



# Outcomes of pregnancies achieved by donor egg in vitro fertilization—A comparison with standard in vitro fertilization pregnancies

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## KEY WORDS

Donor oocytes  
In vitro fertilization

**Objective:** Prior studies on donor egg in vitro fertilization (DE-IVF) outcomes have been limited by the lack of an appropriate control group. Here, we review the obstetric and perinatal outcomes of pregnancies achieved by DE-IVF and compare these pregnancies with those of women who also needed similar assisted reproductive techniques, of similar socioeconomic status, and cared for by a small group of 8 physicians applying consistent diagnostic and treatment approaches.

**Study design:** A retrospective review of 50 consecutive pregnancies achieved by DE-IVF and 50 consecutive pregnancies achieved by standard IVF (STD-IVF) was performed. Comparisons were made for demographic and medical confounding factors and for outcome measures.

**Results:** The 2 groups were nearly identical for gravidity, parity, and multiple gestations but did vary in maternal age. Average age of patients receiving DE-IVF was 41.9( $\pm$ 5.1), whereas the STD-IVF averaged 37.7( $\pm$ 3.6) years ( $P < .001$ ). Key obstetric outcomes did not differ between the 2 groups with the exception of pregnancy-induced hypertension. In patients with DE-IVF, 26% had pregnancy-induced hypertension (PIH) develop, whereas this occurred in only 8% of the STD-IVF group ( $P = .02$ ). Examining nulliparous patients only, 37.1% of DE-IVF had PIH develop, whereas only 8% of STD-IVF group achieved that diagnosis ( $P < .003$ ). An analysis with a multiple logistic regression in nulliparous patients found odds ratios of 7.1 (95% CI, 1.4-36.7) in DE versus STD-IVF, odds ratio 4.9 (95% CI, 1.3-18.3) for multiple gestation versus singleton, and odds ratio 1.0 (95% CI, 0.9-1.1) for maternal age.

**Conclusion:** Nulliparous pregnancies achieved by DE-IVF are associated with an increased risk of PIH; however, excellent outcomes can still be expected.

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Over the past 20 years the use of assisted reproductive techniques has changed the choices available for older women. Although the initial indication for egg donation in vitro fertilization (DE-IVF), which resulted in a

successful pregnancy in 1984 was premature ovarian failure (POF), defined as menopause occurring before the age of 40 years, the predominant indication for egg donation at most IVF centers is now diminished ovarian reserve in women with functioning ovaries. Other candidates for egg donation have included women who have previously failed multiple IVF attempts and women carrying transmittable genetic abnormalities that could affect their offspring.<sup>1</sup>

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**Table I** Patient demographics

	STD-IVF n (%)	DE-IVF n (%)	Comparisons
Total number	50	50	—
Primigravid	25 (50%)	28 (56%)	ns
Nulliparous	37 (74%)	35 (70%)	ns
Singleton	37 (74%)	35 (70%)	ns
Multiple gestation	13 (26%)	15 (30%)	ns
Maternal age (mean $\pm$ SD)	37.7 ( $\pm$ 3.6)	41.9 ( $\pm$ 5.1)	$P < .001$

ns, Not significant.

As DE-IVF has become more frequent, potential obstetric risks associated with this procedure have begun to be explored and reported. Many reports note that these are at increased risk pregnancies, particularly for pregnancy-induced hypertension (PIH). However, these pregnancies are also characterized by advanced maternal age, and the high rates of nulliparity and multiple gestation. These potential confounders make an analysis of the risks related to the egg donation alone difficult to separate. Furthermore, infertility and standard IVF (STD-IVF) may themselves confer greater obstetric risk than pregnancies achieved by natural conception.<sup>2</sup> Here we examine this issue by comparing a group of DE-IVF women with a comparable group of STD-IVF similarly identical in their rates of nulliparity and multiple gestations.

