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## Pregnancy Outcomes in Very Advanced Maternal Age Pregnancies: the Impact of Assisted Reproductive Technologies

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### Abstract

**Objective**—To determine if there are differences in adverse pregnancy outcomes in very Advanced Maternal Age (vAMA) women who conceived with assisted reproductive technologies (ART) compared to spontaneous conceptions.

**Design**—Retrospective cohort study

**Setting**—Academic tertiary-care medical center

**Patients**—472 women 45 years old who delivered at one institution

**Interventions**—Mode of conception

**Main Outcome Measures**—Maternal and neonatal outcomes

**Results**—For singleton pregnancies, vAMA women who conceived with ART were significantly older (47.0±2.3 vs. 45.6±0.1), more likely to be Caucasian (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.

**Conclusions**—vAMA women who conceive following ART are more likely to be Caucasian, older, primiparous and are more likely to proceed with an elective CD compared to vAMA who conceive spontaneously. The increased risk of retained placenta in women who conceive with ART may indicate an underlying risk for placentation defects.

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## Capsule

Very AMA (vAMA) women utilizing ART are more likely to be primiparous, undergo elective cesarean delivery and at increased risk of retained placenta. Oocyte source does not affect outcomes.

## Keywords

Very advanced maternal age (AMA); retained placenta; pregnancy outcomes; ART; donor oocytes

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## Introduction

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 compared to younger aged women. In 2011, the birth rate in women over age 40 increased (aged 40–44) or remained steady (aged 45–49) compared to declining birth rates in all age groups below 40 years (1). In fact, the birth rate for women over 40 has been the highest in more than four decades (1).

Historically, advanced maternal age (AMA) is defined as greater than or equal to ( ) 35 years old given the elevated 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 advanced maternal age (vAMA) group 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 or even those at or over age 45 (4, 12–13).

The use of assisted reproductive technologies (ART) has contributed to the increase in birth rates in women over age 35, including women over age 45 (14). ART 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 advanced maternal age women compared to 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 to in the last 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 if 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 if there are differences in adverse pregnancy outcomes in vAMA women who conceived spontaneously compared to those that conceived through ART. Additionally, with the increased utilization of donor oocytes in the vAMA population, we set out to determine if there were differences in pregnancies conceived with autologous oocytes compared to donor oocytes.

## Methods

This is a retrospective cohort study of women <math>\leq 45</math> 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 was also abstracted on type of ART (IVF +/- donor egg). Spontaneous pregnancy was specified or assumed, if 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 (PPH), need for transfusion, hysterectomy, intensive care unit (ICU) admission, length of stay (LOS), and clinical co-morbidities such as hypertension, preeclampsia, and gestational diabetes. Secondary outcome measures were associated with neonatal outcomes, including gestational age at birth, birth weight, neonatal intensive care unit (NICU) admission, and APGAR score at 5 minutes.

Categorical and continuous variables were evaluated with Chi Square, Fischer's Exact and student's T test. Findings were considered statistically significant if  $p < 0.05$  for all outcomes. Statistical analysis performed with SAS version 9.2, Cary, North Carolina, USA.

## Results

In women with singleton gestations, there was a similar number of women who conceived spontaneously compared to those that conceived with ART. Women who conceived with ART were older (47 vs. 45.6), more likely to be Caucasian (81.1% vs. 75.6%), and were of lower parity (0.2 vs. 1.4) compared to 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 two-fold increase in primary CD rates among ART singleton pregnancies versus spontaneous singleton pregnancies (71.3% vs. 35.3%) (Table 1). Indications for primary CD varied by type of conception. Among singletons conceived spontaneously, women were more likely to

undergo CD for obstetric indications (non-reassuring fetal heart rate or failure to progress) whereas ART pregnancies were more likely to undergo elective primary CD (CD without labor) (Table 2).

In addition, the following co-morbidities, including asthma, diabetes, gestational diabetes, hypertension, heart disease, hepatitis, thyroid disease, neurologic disease or psychiatric disease were evaluated. There were no differences in the rates in women who conceived spontaneously versus those that conceived with ART (data not shown).

Neonatal outcomes were assessed among the groups. There was no difference in birth weight, gestational age at birth, NICU admission rates, and APGAR scores at 5 minutes in both the spontaneous and ART singleton conceptions (Table 1).

Subgroup analysis of pregnancies conceived through ART using autologous versus donor oocytes was performed. There was no difference in the demographics or any of the maternal or neonatal clinical outcomes evaluated (Table 3). If there was no information regarding the source of the oocytes, then treatment cycles were considered to have occurred from autologous oocytes. Seven women at or above age 50 were considered in the autologous oocyte group because the use of donor oocytes was not specifically documented. One woman who delivered at age 50 utilized autologous oocytes that were previously cryopreserved.

