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Pregnancy Outcomes after Assisted Reproductive Technology: A Cross-sectional Study

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ABSTRACT

Background & aim: In the absence of region-specific data, this study investigated pregnancy and childbirth outcomes associated with assisted reproductive technology (ART) in western Iran.

Methods: This population-based cross-sectional study adhered to STROBE guidelines and included 368 women recruited by convenience sampling between November 2, 2022 and August 29, 2023, in Hamadan, western Iran. Data were collected using a validated questionnaire and checklist evaluated by ten faculty experts from Hamadan University of Medical Sciences. Pregnancy outcomes were summarized using frequencies and percentages. Associations between demographic or midwifery factors and categorical pregnancy outcomes were examined using chi-square tests. Logistic regression assessed the relationship between ART modalities and adverse pregnancy and birth outcomes. Analyses were performed using Stata version 14.

Results: Women who conceived through intracytoplasmic sperm injection (ICSI) exhibited significantly higher rates of hypertension, preeclampsia, placental abruption, preterm premature rupture of membranes, oligohydramnios, and emergency cesarean delivery compared with those in the in vitro fertilization (IVF) and intrauterine insemination (IUI) groups ($P<0.05$). The IVF group demonstrated increased risks of placenta previa, antepartum hemorrhage, polyhydramnios, gestational diabetes, postpartum bleeding, intrauterine growth restriction, cesarean delivery, preterm birth, and infants with low birth weight or low Apgar scores ($P<0.05$). Rupture of membranes was significantly more common in the IUI group than in the other ART groups ($P<0.001$).

Conclusion: ART modalities are associated with distinct maternal and neonatal risks. Clear communication of these risks and implementation of tailored risk-reduction strategies are essential. Pre-ART counseling should prioritize individualized risk assessment and education to support safer pregnancy outcomes.

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Introduction

Infertility is a crisis that encompasses a variety of socio-cultural, emotional, physical, and financial challenges, significantly impacting the lives of infertile couples, especially women (1-2). It often leads to issues, such as violence, divorce, social stigma, emotional stress, depression, anxiety, and low self-esteem (3).

Globally, over 80 million individuals are affected by infertility. According to a World Health Organization (WHO) report, a considerable portion of the population experience infertility at some point in their lives. Nearly 17.5% of the adult population, experience infertility (4).

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Estimates suggest that the prevalence of infertility in Iran stands at 20.2% (5).

In light of the rising infertility rates, substantial advancements and innovative technologies have proven beneficial in the treatment and care of infertile couples (6). Among these, assisted reproductive technology (ART) has been widely proposed as a successful and prevalent option (7). Despite remarkable successes, concerns persist regarding the potential adverse effects of these methods on both the mother and the newborn. Similar to any medical intervention, these methods also entail associated risks that should be carefully weighed before undergoing them (8).

Risks associated with ART methods, such as ovarian stimulation and freezing, for example, epigenetic risks or specific maternal risks (9). Risks associated with complications of ARTwhich can lead to premature birth. In addition, there are risks associated with the underlying factors of infertility, such as maternal age or the cause of infertility (10-11). In a cohort study by Tai et al., a multivariable logistic regression analysis revealed a significant increase in the risk of gestational diabetes, preeclampsia, preterm birth, placenta previa, postpartum hemorrhage, and cesarean section in ART pregnancies (12).

Currently, the goal of infertility treatment is no longer solely focused on achieving pregnancy, and a broader approach has emerged in this field (10). The main focus of the subject is a problem-oriented approach that aims to comprehensively manage an infertile couple from the initial visit to the birth of a healthy child (13). ART has aided couples worldwide. However, the use of ART has raised significant concerns regarding pregnancy outcomes and infant health. With the increasing number of children born through fertility treatments, which has surpassed eight million worldwide according to the latest report (4), numerous studies are underway in this area. Analyzing the outcomes of pregnancy following ART can assist in assessing the prognosis of such pregnancies and potentially averting complications through appropriate measures. Therefore, this study aimed to explore the consequences of pregnancy and childbirth resulting from ART in western Iran.

