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Is Diminished Ovarian Reserve Associated with Poor Perinatal Outcomes? A Retrospective Cohort Study

Azalmış Over Rezervi Kötü Perinatal Sonuçlarla İlişkili midir? Retrospektif Bir Kohort Çalışması

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ÖZET
Amaç: İntrasitoplazmik sperm enjeksiyonu (ICSI) tedavisi gören kadınlarda düşük over rezervinin (DOR) olumsuz perinatal sonuçlarla ilişkili olup olmadığını araştırmak.
Gereç ve Yöntemler: Bu retrospektif kohort çalışması bir hastanenin in vitro fertilizasyon (IVF) Ünitesinde yürütülmüş ve 2019-2022 yılları arasındaki kayıtlar analiz edilmiştir. Çalışmada DOR nedeni ile IVF uygulanıp canlı doğum yapan 26 hasta ile ve kontrol grubu olarak erkek faktörü nedeni ile IVF uygulanıp canlı doğum yapan 63 kadının doğum verileri incelenmiştir. Analiz edilen sonuçlar arasında erken doğum (ED), düşük doğum ağırlığı (DDA), erken membran rüptürü (EMR), hipertansif gebelik bozuklukları (GHB), gestasyonel diyabet (GDM), abruptio plasenta, intrahepatik gebelik kolestazı, konjenital anomali ve sezaryen oranı yer almaktadır. Gruplar yaş ve vücut kitle indeksi (VKİ) açısından eşleştirilmiştir. İstatistiksel analizler DOR ile perinatal komplikasyonlar arasındaki ilişkiyi değerlendirmek için lojistik regresyonu içermektedir.
Bulgular: DOR'lu kadınlar birkaç temel alanda önemli ölçüde daha kötü perinatal sonuçlar göstermiştir. Doğum ağırlıkları DOR grubunda kontrol grubuna kıyasla anlamlı derecede düşüktür [2.300 (900-4.000) gr vs. 3.150 (900-4.100) gr, p = 0.011]. Ayrıca, 34 haftadan önce erken doğum oranı DOR grubunda belirgin şekilde daha yüksektir (%29.6' ya karşı %11.1, p = 0.031) ve 3.36'lık bir olasılık oranı (%95 GA: 1.07-10.53) ile önemli ölçüde yüksek bir riske işaret etmektedir. EMR' de DOR grubunda belirgin şekilde daha yaygındı (%25.9' a karşı %7.9, p = 0.021). Buna karşılık, GHB (%14.8' e karşı %12.7, p = 0.787) ve GDM (%7.4'e karşı %6.3, p = 0.854) oranlarında önemli bir farklılık görülmemiştir. Plasental ablasyo, intrahepatik kolestaz ve konjenital anomaliler dahil olmak üzere diğer komplikasyonlar gruplar arasında benzerdi.
Sonuç: DOR, artmış DDA, ED ve EMR riskleri ile ilişkilidir. Bu bulgular, perinatal sonuçları iyileştirmek için DOR'lu kadınlar için özel yönetimin önemini vurgulamaktadır.

Anahtar Kelimeler: Over rezervi, perinatal sonuçlar, intrasitoplazmik sperm enjeksiyonu, düşük doğum ağırlığı