## Discussion

Overall, the number of singleton spontaneous pregnancies in the vAMA group was similar to the number of pregnancies conceived with ART. There was a statistically significant increase in the age of women utilizing ART compared to women with spontaneous conceptions, however this increase was small ( $45.6\pm 0.1$  versus  $47.0\pm 2.3$ ). In recent years, older women who become pregnant are more often primiparous and of better socioeconomic status than in the past where they were more often multiparous and of low socio-economic status (22–23). It has been suggested that social advantage may ameliorate some of the adverse effect of advanced maternal age on perinatal outcome (22, 24). This shift which is seen in our vAMA population who conceived with ART, may account for the similar outcomes among groups despite the potential increased age and the utilization of ART which carries its own inherent increased risk of adverse pregnancy outcomes. The extent to which the spontaneous pregnancies were planned or “intended” is unknown but the incidence rate at this single institution suggests that vAMA women not planning to conceive should continue to use reliable contraception methods.

Pregnancies conceived with ART had a significantly higher rate of retained placenta compared to spontaneous conceptions. Other placentation defects have been reported in pregnancies from ART, including placenta previa, abruption and preeclampsia (25). Placentation defects may be the result of the fertility treatments, as increases in estradiol have been implicated in pregnancy complications associated with abnormal placentation (26). However, other studies in animals, have implicated the in vitro embryo culture on placental development, which ultimately may lead to adverse outcomes in fetal development

including small for gestational age infants (27). As increases in maternal age are also associated with abnormal placentation and its effects (28–29), it will be important to determine if these effects are the result of advanced maternal age or the fertility treatments themselves.

There was a 2-fold increased risk of primary CD in ART singletons. These findings are consistent with other studies indicating that there is a higher rate of obstetric intervention in women who conceive with ART, including a higher rate of induction of labor and CD (25, 30–33). Although this has been attributed to ART pregnancies being of higher risk, studies have not demonstrated increased risk for adverse pregnancy outcomes in older women compared to younger women who underwent oocyte donation, with similar rates of hypertensive disorders, gestational diabetes, and preterm premature rupture of membranes/preterm labor (32). Further, the majority of these interventions in our cohort were elective and not attributed to a high risk pregnancy condition. Actually, these elective CD may be more likely attributed to the higher rate of primiparous women in the ART group, and be independent of the mode of conception as other studies have found that older first time mothers of higher socioeconomic status were more likely to have CD (3). The increased CD rate likely contributed to the significantly increased length of stay in this group. Although the increase was only 1 day, this may lead to unanticipated increased health care costs per individual pregnancy that conceived through ART.

We did not find differences in pregnancy outcomes in vAMA women utilizing autologous versus donor oocytes. Although success rates including clinical pregnancy and live birth rates have been shown to decline with maternal age in women using donor oocytes implicating recipient age as a factor in achieving pregnancy (20), the data is less clear on overall adverse pregnancy outcomes with some studies showing no associated risk of adverse perinatal outcome with recipient age (19). Yet other studies show an increased risk of placental complications of pregnancy such as hypertensive diseases of pregnancy (21), which has been implicated to antigenic dissimilarity between oocyte donor and recipient (34). Larger studies to look at placental defects are needed to determine if this is a phenomenon of maternal age, the ART itself or antigenic dissimilarity among donor and recipient pair, as our ART pregnancies did have a higher rate of placental defects compared to spontaneous conceptions.

It was reassuring that there were no differences in neonatal outcomes among the groups as ART has been associated in adverse neonatal outcomes, including earlier gestational age, low birth weight and very low birth weight (15–16).

In addition to the limitations of a retrospective study, there may also be a component of ascertainment bias. In many cases, spontaneous pregnancy was specified; however, in some instances it was a diagnosis of exclusion when no evidence of ART method was specified after thorough chart review. There may have been instances of “social charting”—where information is deliberately omitted per patient request. Despite the limitations, this is the largest single institution study to date and it is the first study comparing vAMA spontaneous to vAMA ART pregnancies. The outcomes in question are still rare and in many cases comparisons are made with small numbers. Further research is needed, as these findings

may impact the way the vAMA patients are managed, particularly as it relates to elective obstetric intervention, specifically CD. The findings of this study raise the question: is ART an independent risk factor for CD in general, and for elective CD in particular? If so, what is the percent contribution of AMA and vAMA women to the overall increasing trend in cesareans? A prospective study looking at whether ART is a risk factor for CD is needed. Our study looked at short term outcomes of childbirth and delivery method such as retained placenta, postpartum hemorrhage, transfusions, etc but did not address other short or long term outcomes such as infection, readmission rates, and impact on subsequent pregnancies. Studies suggest increase ectopic, stillbirth and abnormal placentation leading to bleeding, hysterectomy or death (35–36). Finally, we evaluated spontaneous vs ART conceptions, and compared ART conceptions based on oocyte source, however, more rigorous characterization of the type of ART methods and the development of standardized documentation criteria is needed so that short and long-term maternal and newborn complications can be monitored.