## Materials and methods

Practice obstetric logs from 1999 through May 2004 were reviewed to identify patients who had achieved pregnancy by assisted reproductive technology with DE-IVF and STD-IVF (using the patient's own gametes). A total of 50 sequential patients were found who had successfully undergone DE-IVF. A second group of 50 sequential patients from our practice were also identified during this same period who had successfully undergone STD-IVF. IVF services were provided from several assisted reproductive technique (ART) centers in the San Francisco area and patients presented for obstetric care after an intrauterine pregnancy had been documented. All patients had been evaluated for underlying medical conditions before the ART. Once their obstetric care was established, all patients were under the care of board-certified obstetrician/gynecologists in 1 of 3 related private practice medical groups at California Pacific Medical Center, San Francisco, Calif. The hospital has a large level III neonatal intensive care unit (NICU) and perinatology consultants available at all times. Institutional review board approval was obtained; office and hospital records of deliveries of all patients were reviewed.

**Table II** Pregnancy outcomes

	STD-IVF	DE-IVF	Comparisons
Group size	50	50	
First-trimester bleeding	7 (14%)	6 (12%)	ns
Gestational diabetes	2 (4%)	5 (10%)	ns
Premature labor	5 (10%)	8 (16%)	ns
Birth weight (g) (mean $\pm$ SD)	3017 ( $\pm$ 788)	3044 ( $\pm$ 751)	ns
PIH	4 (8%)	13 (26%)	$P = .03$
Preeclampsia	2 (4%)	6 (12%)	ns

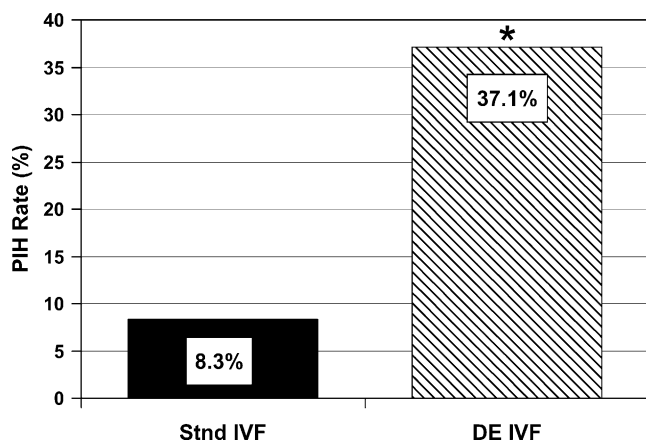
Patients in both groups were given the same standard high-risk obstetric care under the care of the same group of obstetricians. Perinatology consultants were involved whenever there were additional high-risk factors such as hypertension, diabetes, or preterm labor. PIH and preeclampsia were defined according to the American College of Obstetricians and Gynecologists (ACOG) definitions.<sup>3</sup> In brief, PIH is defined as new onset of hypertension after the 20th week of gestation without proteinuria and preeclampsia is defined as PIH with proteinuria and often associated with other signs and symptoms.

Statistical analysis was performed with  $\chi^2$  for categorical variables. Fisher exact test was used whenever a cell size was less than 5, and Student  $t$  test (2-tailed) for continuous variables. Significance was considered when  $P < .05$ . Odds ratios (ORs) and 95% CIs were established, as well as multiple logistic regression.

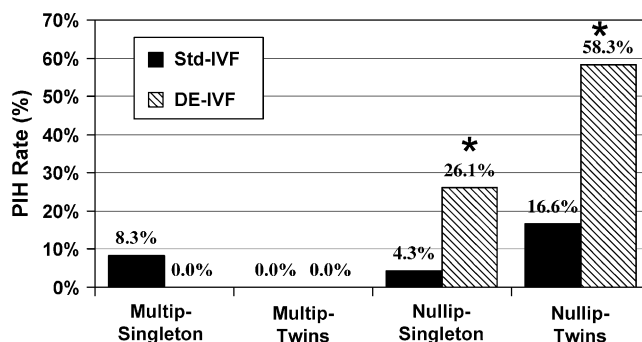
## Results

Table I provides an analysis of the key demographic comparisons between the DE-IVF group and the STD-IVF group. Importantly, the proportions of nulliparous women and multiple gestations were similar between the 2 groups. The only significant difference ( $P < .001$ ) was maternal age. In the DE-IVF group, patient ages ranged from 31 to 50 years with an average age of 41.9 years ( $\pm$ 5.1). In the STD-IVF group, patient ages ranged from 30 to 45 years with an average age of 37.7 years ( $\pm$ 3.6).