Materials and Methods

The STROBE reporting guidelines were utilized in the design of this cross-sectional study. This study was performed on 368 women from November 2, 2022, to August 29, 2023. Data in this study were extracted retrospectively from medical records. Women who became pregnant using ART and were referred to the Women's Hospital in Hamadan, a referral hospital in western Iran, for delivery through convenience sampling were included. Written consent was obtained from all participants.

The inclusion criteria consist of women aged 20-40 years based on similar study (14) who have achieved pregnancy through ART, have no underlying diseases such as diabetes or thyroid disorders or chronic high blood pressure, autoimmune diseases, or clotting disorders prior to pregnancy, and did not take specific medications prior to conception. The diagnosis and confirmation of primary infertility were determined by a physician. The exclusion criteria included women who did not respond to the call, incomplete information in medical records, women with multiples of degree 3 or higher, or women with a history of ART treatment in unknown centers or abroad.

Calculation of the sample size for this study was determined using data from study by Zafari conducted in 2014 (15). According to this study, 40% of women who conceived through ART experienced preterm birth. In the present study, the value of p (proportion of preterm birth) was set to 0.4. By considering a first type error (α) of 0.05 and a desired level of accuracy (d) of 0.05, a sample size of 368 women was determined.

The researcher-designed questionnaire included questions about the mother's age, mother's education level, mother's occupation, spouse's age, spouse's occupation, spouse's education level, type of delivery, and the ART method used. The ART methods were categorized into three groups: IVF, intrauterine insemination (IUI), and intracytoplasmic sperm injection (ICSI). After creating a checklist based on a review of various articles in the field, it was provided to ten faculty members of Hamadan University of Medical Sciences for validation and revision.By incorporating their suggestions and modifications, the final checklist was developed

for data collection. Face validity was checked by five women and subsequently modified. The reliability of this questionnaire (test- retest) was calculated to be 85%. The checklist includes questions regarding complications such as early abortion, late abortion, ectopic pregnancy, premature birth, low birth weight (LBW), cesarean section, fetal abnormalities, perinatal mortality, intrauterine fetal death (IUFD), neonatal mortality (deaths within the first 7 days after birth), and major anomalies (clear abnormalities requiring intervention). These questions were completed in the postpartum period through phone calls. The pregnancy outcomes related to ART were described using frequencies (percentages). To examine the relationship between demographic and midwifery variables with qualitative scale of pregnancy outcomes, the chi-square test was utilized, respectively. Logistic regression was used to assess the association between fertility treatments and pregnancy and birth outcomes, adjusted for age, BMI, education level, occupation, spouse's age, spouse's education, spouse's occupation, economic status, duration of marriage, duration of infertility and cause of infertility (Table 1). A significance level of $p < 0.05$ was utilized for the statistical tests. Data analysis was carried out using Stata software version 14.

Results

The present study comprised 368 women with a mean age of 32.47 years (±3.92 SD) who became pregnant through ART and presented at the hospital for delivery. Table 1 presents general characteristics of participants according to fertility treatments.

Table 1. General characteristics of participants according to fertility treatments