In conclusion, it seems that vAMA pregnancies through IVF (as a whole) compared to spontaneous pregnancies have a higher rate of CD and placental issues. Use of autologous eggs or donor eggs in vAMA IVF pregnancies does not seem to affect outcomes. Clinicians should consider IVF as a risk factor for abnormal placentation and take special consideration when performing second and third trimester ultrasound. Counseling women about the increased risk for CD may be prudent, however, further study is needed to determine if the increased risk of CD is due to IVF, patient-specific clinical or obstetric factors, or the perception that a CD is easier or perceived to be less risky.

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**Table 1:**

Maternal Characteristics and Maternal and Fetal Outcomes in Singleton Gestations Conceived Either Spontaneously or With Assisted Reproductive Technology (ART)

	Spontaneous (n=193)	ART (n=185)	P-value
<b>Maternal Characteristics</b>			
Age (mean)	45.6±0.1	47.0±2.3	<0.05
Race / Ethnicity (% Caucasian)	75.6%	88.1%	<0.002
Parity	1.2±1.8	0.4±0.9	<0.001
<b>Maternal Outcomes</b>			
Post-Partum Hemorrhage (PPH)	3.1%	5.9%	NS
Estimated Blood Loss (ml)			
- Vaginal Delivery (VD)	303±104	324±116	NS
- Cesarean Delivery (CD)	730±284	713±137	NS
Retained Placenta	0%	2.7%	<0.02
Transfusion	2.1%	1.1%	NS
Hysterectomy	0%	0.5%	NS
Rate of ICU Admission	0%	1.1%	NS
Length of Stay (LOS) (mean in days)	3.2±2.2	4.2±3.9	<0.01
Total Cesarean Delivery	49.7%	75.1%	<0.001
- Primary CD	35.3%	71.3%	
- Repeat CD	22.2%	13.5%	
<b>Fetal Outcomes</b>			
Gestational Age (GA) (wks)	38.9±2.4	38.9±2.4	NS
Birth Weight (BW) (g)	3318±527	3284±567	NS
NICU admission rate	1.5%	4.3%	NS
Apgars at 5 min	8.8±1	8.9±0.7	NS

ICU – intensive care unit; NICU – neonatal intensive care unit

**Table 2:**

Indication for Cesarean Section in Singleton Gestations Conceived Either Spontaneously or With Assisted Reproductive Technology (ART)

	Spontaneous (n=150)	ART (n=160)	P-value
Malpresentation	5.6%	7%	NS
Prior uterine surgery	13.2%	14%	NS
Non-Reassuring Fetal Heart Rate (NRFHT)	24.5%	11.4%	<0.04
Failure to Progress	39.6%	23.9%	<0.04
Elective	9.4%	25.4%	<0.02

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**Table 3:**

Maternal Characteristics and Maternal and Fetal Outcomes in Singleton Gestations Conceived through Assisted Reproductive Technologies (ART) using Autologous versus Donor Oocytes

	Autologous Oocytes (n=64)	Donor Oocytes (n=120)	P-value
<b>Maternal Characteristics</b>			
Age (mean)	46.7±2.0	47.1±2.2	NS
Race / Ethnicity (% Caucasian)	90.8%	87.4%	NS
Parity	0.54±0.16	0.32±0.56	NS
<b>Maternal Outcomes</b>			
Post-Partum Hemorrhage (PPH)	0%	4.2%	NS
Estimated Blood Loss (ml)			
- Vaginal Delivery (VD)	317±90	325±122	NS
- Cesarean Delivery (CD)	712±151	719±121	NS
Retained Placenta	1.6%	3.3%	NS
Transfusion	0%	1.7%	NS
Rate of ICU Admission	0%	1.7%	NS
Length of Stay (LOS) (mean in days)	4.7±4.6	4.1±3.4	NS
Total Cesarean Delivery	81.5%	70.8%	NS
- Primary CD	68.8%	71.3%	
- Repeat CD	31.3%	11.8%	
<b>Fetal Outcomes</b>			
Gestational Age (GA) (wks)	38.7±1.8	39.0±2.7	NS
Birth Weight (BW) (g)	3237±585	3317±556	NS
NICU admission rate	4.6%	4.2%	NS
Apgars at 5 min	8.9±0.2	8.8±0.9	NS

ICU – intensive care unit; NICU – neonatal intensive care unit