In the DE-IVF group, 11 patients had POF, 23 patients had decreased ovarian reserve, and the remainder had multiple failed IVF attempts using their own gametes. All the 39 patients (without premature ovarian failure [POF]) were considered to have functioning ovaries. In the STD-IVF group, 21 patients were defined as having decreased ovarian reserve, 5 patients had tubal disease, and male factor affected 23 of the couples. There were no significant differences in outcome in our reviewed patients when ovarian function was considered.



**Figure 1** PIH frequency in nulliparous women analyzed by IVF type. Significant difference between the 2 groups is shown (\* $P < .003$ , OR = 5.9, 95% CI: 1.6-21.5).



**Figure 2** PIH frequency by parity, plurality and IVF type. There are significant differences between STD-IVF and DE-IVF in both nulliparous singletons and nulliparous twin gestations (\* $P < .01$ ).

**Table III** PIH outcomes

Parity (n)	Plurality (n)	PIH (%)	PIH (%): All multiparous vs all nulliparous
<b>STD-IVF</b>			
Multiparous (13)	Singleton (12)	1 (8.3%)	1/13 (7%)
	Twin (1)	0 (0%)	
Nulliparous (37)	Singleton (25)	1 (4.3%)	3/37 (8.1%)*
	Twin (12)	2 (16.6%)	
<b>DE-IVF</b>			
Multiparous (15)	Singleton (12)	0 (0%)	0/15 (0%)
	Twin (3)	0 (0%)	
Nulliparous (35)	Singleton (23)	6 (26.1%)	13/35 (37.1%)*
	Twin (12)	7 (58.3%)	

\*  $P < .003$  (nulliparous DE-IVF vs STD-IVF).

There was a scattering of mild medical problems in both groups. DE-IVF: hypothyroidism (3), chronic hypertension, not on medication (2), Von Willebrand's disease (1), prior ablative cardiac therapy for supraventricular tachycardia (1), mitral valve prolapse (3), chronic migraines with left eye blindness (1), ulcerative colitis (1), endometriosis (2), and prior myomectomy (5). For patients in the STD-IVF group: hypothyroidism (2), hyperthyroidism (1), Crohn's disease (1), rheumatoid arthritis (1), thrombophilias (2) (factor V Leiden and MTHFR homozygous, both received anticoagulation therapy), chronic pyelonephritis (1), and prior myomec- tomies (4).

The egg donors ranged in age from 20 to 38 years. Most were anonymous, but 3 involved sisters of the recipients. There were 34 nulliparous patients, 7 of whom had subsequent repeat pregnancies again using DE-IVF and are included in this study.

In the DE-IVF group, initially there were 18 multiple gestations noted. One pregnancy resulted in spontaneous reduction from triplets to a singleton in the first trimester, a 16-week demise of a twin was noted

in another pregnancy, and a 25-week spontaneous demise of a twin was documented in a third patient. Fifteen sets of twins were delivered after 33 weeks' gestation. One patient had a heterotopic pregnancy and underwent a laparotomy and right salpingectomy at 9 weeks' gestation; she carried the remaining intrauterine pregnancy to term. For the STD-IVF group, multiple gestations initially were documented in 18 of the pregnancies, with spontaneous losses from twins to singleton in 5 pregnancies, all during the first trimester, and triplets spontaneously reducing to twins in 1 pregnancy. Four patients chose to have a reduction procedure from triplets to twins. One triplet gestation was carried to 32 weeks. Thirteen sets of twins were delivered after 35 weeks' gestation.