ABSTRACT
Objective: To investigate whether diminished ovarian reserve (DOR) is associated with adverse perinatal outcomes in women undergoing intracytoplasmic sperm injection (ICSI) treatment.
Materials and Methods: This retrospective cohort study was performed in the In Vitro Fertilization (IVF) Unit of a hospital, examining records spanning from 2019 to 2022. The study involved 26 women diagnosed with DOR who achieved live births through ICSI. These patients were compared to a control group of 63 women who underwent IVF treatment due to male factor infertility, also resulting in live births. Outcomes analyzed included preterm birth (PTB), low birth weight (LBW), preterm premature rupture of membranes (PPROM), hypertensive disorders of pregnancy (HDP), gestational diabetes (GDM), abruptio placenta, intrahepatic cholestasis of pregnancy, congenital anomaly, c-section rate. The groups were matched by age and body mass index (BMI). Statistical analyses included logistic regression to evaluate the association between DOR and perinatal complications.
Results: Women with DOR demonstrated significantly poorer outcomes in several key areas. Birth weights were significantly lower in the DOR group compared to controls [2.300 (900–4.000) gr vs. 3.150 (900–4.100) gr, p = 0.011]. Additionally, the rate of PTB before 34 weeks was markedly higher in the DOR group (29.6% vs. 11.1%, p = 0.031), with an odds ratio of 3.36 (95% CI: 1.07–10.53), indicating a significantly elevated risk. PPROM was also notably more prevalent in the DOR group (25.9% vs. 7.9%, p = 0.021). In contrast, rates of HDP (14.8% vs. 12.7%, p = 0.787) and GDM (7.4% vs. 6.3%, p = 0.854) showed no significant differences. Other complications, including placental abruption, intrahepatic cholestasis, and congenital anomalies, were similar between the groups.
Conclusion: DOR is associated with increased risks of LBW, PTB, and PPROM. These findings emphasize the importance of tailored management for women with DOR to improve perinatal outcomes.

Keywords: Ovarian reserve, perinatal outcomes, intracytoplasmic sperm injection, low birth weight

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INTRODUCTION

Diminished ovarian reserve (DOR) is a clinical condition characterized by a diminished response to ovarian stimulation during assisted reproductive treatments (ART), often resulting in lower oocyte retrieval, using high gonadotropin doses, decreased implantation rates, and challenges in achieving a successful pregnancy (1). The prevalence of DOR is increasing, partly due to delayed childbearing, which exposes more women to the natural decline in ovarian function. An estimate of 9–24% of women undergoing In Vitro Fertilization (IVF) are poor ovarian responders (2).

The outcome of an IVF cycle is significantly influenced by the ovarian response to gonadotrophin stimulation, among various other factors (3). A suboptimal ovarian response not only correlates with lower success rates in IVF treatments but also poses a heightened risk of obstetric and perinatal complications (4) in subsequent pregnancies when compared to alternative methods like intrauterine insemination (5).

The relationship between DOR and adverse maternal and neonatal outcomes remains a subject of ongoing debate. Several studies researched that women with poor ovarian response may be at increased risk of gestational diabetes (GDM), hypertensive disorders of pregnancy (HDP), preterm birth (PTB), and other complications (6, 7). For instance, Li et al., observed that certain Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) groups, particularly older women with low ovarian reserve, showed higher incidences of GDM, HDP, and first-trimester pregnancy loss compared to women with normal ovarian function (6). On the other hand, some evidence contradicts these findings. Jin et al., reported that among women under 38 years of age, DOR did not increase the likelihood of maternal complications or adverse neonatal outcomes such as low birth weight (LBW) or PTB in singleton pregnancies (7). The discrepancies in the literature may be attributed to differences in study populations, methodologies, and the criteria used to define DOR. For example, while some studies focus on older women undergoing ART, others investigate younger populations with varying degrees of ovarian reserve. Moreover, confounding factors such as age, body mass index (BMI), and preexisting medical conditions often complicate the interpretation of results.

Despite these difficulties, which can make IVF seem like a last resort, infertile couples need to weigh its disadvantages against the chances of success and the possibility of achieving a live birth. This underscores the importance of conducting further research and in-depth studies on the subject. This study aims to evaluate whether DOR is associated with poorer perinatal outcomes, including adverse maternal and neonatal complications. Understanding these associations is critical for informing clinical management and improving outcomes in this growing patient population.

MATERIALS METHODS

This research involved a retrospective cohort of women who achieved a singleton live birth following fresh embryo transfer during intracytoplasmic sperm injection (ICSI) cycles at the University of Health Sciences Konya City Hospital IVF Unit, from 2019 to 2022. The outcome of 26 live birth patients who underwent ICSI due to DOR, were compared with the obstetric and perinatal outcomes of 63 live birth patients who underwent ICSI due to male factor as a control group. To exclude maternal factors, we included patients who underwent ICSI due to male factor and had a singleton live birth after fresh single embryo transfer as a control group. The controls were matched by age and BMI. Complications for mothers and newborns were compared between the DOR group and the control group.