Characteristics	IVF (N=200) N (%)	IUI (N=111) N (%)	ICSI (N=57) N (%)	P-Value
Age (yrs)				
≤30	41 (20.50)	66 (59.46)	9 (15.79)	<0.001±
> 30	159 (79.50)	45 (40.54)	48 (84.21)	
BMI (kg/m²)				
<20	18 (9.00)	26 (23.42)	9 (15.79)	
20 -25	46 (23.00)	44 (39.64)	13 (22.81)	<0.001*
25- 30	84 (42.00)	32 (28.83)	22 (38.60)	
>30	52 (26.00)	9 (8.11)	13 (22.81)	
Educational level				
Primary	47 (23.50)	11 (9.91)	15 (26.32)	
High school	95 (47.50)	27 (24.32)	17 (29.82)	<0.001*
Diploma	54 (27.00)	41 (36.94)	17 (29.82)	
Academic	4 (2.00)	32 (28.83)	8 (14.04)	
Occupation				
House maker	195 (97.50)	85 (76.58)	52 (91.23)	<0.001±
Employee	5 (2.50)	26 (23.42)	5 (8.77)	
Spouse's age (yrs)				
≤30	24 (12.00)	50 (45.05)	8 (14.04)	<0.001±
> 30	176 (88.00)	61 (54.95)	49 (85.96)	
Spouse's education level				
Primary	46 (23.00)	18 (16.22)	14 (24.56)	
High school	86 (43.00)	24 (21.62)	19 (33.33)	<0.001*
Diploma	52 (26.00)	36 (32.43)	19 (33.33)	
Academic	16 (8.00)	33 (29.73)	5 (8.77)	
Spouse's occupation				<0.001*
Unemployed	36 (18.00)	5 (4.50)	12 (21.05)	
Self-employed	123 (61.50)	80 (72.07)	29 (50.88)	
Employee	3 (1.50)	19 (17.12)	6 (10.53)	
Manual worker	38 (19.00)	7 (6.31)	10 (17.54)	
Economic status				<0.001±
Poor	64 (32.00)	12 (10.81)	21 (36.84)	

Characteristics	IVF (N=200) N (%)	IUI (N=111) N (%)	ICSI (N=57) N (%)	P-Value
Moderate	136 (68.00)	99 (89.19)	36 (63.16)	
Duration of marriage (yrs)				
< 5	13 (6.50)	76 (68.47)	9 (15.79)	<0.001*
5-10	53 (26.50)	7 (6.31)	21 (36.84)	
>10	134 (67.00)	28 (25.23)	27 (47.37)	
Duration of infertility (yrs)				
1-3	9 (4.50)	59 (53.15)	9 (15.79)	
4-6	30 (15.00)	22 (19.82)	17 (29.82)	<0.001*
7-9	72 (36.00)	14 (12.61)	20 (35.09))	
>10	89 (44.50)	16 (14.41)	11 (19.30)	
Cause of infertility				
Male factor	12 (6.00)	22 (19.82)	50 (87.72)	<0.001
Female factor	64 (32.00)	55 (49.55)	0	
Both	124 (62.00)	34 (30.63)	7 (12.28)	

±Fisher exact test; *Chi-squre test

The distribution of these characteristics was statistically different across the studied treatment group. The age of participants and their spouse in the IVF and ICSI groups were mostly over 30 years old, while for the IUI group they were mostly under 30. Most participants who used IVF had infertility duration of more than 10 years (44.5%), while this duration for the IUI and ICSI groups was 14.4% and 19.3%, respectively. Table 2 presents the pregnancy and birth outcomes for the three fertility treatments.

Table 2. Pregnancy and birth outcomes according to fertility treatments

Outcomes	IVF (N=200) N (%)	IUI (N=111) N (%)	ICSI (N=57) N (%)	P-Value
Hypertension (yes)	125 (62.50)	19 (17.12)	44 (77.19)	<0.001
Preeclampsia (yes)	74 (37.00)	10 (9.01)	32 (56.14)	<0.001
Placenta previa (yes)	58 (29.00)	10 (9.01)	11 (19.30)	<0.001
Placental abruption (yes)	75 (37.50)	9 (8.11)	22 (38.60)	<0.001
Pregnancy bleeding (yes)	131 (65.50)	19 (17.12)	33 (57.89)	<0.001
PPROM (yes)	82 (41.00)	16 (14.41)	25 (43.86)	<0.001
ROM (yes)	30 (15.00)	35 (31.53)	12 (21.05)	0.003
Polyhydramnios (yes)	22 (11.00)	8 (7.21)	4 (7.02)	0.44
Oligohydramnios (yes)	67 (33.50)	15 (13.51)	25 (43.86)	<0.001
Gestational diabetes (yes)	84 (42.00)	28 (25.23)	14 (24.56)	0.003
Postpartum bleeding (yes)	20 (10.00)	6 (5.41)	8 (14.04)	0.16
Emergency caesarean section (yes)	97 (48.50)	14 (12.61)	29 (50.88)	<0.001
IUGR (yes)	70 (35.00)	11 (9.91)	16 (28.07)	<0.001
Preterm labor (yes)	94 (47.00)	18 (16.22)	26 (45.61)	<0.001
LBW (yes)	109 (54.50)	18 (16.22)	27 (47.37)	<0.001
Delivery type (caesarian)	124 (62.00)	18 (16.22)	32 (56.14)	<0.001
Minute Apgar score				
5	2 (1.00)	0	0	
6	34 (17.00)	5 (4.50)	9 (15.79)	<0.001
7	46 (23.00)	4 (3.60)	14 (24.56)	
8	84 (42.00)	25 (22.52)	19 (33.33)	
9	30 (15.00)	47 (42.34)	13 (22.81)	

