ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Pregnancy outcomes in very advanced maternal age pregnancies: the impact of assisted reproductive technology

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Objective: To determine whether there are differences in adverse pregnancy outcomes in very advanced maternal age (vAMA) women who conceived with assisted reproductive technologies (ART) compared with spontaneous conceptions.
Design: Retrospective cohort study.
Setting: Academic tertiary care medical center.
Patient(s): A total of 472 women aged ≥45 years who delivered at one institution.
Intervention(s): Mode of conception.
Main Outcome Measure(s): Maternal and neonatal outcomes.
Result(s): For singleton pregnancies, vAMA women who conceived with ART were significantly older (47.0 ± 2.3 vs. 45.6 ± 0.1 years), more likely to be white (88.1% vs. 75.6%), and less parous (0.4 ± 0.9 vs. 1.2 ± 1.8) than vAMA women who conceived spontaneously. They were at significantly increased risk for cesarean delivery (CD) (75.1% vs. 49.7%) and were more likely to undergo elective primary CD without labor (25.4% vs. 9.4%). Risk of retained placenta was also significantly higher (2.7% vs. 0%). Rates of other maternal complications and neonatal outcomes were similar. Subgroup analysis of ART singleton pregnancies did not demonstrate differences in women using autologous oocytes versus donor oocytes.
Conclusion(s): Very advanced maternal age women who conceive after ART are more likely to be white, older, primiparous, and are more likely to proceed with an elective CD compared with vAMA women who conceive spontaneously. The increased risk of retained placenta in women who conceive with ART may indicate an underlying risk for placentation defects. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Very advanced maternal age (AMA), retained placenta, pregnancy outcomes, ART, donor oocytes

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In the United States, the age at first birth is increasing as more women are delaying childbirth due to societal changes, cultural expectations, and financial situations (1). This has led to an increased birth rate in women of advanced maternal age (AMA) compared with younger aged women. In 2011, the birth rate in women more than age 40 years increased (aged 40–44 years) or remained steady (aged 45–49 years) compared with declining birth rates in all age groups less than 40 years (1). In fact, the birth rate for women more than 40 years of age has been the highest in more than four decades (1).

Historically, AMA is defined as ≥35 years old given the increased genetic and obstetric risk. Older gravidas are at higher risk of aneuploidy, development of gestational diabetes, hypertensive disorders, and operative delivery, which includes the higher incidence of cesarean delivery (CD) and associated complications (2, 3). Similar findings have been confirmed for the very AMA (vAMA) group

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defined as ≥45 years old (4–12). Due to increasing prevalence of AMA women, some researchers have suggested that the period of obstetric risk is better characterized after age 40 years or even those at or more than age 45 years (4, 12, 13).

The use of assisted reproductive technology (ART) has contributed to the increase in birth rates in women more than age 35 years, including women more than age 45 years (14). Assisted reproductive technology has been associated with adverse pregnancy outcomes, including earlier delivery of pregnancies, low birth weight, very low birth weight, preterm delivery, and other potential complications associated with abnormal placentation (15, 16), but not cytogenetic genetic abnormalities, in AMA women compared with spontaneous conceptions (17). More recently, studies have emerged that the underlying infertility and time to pregnancy are risk factors for adverse pregnancy outcomes, independent of maternal age (18). Thus, infertility and utilization of ART may carry an independent increased risk of adverse pregnancy outcomes for AMA and more significantly for vAMA women. In addition to the utilization of ART, oocyte donation has given an even larger population of vAMA women the opportunity to become pregnant, with oocyte donation cycles almost doubling in the past decade (19). However, despite controlling for oocyte age, success rates including live birth rates decrease with increasing recipient age (20). Furthermore, it is still unclear whether donor oocytes decrease or contribute to the potential increased risk of adverse pregnancy outcomes (19, 21).