Inclusion criteria for the study were; patients who underwent ICSI due to DOR and achieved live births as the study group (n=26) and patients who underwent ICSI due to male factor and achieved live births, as the control group (n=63). At the same time, patients who had a single fresh 3rd or 5th day embryo transfer and had a single live birth. Exclusion criteria; Patients over 40 years of age, due to age-related perinatal and obstetric risks, patients with systemic diseases, endometrioma/endometriosis, polycystic ovary syndrome, patients with more than 1 embryo transfer, frozen embryo transfer cycles. Information about the patients was obtained from infertility files and computerized data. Each participant in this study signed a written informed consent. Ethical approval of this manuscript was obtained from Karatay University Faculty of Medicine (Date: 26.12.2024, number: 2024/008).

Patients born at 24 weeks and over were accepted as live births. Among the maternal and neonatal complications analyzed were HDP, PTB, preterm premature rupture of membranes (PPROM), LBW, GDM and abruptio placenta, intrahepatic cholestasis, c- section rate, fetal anomaly. Patients defined as, DOR if two out of these three criteria were met; 1) Anti-Müllerian Hormone (AMH) < 1.2 ng/mL, 2) Antral Follicle Count (AFC) < 7 on days 2–4 of the menstrual cycle, 3) basal serum Follicle-Stimulating Hormone (FSH) > 10 U/L. Patients with hypertensive disorders were diagnosed according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria (8). In the current study, HDP includes gestational hypertension and pre-eclampsia and excludes chronic hypertension. PTB is characterized by a live birth occurring before 37 weeks of pregnancy. LBW is identified when a full-term newborn's birth weight is under 2500 grams. The diagnosis of GDM according to WHO criteria is made when one or more of the following criteria are met: fasting plasma glucose ≥ 7.0 mmol/l; 2-hour plasma glucose ≥ 11.1 mmol/l following a 75 g oral glucose load; random plasma glucose ≥ 11.1 mmol/l in the presence of diabetes symptoms (9). Intrahepatic cholestasis of pregnancy is characterized by pruritus and an elevation in serum bile acid concentrations, typically developing in the late second and/or third trimester and rapidly resolving after delivery (10).

Ovarian stimulation protocol

Basal hormone profiles were assessed on the 2nd or 3rd day of menstruation for all patients. To rule out persistent cysts, transvaginal ultrasonography was performed. Patients were administered either a fixed or flexible short antagonist protocol,

with individualized doses of recombinant Follicle-Stimulating Hormone (recFSH) (Gonal f, Merck, Italy) or recFSH+Human Menopausal Gonadotropin (HMG) (75-150 IU of Merional, IBSA, Switzerland) initiated on the 2nd or 3rd day of the cycle based on BMI. Patients were recalled every 2-3 days for transvaginal folliculometry, and measurements of Luteinizing Hormone (LH), estradiol, and progesterone. Upon the dominant follicle exceeding 12mm, a Gonadotropin-Releasing Hormone (GnRH) antagonist (Cetrorelix, Merck, Italy) was added for flexible antagonist protocol. GnRH antagonist (Cetrorelix, Merck, Italy) was added on day 6th day of stimulation in patients using a fix antagonist protocol. When follicles reached a size of 17-18mm, final maturation was induced with recHCG (Ovitrelle, Merck, Italy). Oocyte retrieval was conducted under anesthesia 34-36 hours after triggering. All patients underwent standard ICSI with Metaphase II (MII) oocytes. The highest-quality embryos from day 3 or day 5 were transferred using a soft catheter under ultrasound guidance. Post-transfer, patients received routine luteal support of 3x200mg intravaginal progesterone (Progestan caps, Koçak Farma, Istanbul). Patients were invited back to the hospital for a pregnancy test 12 days following the transfer.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). The conformity of continuous variables to normal distribution was evaluated by Kolmogorov-Smirnov test and histograms. Continuous variables showing normal distribution were expressed as mean ± standard deviation (Mean ± SD) and continuous variables not showing normal distribution were expressed as median (Min-Max). Categorical variables were expressed as n (%). In intergroup comparisons, Independent t-test was used for variables with normal distribution and Mann-Whitney U test was used for variables without normal distribution. Chi-square test or Fisher exact test was used when appropriate for analyses of categorical variables. Logistic regression analysis was performed to evaluate the risk factors for PPROM. The results of the regression analysis are reported with odds ratios (odds ratios, OR) and 95% confidence intervals (confidence intervals, CI). In all statistical tests, a value of $p < 0.05$ was accepted as the limit of statistical significance. Patients born at 24 weeks and over were accepted as live births.