Outcomes	IVF (N=200) N (%)	IUI (N=111) N (%)	ICSI (N=57) N (%)	P-Value
10	4 (2.00)	30 (27.03)	2 (3.51)	
Minute Apgar score				
7	2 (1.00)	0	1 (1.75)	
8	48 (24.00)	10 (9.01)	19 (33.33)	<0.001
9	115 (57.50)	20 (18.02)	24 (42.11)	
10	35 (17.50)	81 (72.97)	13 (22.81)	

Statistical test: Chi-squre test

Discussion

The current study, aimed at investigating the pregnancy outcomes associated with ART, revealed that high blood pressure, preeclampsia, placental abruption, preterm premature rupture of membranes, oligohydramnios, and emergency cesarean section were more prevalent in the ICSI group compared to the IVF and IUI groups. Participants in the IVF group exhibited a higher incidence of pregnancy bleeding, polyhydramnios, gestational diabetes, postpartum hemorrhage, intrauterine growth retardation (IUGR), cesarean delivery, preterm birth, low birth weight, and low Apgar score.

The utilization of ART has significantly increased worldwide, enabling pregnancy for many infertile couples (11). While assisted reproductive technologies may offer the best solution for women facing infertility challenges, they are not without risks. ART carries various perinatal risks that have the potential to affect both the mother and the developing fetus (9).

Wennerholm et al. reported that most pregnancies resulting from ART are uncomplicated and result in the birth of healthy children. However, it is well-known that pregnancies following ART are more prone to maternal complications, such as gestational hypertension, preterm labor, and LBW, compared to spontaneous pregnancies (16). It is important to note that most complications arise from multiple pregnancies. Tai et al. reported that women who conceive through ART have a higher likelihood of having twins or multiples, which significantly increasing the risk of stillbirth or abnormal growth (12). In our study, there was not multiple pregnancies. Multiple pregnancies can partially account for this phenomenon. For pregnancies resulting from ART, pre-delivery and intra-delivery monitoring should be intensified. Fertility specialists should strive to achieve singleton pregnancies. Additionally, patients should receive appropriate counseling regarding the risks associated with ART, particularly those associated with multiple pregnancies. Banica et al. also noted that the risk is directly proportional to the number of transferred embryos, establishing multiple pregnancies as an independent risk factor (8). Implementing protocols for single embryo transfer (ET) can significantly reduce the risk of childbirth complications and perinatal outcomes compared to multiple pregnancies. In a systematic study comparing adverse neonatal outcomes in singleton pregnancies resulting from fresh or frozen ET with spontaneous pregnancies, ART was associated with low birth weight, preterm birth, and small for gestational age (17), which aligns with the findings of the current study. Despite advancements in ART protocols, vigilance in monitoring adverse neonatal outcomes in these pregnancies remains crucial. Da Silva et al. demonstrated that infants conceived through ART have lower average weight, height, and head circumference at birth. However, over 90% of the impact of ART on these outcomes was attributed to multiple pregnancies. The findings of this study indicated that the potential negative impact on child health outcomes is mainly due to the higher incidence of multiple pregnancies and not solely due to ART (18). Since all the pregnancies in the current research were singleton pregnancies resulting from ART, the reasons for increased adverse pregnancy outcomes associated with singleton pregnancies and ART remain unclear and warrant further investigation. Additional studies with large

populations are necessary to confirm these results. However, in an observational study, no differences were observed in birth weight, umbilical artery pH, Apgar scores at 1 and 5 minutes, and gestational age at delivery between the ART group and spontaneous pregnancies (9), which contradicts the present research and the aforementioned studies. The cause of this contradiction may be due to a change in the geographical area.