Although several large population studies of vAMA patients have found increased risks of adverse pregnancy outcomes (2–12), none have addressed outcomes relative to fertility treatment despite the increased utilization of ART in the AMA and vAMA population. Given the risk of adverse pregnancy outcomes in vAMA women and potential independent risks associated with ART, we set out to determine whether there are differences in adverse pregnancy outcomes in vAMA women who conceived spontaneously compared with those who conceived through ART. In addition, with the increased utilization of donor oocytes in the vAMA population, we set out to determine whether there were differences in pregnancies conceived with autologous oocytes compared with donor oocytes.

MATERIALS AND METHODS

This is a retrospective cohort study of women ≥45 years old, who delivered at Cedars-Sinai Medical Center between January 2000 and October 2010. The Institutional Review Board approval was obtained at Cedars-Sinai Medical Center. Patients were identified from a department electronic database. Clinical information was supplemented by thorough review of prenatal records and chart audits because of the high prevalence of ART information regarding mode of conception is routinely documented in the patient's medical record. Data were also abstracted on type of ART (IVF ± donor egg). Spontaneous pregnancy was specified or assumed if a specific ART method was not documented. Only the first pregnancy was included for women who were vAMA with more than one pregnancy during the study period. Twins and higher order gestations were excluded.

Primary outcome measures focused on maternal complications, including cesarean delivery rates, postpartum hemorrhage, need for transfusion, hysterectomy, intensive care unit (ICU) admission, length of stay, and clinical comorbidities such as hypertension, preeclampsia, and gestational diabetes. Secondary outcome measures were associated with neonatal outcomes, including gestational age at birth, birth weight, neonatal ICU admission, and APGAR score at 5 minutes.

Categorical and continuous variables were evaluated with χ^2 test, Fisher's exact test, and Student's t test. Findings were considered statistically significant if $P<.05$ for all outcomes. Statistical analysis performed with SAS version 9.2.

RESULTS

For singleton gestations, there was a similar number of women who conceived spontaneously compared with those who conceived with ART. Women who conceived with ART were older (47 vs. 45.6 years), more likely to be white (81.1% vs. 75.6%), and were of lower parity (0.2 vs. 1.4) compared with women who conceived spontaneously (Table 1).

For singleton pregnancies, there was no increased risk of postpartum hemorrhage, blood loss at delivery, transfusion, or admission to the ICU. However, there was a higher risk of retained placenta in the ART singleton group. Furthermore, there was a twofold increase in primary CD rates among ART singleton pregnancies versus spontaneous singleton pregnancies (71.3% vs. 35.3%) (Table 1). Indications for

TABLE 1

Maternal characteristics and maternal and fetal outcomes in singleton gestations conceived either spontaneously or with assisted reproductive technology (ART).

Variable	Spontaneous (n = 193)	ART (n = 185)	*P* value
Maternal characteristic			
Age (y, mean)	45.6 ± 0.1	47.0 ± 2.3	<.05
Race/ethnicity (% white)	75.6	88.1	<.002
Parity	1.2 ± 1.8	0.4 ± 0.9	<.001
Maternal outcome			
Postpartum hemorrhage	3.1%	5.9%	NS
Estimated blood loss (mL)			
Vaginal delivery	303 ± 104	324 ± 116	NS
Cesarean delivery	730 ± 284	713 ± 137	NS
Retained placenta	0	2.7%	<.02
Transfusion	2.1%	1.1%	NS
Hysterectomy	0	0.5%	NS
Rate of ICU admission (%)	0	1.1	NS
Length of stay (mean in d)	3.2 ± 2.2	4.2 ± 3.9	<.01
Total CD	49.7%	75.1%	<.001
Primary CD	35.3%	71.3%	
Repeat CD	22.2%	13.5%	
Fetal outcome			
Gestational age (wk)	38.9 ± 2.4	38.9 ± 2.4	NS
Birth weight (g)	3,318 ± 527	3,284 ± 567	NS
NICU admission rate (%)	1.5	4.3	NS
Apgar score at 5 min	8.8 ± 1	8.9 ± 0.7	NS

Note: CD = cesarean delivery; ICU = intensive care unit; NICU = neonatal intensive care unit; NS = not significant.

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