RESULTS

A comparison was made of the demographic and hormonal characteristics of the DOR and control groups (Table 1). The analysis revealed no statistically significant differences in age (33.63 ± 5.09 years vs. 32.89 ± 4.04 years, p = 0.464) or BMI [23.67 (20.00-33.00) kg/m2 vs. 23.80 (19.45-30.05) kg/m2, p = 0.476] between the groups. However, a significant difference was observed in antral follicle count (AFC) [5.00 (2.00-12.00) vs. 11.00 (8.00-13.00), p = 0.001] and antimüllerian hormone (AMH) levels (0.92 ± 0.36 ng/mL vs. 3.04 ± 0.96 ng/mL, p = 0.001) were significantly lower in the DOR group compared to the control group.

The total FSH dose required was significantly higher in the DOR group (2834.26 ± 606.07 IU vs. 1826.19 ± 338.15 IU, p = 0.001), while serum estradiol levels on the hCG day were

Table 1. Comparison of clinical and hormonal parameters between DOR and controls

Variables	DOR (n=27)	Control Group (n=63)	p-value
Age (years)	33.63 ± 5.09	32.89 ± 4.04	0.464*
BMI (kg/m^2)	23.67 (20.00-33.00)	23.80 (19.45-30.05)	0.476**
AFC (n)	5.00 (2.00-12.00)	11.00 (8.00-13.00)	0.001**
AMH (ng/mL)	0.92 ± 0.36	3.04 ± 0.96	0.001*
FSH (U/L)	13.11 ± 2.63	6.55 ± 2.18	0.012*
LH (U/L)	8.00 (2.82-13.00)	5.99 (3.89-13.59)	0.066**
E2 (ng/L)	40.80 ± 13.48	39.23 ± 11.41	0.574*
Progesterone (µg/L)	0.84 ± 0.26	1.00 ± 0.22	0.004*

AMH: anti-müllerian hormon *independent t test(mean+SD), **Mann Whitney U test[Median(Min-Max)]. DOR: diminished ovarian reserve, BMI: body mass index, AFC: antral follicle count, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, n: number

Table 2. Comparison of IVF cycle parameters and laboratory outcomes between DOR and control groups

Variables	DOR (n=27)	Control Group (n=63)	p-value
Total FSH Dose (IU)	2834.26 ± 606.07	1826.19 ± 338.15	0.001*
E2 on hCG Day (ng/L)	1079.37 ± 251.01	2578.62 ± 527.10	0.001*
Endometrial Thickness on hCG Day (mm)	10.42 ± 2.23	12.10 ± 1.74	0.001*
Stimulation Duration (days)	10.00 (8.00-12.00)	10.00 (9.00-11.00)	0.756**
Oocytes Retrieved (n)	4.89 ± 1.87	10.43 ± 2.80	0.001*
MII Oocytes (n)	3.30 ± 1.46	7.08 ± 2.16	0.001*
Total Embryos (n)	2.19 ± 0.96	4.90 ± 1.49	0.001*
Number of Embr. Transferred	1.57± 0.62	2.09 ± 0.70	<0.001
Blastocyst Transfer (n)	0	12(19.04)	0.002
Endometrial Thickness on Transfer Day (mm)	11.45 ± 2.15	12.71 ± 1.73	0.004*

IVF: In Vitro Fertilization FSH:follicle stimulating hormone E2: estradiol DOR: diminished ovarian reserve*independent t test(mean+SD), **Mann Whitney U test[Median(Min-Max)]. HCG: human chorionic gonadothropin, mm: milimeter