In a meta-analysis study, Almasi-Hashiani et al. evaluated the risk of preeclampsia among women who conceived through ART. The meta-analysis showed a significant increase in the risk of preeclampsia among women who underwent ART compared to those who conceived naturally. The findings of this review indicated that the use of ART increases the likelihood of preeclampsia by 1.71 times (19). Another study examined the association between laboratory fertilization and preeclampsia, revealing that IVF was linked to the occurrence and progression of preeclampsia (20), which aligns with the findings of the current study. The probable cause may be that the male infertility factor, which predominates in ICSI, could be associated with vascular or placental problems.

Furthermore, Nagata et al. reported that women who conceived through IVF-ET face a higher risk of placenta previa and placenta accreta compared to spontaneous pregnancies, leading to an increased risk of blood transfusion (19), which aligns with the findings of the current research. Obstetricians and gynecologists should be mindful of the elevated risk of adverse outcomes in these women.

Infertility cases are typically more common in older individuals. In the present study, participants and their spouses in the IVF and ICSI groups were predominantly over 30 years old. The prevalence of overweight and obesity was higher in the IVF group compared to the ICSI and IUI groups. These findings suggest that underlying medical conditions, such as being overweight can increase the risk for women. Weight optimization, dietary interventions, and other aspects of care may yield positive effects on fertility and pregnancy outcomes (21). To optimize results, healthcare providers and caregivers should conduct a comprehensive medical assessment and address women's health issues before initiating ART.

The current study had limitations, including the absence of a control group. It is suggested that in future studies, the ART group should be subdivided into two categories, including fresh ET and frozen ET. Also, pregnancy complications, perinatal outcomes, and neonatal consequences should be analyzed separately for each case.

Conclusion

The findings indicated that high blood pressure, preeclampsia, placental abruption, preterm premature rupture of membranes, oligohydramnios, and emergency cesarean section were more prevalent in the intracytoplasmic sperm injection group compared to the in vitro fertilization and intrauterine insemination groups. Participants in the IVF group experienced higher rates of placenta previa, bleeding during pregnancy, polyhydramnios, gestational diabetes, postpartum bleeding, intrauterine growth restriction, cesarean delivery, preterm labor, and infants with low birth weight and low Apgar scores. However, neonates born through ART may face a higher risk of prematurity, low birth weight, and other disabilities. Even singleton infants conceived through egg induction and laboratory fertilization may be at a higher risk compared to singletons resulting from natural pregnancies. Women must understand that ART carries a higher risk of pregnancy complications. Healthcare professionals must ensure that these risks are effectively communicated, and strategies are discussed and implemented to mitigate them. Therefore, assessing the risks associated with ART before pregnancy and providing counseling on risk reduction strategies should be a fundamental aspect of pre-ART care.

Declerations

Acknowledgments

Not applicable.

Conflicts of interest

The authors declared no conflicts of interest.

Ethical considerations

All participants were enrolled in the study with formal consent .

Code of Ethics

The present study was approved by the Ethics Committee of Hamadan University of Medical Sciences with Code: IR.UMSHA.REC.1401.581.

Use of Artificial Intelligence (AI)

No artificial intelligence (AI) tools were used in the writing or analysis of this manuscript.

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Authors' contribution

EJ and SA conceived the study, developed the study protocol, conducted the research, and reviewed the articles. EA analyzed the data and drafted the manuscript. All authors read and approved the final manuscript.

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