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The impact of assisted reproductive technology on pregnancies with very advanced maternal age

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Abstract

Objective: Since assisted reproductive technology has become an available choice of conceiving, maternal age of 45 years or more has increased significantly. For this group of women, medical literature uses the term "very advanced maternal age". It was demonstrated in a number of studies that very advanced maternal age was highly associated with an increased risk of pregnancy complications and adverse perinatal outcomes. Asisted reproductive technology is also a risk factor for potential pregnancy complications. In this study, we aimed to report pregnancy complications and outcomes in women with very advanced maternal age who conceived with assisted reproductive technology compared with spontaneous conceptions.

Methods: In this retrospective cohort study we examined the outcome of pregnant women aged 45 years or more who presented to our outpatient clinic consecutively between 2015 and 2023. Demographic and obstetrical data were recorded in all patients within the study window. The study group were divided into two groups: women those who conceived spontaneously and those who conceived with ART. The ART group included patients who underwent in-vitro fertilisation(IVF) or intra-uterine insemination(IUI) treatment.

Results: More than half of pregnancies in very advcanced maternal age resulted in pregnancy loss. We found no significant results in terms of, BMI, HTDP, DM and FGR. We did found that VAMA with ART pregnancies had higher CD rate(OR 4.0, 95% CI= 1.7-9.2), NICU admission(OR 4.3, 95% CI= 1.3-13.6), PB(OR 11.9, 95% CI= 3.2-43.2), and live birth rate(OR 2.3, 95% CI= 0.9-5.3) compared with VAMA with spontaneous pregnancies, but lower rates of birth weight(OR 0.9, 95% CI= 0.997-0.999), gestational age at birth(OR 0.5, 95% CI= 0.5-0.9), and pregnancy loss(OR 0.3, 95% CI= 0.1-0.8).

Conclusion: The use of assisted repsoductive technology in women with very advanced maternal age is a risk factor for advanced perinatal outcome. However, despite increased advanced perinatal outcome, higher live birth rates were detected. This may be a result of more attentive perinatal care.

Keywords: Advanced maternal age, assisted reproductive technology, preeclampsia, pregnancy complications, preterm birth

Introduction

Medical literature uses the term "advanced maternal age(AMA)" for pregnancies in women aged over 35 years and "very advanced maternal age (VAMA)" for pregnancies in women aged over 45.[1-3]

Numerous studies demonstrated that VAMA were highly associated with an increased risk of pregnancy complications and adverse perinatal outcomes(APO).[4,5] Diabetes mellitus (DM), hypertensive disorders of pregnancy (HTDP), higher cesarean delivery rates (CD), preterm birth (PB), low birthweight, and fetal growth restriction (FGR) are more common among these women.[4-9] ART is also a risk factor for potential pregnancy complications and has become very common among patients over 45 years.[10-12] Although we know that VAMA is associated with APO, we really do not know whether these results are associated with increasing use of ART or with advanced maternal age itself. Most studies on this subject compare AMA or/and VAMA groups with normal age groups(<35years) but does not examine the effect of ART on APO on this group.[7,12,13] There are few studies addressing outcomes in women with VAMA relative to ART despite its increased use.[14-16]

In this study, we aimed to report APO in women with VAMA and to compare women of VAMA conceived with ART and those who conceived spontaneously to better unterstand the effect of ART on APO in this age group.

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Methods

This was a retrospective cohort study examining pregnant women aged 45 years or more who presented to our outpatient clinic consecutively between 2015 and 2023. Twins or higher order of pregnancies and patients with missing information were excluded from the study group. Ethical approval was obtained from Kartal Dr Lutfi Kırdar City Hospital ethics committee (no:010.99/2/19). Descriptive data of the pregnant women such as age, gravidity, parity, gestational age during hospital admission, gestational age at birth, gestational weight at birth, height, pregnancy outcome, conceiving method, and perinatal outcome were recorded from our hospital's electronic database. The families were contacted by phone to obtain information if the birth did not take place in our hospital.

Pregnancy loss was defined as a failure to achieve a healthy pregnancy before 24 weeks of gestation.[17] FGR were considered with an estimated fetal weight below the 10th centile.[18] HTDP was defined as a pregnant woman with chronic hypertension, gestational hypertension, or preeclampsia.[19] Preterm birth was defined as a birth occurring before 37 weeks of pregnancy.[20] All women who had pre-gestational diabetes or were diagnosed with diabetes during pregnancy were included in the DM group.

The study group were divided into two groups: women those who conceived spontaneously and those who conceived with ART. The ART group included patients who underwent in-vitro fertilisation (IVF) or intra-uterine insemination (IUI) treatment. It could not be recorded whether the patients concieved with oocyte donation or not because this method is not legal in our country so patients avoid saying even if they concieved with oocyte donation in other countries.