Table 3. Comparison of obstetric and neonatal outcomes between DOR and control groups

Variables	DOR (n=27)	Control Group (n=63)	p-value
Birth weight(gr)	2300.0 (900.0 – 4000.0)	3150.0 (900.0 – 4100.0)	0.011*
Birth week	38.0 (26.0 – 40.0)	38.0 (28.0 – 40.0)	0.172*
Preterm birth<34 week(n)	8 (29.6%)	7 (11.1%)	0.031**
Preterm birth<37 week(n)	13 (48.1%)	19 (30.2%)	0.102**
GDM(n)	2 (7.4 %)	4 (6.3 %)	0.854**
HDP(n)	4 (14.8 %)	8 (12.7 %)	0.787**
PPROM (n)	7 (25.9 %)	5 (7.9 %)	0.021**
Abruptio placenta(n)	1 (3.7 %)	2 (3.2 %)	0.898**
Intrahepatic cholestasis(n)	1 (3.7 %)	1 (1.6 %)	0.533**
C-Section Rate(n)	19 (70.4 %)	40 (63.5 %)	0.529**
Congenital Anomaly(n)	1 (3.7 %)	3 (4.8 %)	0.823**

DOR: diminished ovarian reserve *Mann Whitney U test[Median(Min-Max)], ** Chi Square test(n%). GDM: gestational diabetes mellitus, PTB: preterm birth, LBW: low birth weight, PPROM: preterm premature rupture of membranes, HDP: hypertensive disorders of pregnancy,gr: grams, c-section: cesarean

Table 4. Logistic regression analysis of factors associated with PPROM in IVF patients

Variable	Coefficient	Std. Error	Wald	p-value	Odds Ratio	95% CI
Constant	-2.812	5.547	0.257	0.612		
BMI	-0.075	0.122	0.378	0.538	0.92	0.72 - 1.17
Age	0.041	0.077	0.292	0.588	1.04	0.89 - 1.21
DOR group	2.025	0.766	6.979	0.008	7.57	1.68 - 34.05
ET on Tx Day	0.004	0.184	0.006	0.979	1.00	0.69 - 1.44
ET on hCG Day	0.306	0.200	2.346	0.125	1.35	0.91 - 2.01
Stimulation Duration	-0.320	0.300	1.135	0.286	0.72	0.40 - 1.30

DOR: diminished ovarian reserve BMI: body mass index Et: endometrial thickness,tx: transfer

markedly lower in the DOR group (1079.37 ± 251.01 ng/L vs. 2578.62 ± 527.10 ng/L, p = 0.001). A significant difference was observed in the number of oocytes retrieved between the two groups (4.89 ± 1.87 vs. 10.43 ± 2.80, p = 0.001). Furthermore, a lower proportion of M2 oocytes was observed in the poor responder group (3.30 ± 1. 46 vs. 7.08 ± 2.16, p = 0.001), and total embryos formed (2.19 ± 0.96 vs. 4.90 ± 1.49, p = 0.001) (Table 2).

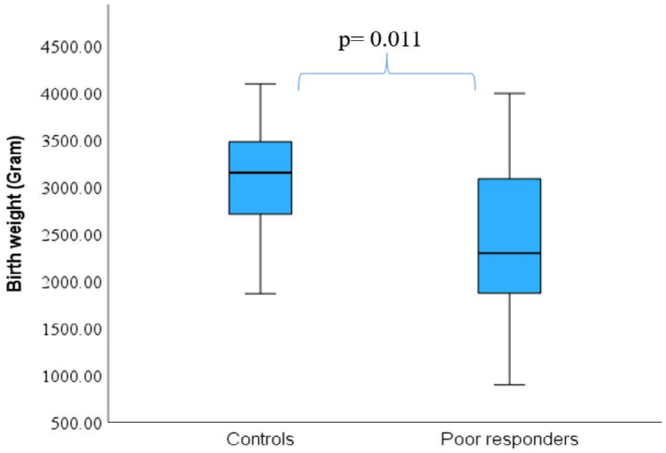

Figure 1. Box Plot Graph Comparing Birth Weight Between DOR and Control Groups in IVF Patients