Pregnancy complications are shown in Table II. The important findings were the increased incidence of PIH and preeclampsia in the DE-IVF group. In this group, 1 patient was hypertensive before 20 weeks' gestation and developed proteinuria at 38 weeks' gestation. She presented to the emergency department on postpartum day 3 (1 day after discharge) with hypoxia and a pleural

**Table IV** PIH by age category (nulliparous women)

	30-34 y	35-39 y	40-44 y	45-50 y
DE-IVF	3 (1)	5 (2)	14 (5)	13 (5)
(with PIH)	33.3%	40%	35.7%	38.5%
STD-IVF	7 (1)	18 (1)	11 (1)	1 (0)
(with PIH)	14.3%	5.56%	9%	0%

effusion. Another patient had a deep venous thrombosis and pulmonary embolus develop on postpartum day 7. In the STD-IVF group, 1 patient experienced a small bowel obstruction that required a small bowel resection during the postpartum period.

The cesarean birth rate for the DE-IVF group was 42.8%; excluding multiple gestations, the cesarean birth rate was 31.42%. For the STD-IVF group, the cesarean birth rate was 46%, and excluding multiple gestations, the cesarean section rate was 40.54%. There were no elective cesarean sections done in either group.

In the DE-IVF group, 1 pregnancy resulted in spontaneous rupture of membranes at 20 weeks' gestation and subsequent delivery of a stillborn infant. As previously stated, there was intrauterine fetal demise of a twin at 25 weeks' gestation, but there were no other reported stillbirths in this population. Only 1 infant had a 5-minute Apgar score less than 7—a second twin delivered by emergency cesarean section because of bradycardia. In the STD-IVF group, there were no stillbirths and no infant with a 5-minute Apgar less than 7. A total of 15 patients in the DE-IVF group had small-for-gestational-age (SGA) infants, 5 of whom had POF. Fourteen patients in the STD-IVF group had SGA infants. The most common postpartum complication was postpartum depression that was noted in 5 patients (10%) in the DE-IVF group and in 8% of the STD-IVF group.

To further investigate the relationship between DE-IVF and PIH, we undertook a subgroup analysis. Table III shows the relationship between parity and multiple gestations for both DE-IVF and STD-IVF. The results clearly indicate that nulliparous women carry the greatest differential risk of PIH compared with STD-IVF (37.1% vs 8.1%,  $P < .003$ ) as illustrated in Figure 1. This difference was true for singletons and for multiple gestations (Figure 2). Within this group of DE-IVF nulliparous women, we further analyzed the effect of maternal age. The mean age of women who had PIH develop was 41.6 ( $\pm 3.6$ ) years, whereas the mean age of those who did not have PIH develop was 42.1 ( $\pm 5.4$ ) years. This younger age (but not significantly so) for those who had PIH develop is contrary to the hypothesis of increasing maternal age being related to the development of PIH. Patients were stratified by 5-year increments with no increasing incidence of PIH being noted (Table IV). Multiple logistic regression was then per-

**Table V** Multiple logistic regression analysis of nulliparous IVF patients

	OR	95% CI	P value
DE vs STD IVF	7.1	1.4-36.7	.019
Multiple vs singleton	4.9	1.3-18.3	.017
Maternal age	1.0	0.9-1.1	.927

formed on the nulliparous group examining the inner relationship of maternal age, multiple gestation, and IVF type (Table V). Maternal age fell out as a confounder with an OR of 1.0.

The only patient who had severe preeclampsia develop was in the DE-IVF group. She had 2+ proteinuria develop at 38 weeks' gestation, delivered vaginally after induction, and had a pleural effusion develop on postpartum day 3. She required a 1-week intensive care hospitalization, but ultimately recovered without sequelae.

## Comment

Donor egg IVF has now been proven to be a successful option of ART for many women. In 2000, 308 programs reported use of donor oocytes to the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. A total of 7581 fresh donor oocyte cycles were initiated with a delivery rate per transfer of 43.7%.<sup>4</sup> Despite the popularity of this procedure, there is only limited literature to warn of specific risks. To properly assess risks one needs to have a carefully constructed control group. Unfortunately, most prior analyses of DE-IVF pregnancies have been handicapped by the lack of an appropriate comparison group. Infertility, ART procedures, parity, multiple gestations, and advanced maternal age may all confer independent risks and can confound the analysis.