In the analysis results, the descriptive statistics of continuous variables are shown as mean ± standard deviation, and the descriptive statistics of categorical variables as numbers (n) and percentages (%). Analyses were conducted using the SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) version 22 software package. The normality of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to analyze quantitative independent data, and the Chi-square test and Fisher's exact test were used to analyze qualitative independent data. P-values of <0.05 were considered statistically significant.

Results

During the study period, 166 pregnant women with VAMA were admitted to our hospital. Fifteen patients were excluded due to missing information or not meeting the inclusion criteria. A total of 151 women were finally included in the analysis, with a mean of 46±1.35SD years (range 45-51) Of these, 78 (51.6%) pregnancies resulted in pregnancy loss and 73 (48.4%) resulted in live birth. When we examined pregnancy losses, 48 (61.5%) resulted in spontaneous abortion, 27 (34.7%) in fetal demise, two (2.5%) in molar pregnancy, and one (1.3%) in ectopic pregnancy (Figure 1).

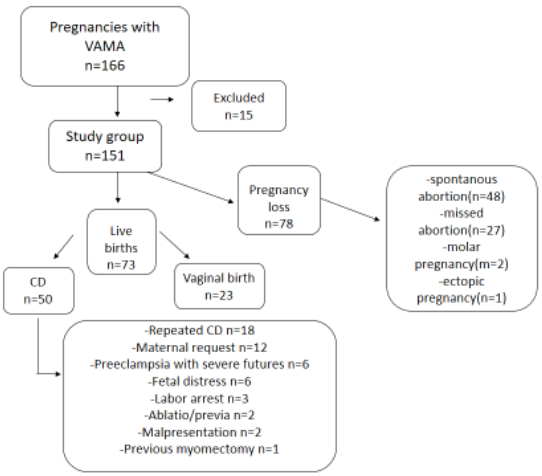

Figure 1. Flowchart of the study group

When evaluating the results of live births, 50 (68.4%) of the live births were born by CD. 18 CD (36%) were performed due to a previous cesarean section; 12 (24%) were performed by maternal request, 6 (12%) were performed due to a preeclampsia with severe features, and 6 (12%) due to fetal distress. Primary CD (first CD of a women) was performed in 32 (43.8%) patients.

Of the 151 pregnant women, 28 had an ART and 123 had a spontaneous pregnancy. When comparing the results (Table 1), we found no significant results in terms of , BMI, HTDP, DM and FGR. We did found that VAMA with ART pregnancies had higher CD rate(OR 4.0, 95% CI= 1.7-9.2), NICU admission(OR 4.3, 95% CI= 1.3-13.6), PB(OR 11.9, 95% CI= 3.2-43.2), and live birth rate(OR 2.3, 95% CI= 0.9-5.3) compared with VAMA with spontaneous pregnancies, but lower rates of birth weight(OR 0.9, 95% CI= 0.997-0.999), gestational age at birth(OR 0.5, 95% CI= 0.5-0.9), and pregnancy loss(OR 0.3, 95% CI= 0.1-0.8).

Table 1. Distribution of pregnancy complications and results between women with VAMA who conceived with ART compared with spontaneous conceptions

	ART (n=28)	Spontaneous (n=123)	P value
Maternal age (years)	46.8± 1.7	45.9 ± 1.1	0.01
Pregnancy loss	9 (32.1%)	69 (56.0%)	0.01
Live birth	19 (67.9%)	54 (43.9%)	0.02
Gestational age at birth (weeks) (min-max)	35.9 (30-41)	37.9 (28-41)	0.02
CD	17 (60.7%)	34 (27.6%)	0.01
Nulliparity	23 (82.1%)	7 (5.7%)	<0.01
Birthweight (gram) (min-max)	2686 (1800-3850)	3203 (1500-4000)	<0.01
DM	3 (10.7%)	8 (6.5%)	0.30
HTDP	5 (17.9%)	21 (17.1%)	0.92
NICU admission	9 (50%)	10 (18.9%)	0.01
Preterm birth	8 (28.6%)	4 (3.3%)	<0.01
FGR	3 (10.7%)	5 (4.1%)	0.16
BMI	26.7± 10.2	29.4± 5.1	0.17

Note: Values are stated as mean ± SD and number and percentage (%).

Abbreviations: ART, assisted reproductive technology; BMI, Body mass index; CD, caesarean delivery; DM, diabetes mellitus; FGR, fetal growth restriction; ; HTDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit; VAMA, very advanced maternal age

Discussion

In our study, we evaluated VAMA pregnancies and compared outcomes in women with VAMA who conceived with ART and those of spontaneous conceptions. We found that CD rates, NICU admissions, preterm labor, maternal age, and live birth rates were significantly higher in the ART group. There was no significance in terms of HTDP, diabetes, and FGR. However, birthweight, gestational age at birth, and pregnancy loss were significantly lower in the ART group.