Birth weight was significantly lower in the DOR group [2300.0 (900.0–4000.0) g vs. 3150.0 (900.0–4100.0) g, p = 0.011] (Figure 1). However, no significant difference was observed in gestational age at birth [38.0 (26.0–40.0) weeks vs. 38.0 (28.0–40.0) weeks, p = 0.172]. Preterm birth (PTB) rates of less than 34 weeks were 29.6% in the DOR group and 11.1% in the control group (p = 0.031). The odds ratio for PTB before 34 weeks was 3.36 (95% CI: 1.07–10.53), indicating a significantly increased risk in the DOR group. Similarly, the incidence of PPROM was significantly higher in the DOR group (25.9% vs. 7.9%, p = 0.021), with an associated odds ratio of 7.57 (95% CI: 1.68–34.05), suggesting a strong association between DOR and PPROM. The rates of GDM and HDP were similar between the groups (7.4% vs. 6.3%, p = 0.854; and 14.8% vs. 12.7%, p = 0.787, respectively). No significant differences were found in placental abruption (3.7% vs. 3.2%, p = 0.898), intrahepatic cholestasis (3.7% vs. 1.6%, p = 0.533), or congenital anomalies (3.7% vs. 4.8%, p = 0.823). Cesarean section rates were higher in the DOR group (70.4% vs. 63.5%), but the difference did not reach statistical significance (p = 0.529) (Table 3).

Logistic regression analysis was performed to assess factors associated with PPROM risk. The analysis revealed that DOR were significantly associated with an increased risk of PPROM in IVF patients compared to controls (Odds Ratio [OR] = 7.57, 95% CI: 1.68-34.05, p = 0.008). BMI (OR = 0.92, 95% CI: 0.72-1.17, p = 0.538), age (OR = 1.04, 95% CI: 0.89-1.21, p = 0.588), endometrial thickness on the day of transfer (OR = 1.00, 95% CI:

0.69-1.44, p = 0. 979), endometrial thickness on hCG day (OR = 1.35, 95% CI: 0.91-2.01, p = 0.125) and duration of stimulation (OR = 0.72, 95% CI: 0.40-1.30, p = 0.286) were not significantly associated with PPROM (Table 4).

DISCUSSION

Having DOR is associated with increased implantation failure , reduced rates of live births (11) and higher miscarriage rates (12). In this article, we investigate whether DOR is also linked to poor obstetric outcomes. We compared the perinatal outcomes of patients with DOR who underwent IVF and had live births with a control group who underwent IVF due to male factors and also had live births. We found that the group with DOR had statistically higher risks of LBW (2.300 gr vs. 3500 gr, p=0.011), PPROM (7 vs 5, p=0.020) and PTB rates of less than 34 weeks (p = 0.031) than the control group.

An expanding body of research endorses the developmental origins of health and disease (DOHaD) hypothesis, suggesting that the foundational elements for chronic conditions are set during early life, particularly through the intrauterine environment (13). For example, compared to infants of normal birth weight, those born with lower weights are at a higher risk of encountering hypertension, diabetes, and other metabolic disorders during both childhood and adulthood (14). Therefore, investigating exposures during the intrauterine period is crucial for researching the etiologies of diseases. Some publications have found that high gonadotropin doses used in patients with low ovarian reserve are associated with aneuploidy and low blastocyst formation (15), while other research fails to observe this correlation (16, 17). LoraK.Shahine et al., found that the number of blasts developing in patients with low ovarian reserve was low and the aneuploidy rate was high (18). In our own study, we found a statistically lower rate of blast transfer in the DOR group.

