parity	1.3611	1.0703	1.7308	0.011
Prior Cesarean	1.8975	1.1381	3.1636	0.014
HbA1c	1.5404	0.9322	2.5454	0.091
Group 2(vs.Group 1)	0.2492	0.1344	0.4621	<0.001
Group 3(vs. Group 1)	0.1750	0.0917	0.3341	<0.001

Discussion

This study examined maternal and neonatal outcomes based on the number of abnormal values in the 75 g OGTT test. While significant differences were observed in patients' HbA1c levels and cesarean section rates, no differences were observed in neonatal outcomes.

Prenatal care for patients with GDM focuses on identifying and managing patients with impaired glucose metabolism. The pathogenesis of the relationship between hyperglycemia and poor maternal-fetal outcomes involves insulin resistance exacerbated by placental hormones (e.g., human placental lactogen), leading to maternal hyperglycemia that crosses the placenta and induces fetal hyperinsulinemia. This “fetal fuel hypothesis” (Pedersen’s hypothesis) results in accelerated fetal growth, macrosomia, and metabolic disturbances such as neonatal hypoglycemia due to abrupt cessation of maternal glucose supply at birth.^{10,11} Hyperglycemia also promotes oxidative stress and inflammation, contributing to endothelial dysfunction and increased risks of preeclampsia, cesarean delivery, and long-term maternal type 2 diabetes.¹²

Unlike patients with pre-existing diabetes, patients with true GDM are not at risk for congenital anomalies in the fetus because the onset of the disorder occurs after the major organogenesis period. Randomized trials have consistently shown that maternal hyperglycemia significantly increases the chance of having a macrosomic newborn.¹³ Macrosomia rates were low across groups (10-15%), with no significant differences. The mean birthweights (2.6-3.0 kg) are consistent with these low macrosomia rates, as only a small proportion exceeded 4500 g.

Macrosomia is associated with an increased risk of adverse neonatal outcomes, such as operative delivery (cesarean or instrument-assisted vagi-

nal), maternal trauma, shoulder dystocia, and related complications.¹⁴

Newborns from pregnancies complicated by GDM are at increased risk for various morbidities, including hypoglycemia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, polycythemia, respiratory disorders, and/or cardiomyopathy. These risks are largely related to maternal and, in turn, fetal hyperglycemia.¹⁵ The study screened for hypoglycemia and hyperbilirubinemia in newborns, with a hyperbilirubinemia rate of 30%. However, no association was observed with the number of positive OGTT values.

In a meta-analysis of 25 studies, both retrospective and prospective studies found that pregnant women with an abnormal OGTT result had a significantly increased risk of adverse outcomes compared to those with a completely normal OGTT result.¹⁶ Additional outcome studies specific to the 75 g OGTT, such as those from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, have informed IADPSG criteria and demonstrated a continuous association between maternal glucose levels and adverse outcomes, even below diagnostic thresholds.^{17,18} Prospective cohorts like the Atlantic DIP study further highlight that treating GDM based on 75 g OGTT reduces macrosomia and cesarean rates, emphasizing the need for tailored management.¹⁹ In contrast, studies questioning single vs. multiple abnormalities in 75 g OGTT suggest that even isolated hyperglycemia may warrant intervention, though evidence is mixed.^{20,21}

In the literature, a similar study was conducted with 100 g OGTT, comparing maternal and fetal outcomes with single or double abnormal values. No differences were observed in other maternal and neonatal outcomes except for macrosomia and insulin requirement.²² In another study using a 100 g OGTT, no differences were observed in maternal and fetal outcomes when comparing pregnant women diagnosed with GDM based on a single positive value.²³

The study clearly addressed this issue by comparing the effects of single, double, or triple abnormal values on maternal and neonatal outcomes in pregnant women diagnosed with GDM using a 75 g OGTT. We added the following statement to the section. Institutional GDM management performed according to ACOG guidelines may have reduced risks in high HbA1c groups, helping to explain the absence of differences in newborns. Specific and detailed variable recording: A series of clinical variables, inclu-

ding age, parity, gravidity (gravida), gestational age, HbA1c, treatment type, week of delivery, newborn weight, Apgar scores, NICU requirement, newborn hypoglycemia, and hyperbilirubinemia, were systematically recorded.

The significance of HbA1c differences and the finding of differences in cesarean rates between groups yield practical implications for treatment and follow-up.

Interestingly, insulin requirement was highest in Group 1 (single abnormal value; 95%) and decreased progressively with the number of abnormal OGTT values (70% in Group 2 and 30% in Group 3; $p < 0.001$). This counterintuitive pattern may reflect differences in the underlying pathophysiology; isolated abnormalities (particularly fasting or early-postprandial hyperglycemia) could indicate more pronounced insulin resistance in some cases, prompting earlier and more aggressive insulin initiation in clinical practice, whereas multiple abnormalities might have been managed more conservatively or responded better to dietary intervention in our cohort.

Limitations

Due to its retrospective nature, the study may limit causality inferences and carries a risk of selection bias. Furthermore, the results are limited to a single hospital and a specific population, thus limiting generalizability. The small sample size may make it difficult to statistically detect some rare complications. There is a possibility that some clinical variables may be missing or of limited reliability in retrospective records (e.g., HbA1c, treatment details).

In conclusion, the findings of this study show that an increase in the number of abnormal values in pregnant women diagnosed with GDM using a 75 g OGTT may create a significant difference in some maternal parameters, but no significant differences were found in neonatal outcomes. HbA1c levels were found to be significantly higher in Group 3, a finding that may be related to this and points to the importance of controlling maternal glucose metabolism. The difference in cesarean section rates between groups also indicates the need to review the recommended management strategies based on the clinical picture.

Overall, the study provides a valuable contribution to investigating the potential impact of different positivity levels of the 75 g OGTT on GDM management and birth outcomes. However, due to the limitations of the retrospective, single-center design, the generalizability of the findings is limited, and con-

firmation by larger, multicenter, prospective studies is recommended. Furthermore, further studies would be beneficial in terms of controlling confounding criteria and harmonizing diagnostic criteria.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Ethics Committee of Ankara City Hospital Ethical Committee (TABED 2-24-123).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Author contribution

BBÖ: Design the method to achieve results, Data collecting and processing, Literature scan, Article writing

GRT: Data collecting and processing

DO: Analysis-Comment, Critical examination

ÖK: Organizing the execution of the work

DŞ: Article writing, Critical examination

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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