In our population, more than half of all VAMA pregnancies resulted in pregnancy loss. In 2019, Magnus et al. reported that the risk of miscarriage was 10% in women aged between 25-29 years and rose significantly after the age of 30 reaching 57% in VAMA.[21] However, these rates include only clinically recognized pregnancies and the total rate among all ages may be as high as 31%.[22]

The primary CD rate was 43.8% in VAMA group, which is quite high considering that the primary CD rate in our hospital in the last 3 years was 10-20%. In 2023, Sugai et al.[23] showed higher CD rate for pregnant patiens in older age(≥45 years) (OR, 2.87 95% CI, 2.50–3.30)than those aged <45 years. It has been suggested that the reason of higher CD rate among older patients is that arteriosclerosis of the uterine arteries which causes a decrease in contractility of myometrium and negatively effect the progression of labor.[24] ART pregnancies are also found to be a risk factor for CD. In our study, we found that CD rates were 4-fold increased in the VAMA group conceiving with ART than those who conceived spontaneously. In a meta-analysis in 2021, Lodge-Tulloch et al.[25] demonstrated that ART pregnancies were associated with a 1.91-fold increase of elective CD and 1.38-fold increase of emergency CDs .This increase in the elective CD rate may be explained by patients with long-term infertility and a possible difficulty of conceiving again due to advanced age requesting a CD out of fear of harm to the baby. The increase of emergency CD may also be a result of pregnancy complications due to ART. Another explanation might be that physicians have a lower threshold to recommending CD in this population.

In recent studies, it has been suggested that women who become pregnant older are more often primiparous and they have higher socioeconomic status, which may ameliorate the effect of VAMA on perinatal outcomes.[26-27] Despite the more advanced age, the use of ART to conceive, and higher rates of preterm labor, more attentive maternal and perinatal care may increase rates of liveborn babies. In our study, the ART group had higher liveborn rate which may be a result of older and mostly nulliparous women in this group.

We found significantly higher rates of PB among pregnancies conceived with ART. In a multicenter cohort study in China, they also found higher risks of DM, HTDP, CD and PB for those aged ≥45 years.[28] In previous studies, ART was also found associated with higher rates of preterm labor. However, the reason for the higher rates of preterm birth was not iatrogenic due to pregnancy complications. It was thought that this may be the result of an unknown intrinsic factor.[29-32] This also may explain why, in our study, we found higher preterm birth rates in the ART group without higher rates of HTDP, diabetes, or FGR.

Many studies reported a higher incidence of HTDP, diabetes, and FGR in pregnancies with AMA.[33-38] Increased risks were also found in pregnancies with ART compared with spontaneously conceived pregnancies.[39-41] In a population based cohort study in Netherland, author found markedly increased risks for gestational diabetes (four times higher), hypertensive disorders (11 times higher), SGA neonates (three times higher), and prematurity (three times higher) compared with the reference group.

This risk was doubled even in women aged 40-44 and 45-49 years.[42]

In our study, we found no significant difference in terms of HTDP, DM, and FGR between pregnant women age over 45 years who conceived with ART and who did not. The reason for this may be that we did not include multiple pregnancies in the study group. In practice guideline of Genetics Committee of Society of Obstetricians and Gynaecologists of Canada stated that the majority of APO after ART arise as a result of multiple pregnancies.[43] Another possible reason, as mentioned previously, women who become pregnant aged over 45 years have better socioeconomic status, self-care, and they usually have better prenatal care.

Our study has some strengths and limitations. The retrospective nature of the study and the relatively small sample number are the main limitations. Due to the small number of cases, it is not possible to analyze ART subgroups such as intrauterine insemination or in vitro fertilization. Oocyte donation is not legal in our country, and some of patients do not state that they have received donated oocytes in other countries despite becoming pregnant in this way. Women who become pregnant through oocyte donation are increasing in daily practice and should be examined as a separate subgroup. Another limitation is we do not know genetic studies if performed and long-term outcomes of the newborns. The strength of our study is that we report the experience of a single tertiary center. Another strength is that is that we included all patients aged over 45 years who were admitted with a diagnosis of pregnancy, not just those who resulted in birth so we can give the overall results of VAMA pregnancies.

Conclusion

The use of ART in VAMA is a risk factor for APO. However, despite increased APO, higher live birth rates were detected. This may be a result of more attentive perinatal care. Prospective studies with a larger number of patients are needed to predict and prevent pregnancy complications in this extreme population.

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