A study investigates maternal and neonatal complications in women with DOR undergoing IVF or ICS) cycles. Conducted with 193 in the DOR group and 386 in the control group. The results indicated a significantly higher incidence of HDP in the DOR group (5.7%) compared to the control group (2.1%, p= 0.021). Although the incidences of PTB (10.9% vs. 7.5%, p= 0.174) and LBW (6.2% vs. 5.4%, p= 0.704) were higher in the DOR group, these differences were not statistically significant (19). However, in our study, we did not find a significant difference in HDP between the DOR and control groups. With a reduced number of oocytes, DOR is a prevalent condition linked to ovarian aging. Per the advisory statement from the American Society for Reproductive Medicine, the aging of ovaries is linked to irregularities in luteal phase function (20). The production of progesterone and estradiol metabolites during the luteal phase is significantly reduced in women of advanced age. Additionally, it has been documented that vascular issues and hypertensive pregnancy disorders are associated with dysfunction in the luteal phase (21). In our study, the lack of a higher incidence of HDP compared to the control group might be due to the control group not consisting of women of advanced maternal age. A study, which supports our research, also shows that women with a history of HDP do not necessarily exhibit DOR, as measured by AMH levels, compared to women with uncomplicated pregnancies (22).

Zhu et al. (23), examined the effects of DOR on the outcomes of IVF/ICSI among young women aged ≤35 years. The study found that women with DOR had significantly lower rates of blastocyst formation, embryo implantation, clinical pregnancy, and live birth compared to their non-DOR counterparts. However, there were no significant differences in high-quality embryo rates, miscarriage rates, or LBW incidences between the two groups. The study concludes that while DOR reduces clinical pregnancy and live birth rates, it does not increase the risk of perinatal complications or affect the LBW incidence in infants. These findings align with a major study showing no significant differences in low birth weight rates between women with fewer than four oocytes and those with normal ovarian reserve after adjusting for confounders (24). Additionally, a previous study found that infants from IVF patients with low ovarian responsiveness had similar birth weights to those with normal responsiveness, with no significant differences in low birth weight or size for gestational age (25). This may be due to the fact that patients over 35 years of age were also included in the study group and the number of participants was low.

There are also reports in the literature that PTB is increased in IVF pregnancies (26). There is a meta-analysis evaluating the association between IVF or ICSI and the risk of spontaneous PTB in singleton pregnancies compared to natural conception. Based on data from 15 cohort studies comprising over 61,000 pregnancies, the analysis reveals that sPTB (<37 weeks) occurs more frequently in IVF/ICSI pregnancies (10.1%) than in naturally conceived ones (5.5%), with an odds ratio of 1.75. The study highlights a significant increase in PTB risk for IVF/ICSI pregnancies but calls for caution in interpretation due to the low quality of evidence (27). A study investigates the impact of infertility causes on perinatal outcomes, specifically PTB and LBW, in singleton pregnancies achieved via IVF or ICSI. Using data from the Human Fertilization and Embryology Authority (HFEA), the study found that ovulatory and tubal disorders significantly increase the risk of PTB and LBW compared to unexplained infertility, while male factor infertility showed no significant impact. The findings suggest that the underlying cause of infertility plays a crucial role in perinatal risks (28). In our study, we found that the rate of PTB below 34 weeks of gestation was statistically significantly higher in patients who underwent IVF due to DOR than in patients who underwent IVF due to male factor.

Limitation of this paper is that it is retrospective and includes very few patients. Due to the retrospective design of our study, no prior power analysis was performed. However, a post hoc power analysis based on birth weight difference yielded 82% statistical power (Cohen's d = 0.73, α = 0.05). Another weakness is the lack of a control group of non-IVF patients. In addition, other potential confounders (such as smoking, socioeconomic status, chronic diseases) could not be evaluated because they were not included in the recorded data. On the other hand the control group was selected only

from patients with male factor-related infertility, which may lead to differences in hormonal environment and may lead to selection bias. In future studies, comparisons with groups with different causes of infertility are recommended.

CONCLUSION

In summary, this study highlights the significant impact of DOR on perinatal outcomes in women undergoing ICSI. While DOR was associated with an increased risk of adverse outcomes such as LBW, PTB before 34 weeks, and PPROM, it did not appear to exacerbate HDP or GDM compared to controls. These findings emphasize the need for personalized management strategies in patients with DOR to mitigate risks and optimize both maternal and neonatal outcomes. Further research with larger cohorts and diverse populations is warranted to deepen our understanding and improve clinical care for this unique patient group.

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