The first confounding risk is that of ovarian functional status. There have been reports that women with functioning ovaries were at greater risk for complications such as PIH than those women who had ovarian failure before DE-IVF.<sup>5</sup> Our study did not reflect that finding. Prior reviews have also suggested a relationship between functioning ovaries and SGA infants.<sup>6</sup> Again, in our study the incidence of SGA infants (<2500 g at term) was equal between the 2 groups, and one third of the patients in the DE-IVF group who had an SGA infant also had nonfunctioning ovaries.

Many of the earlier studies did not match well for nulliparity and multiple gestations that are highly correlated to the development of PIH and preeclampsia. The near identical rates of nulliparity and multiple gestations led to our most important conclusion that PIH is significantly increased primarily in nulliparous women.

Establishing proper age controls, especially for women over age 40 years has been challenging for every investigator. This will always be an issue, as DE-IVF in the United States is largely used as a last resort in older or perimenopausal women.<sup>7</sup> Our 2 groups were of roughly similar older ages (37.7 and 41.9 years), but they were significantly different. Prior reports of oocyte donation to women older than 45 years reflect high success rates in establishing pregnancies, but high complication rates, often secondary to multiple gestations.<sup>7</sup> Reproductive Medicine and the Society for ART have issued guidelines for considering the age of the donor rather than the recipient when selecting the number of embryos for transfer.<sup>8</sup>

Our most important finding is that DE-IVF is associated with a significant increase in PIH/preeclampsia. This is very strong when looking at nulliparous pregnancies (OR = 5.9) and holds true in both singletons and multiple gestations. The findings that DE-IVF nulliparous women who had PIH develop were not older than other DE-IVF nulliparous women, and the multiple logistic regression analysis OR of 1.0 for maternal age indicates that the other risk factors of parity, plurality, and egg donation were more important than age.

In most of the DE-IVF outcomes published, PIH is a significant risk, reportedly in the frequency of 20% to 50%. This has been attributed to the fact that these pregnancies are immunologically foreign to the recipient. It is proposed that PIH/preeclampsia is the consequence of an inadequate immune response between the mother and the conceptus leading to poor placental invasion and release of factors into the maternal circulation, recruiting more blood flow by increasing perfusion pressure.<sup>9</sup> This could explain why women are more at risk of preeclampsia in their first pregnancy and why parous women who later conceive by a new partner also have an increased susceptibility to the syndrome.<sup>10</sup>

The strengths of this study include the homogeneity of the obstetric care and the ability to have an appropriate control group for the DE-IVF study population. Although studies have been performed from the perspective of the fertility clinic with many obstetric providers involved, this approach removes this variable from consideration. The close matching of the control group for infertility, IVF procedure, parity, and frequency of multiple gestations is a unique feature of this study and makes the results more compelling. The multiple logistic regression analysis also addresses well the issue of maternal age. The limitations of this study are the relatively small sample size.

In summary, DE-IVF has excellent overall obstetric outcomes. When compared with STD-IVF there are very few differences. The 1 outcome that is statistically much higher in DE-IVF is PIH/preeclampsia. Because most of these mothers and infants still do well, the importance of this finding may be of greater relevance for the study of the cause of preeclampsia.

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*Editor's note:* This manuscript was revised after these discussions were presented.

## Discussion

**DR RICHARD P. MARRS**, Los Angeles, Calif. The authors have performed a retrospective analysis of obstetric outcomes in patients undergoing IVF-ET with their own oocytes (STD-IVF) compared with patients using donor oocytes during IVF (DE-IVF). The primary focus was to determine what factors relate to PIH or other obstetric complications, such as prematurity, diabetes.

The authors reviewed obstetric records of 50 DE-IVF and 50 STD-IVF pregnancies. The groups were similar as to gravidity, parity, and multiple gestations but were different in mean age, with the DE-IVF group being older. The authors identified an increased risk of PIH within the DE-IVF group and correlated it with parity. Because the DE-IVF group was older compared with