Increased risk of pregnancy-induced hypertension in young recipients of donated oocytes

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Objective: To assess the rates of select obstetric outcomes in oocyte donation (OD) recipients aged <35 years and ≥40 years and compare them to similarly aged IVF patients.
Design: Retrospective anonymous questionnaire study.
Setting: University-based IVF center.
Patient(s): Live-birth outcome was experienced by 199 OD recipients and 488 IVF patients <35 or ≥40 years.
Intervention(s): The OD or IVF cycles.
Main Outcome Measure(s): Response rate, pregnancy outcome, and complications.
Result(s): Response rate was 60%. The OD recipients had significantly higher rates of pregnancy-induced hypertension (PIH) than their IVF counterparts. The OD <35 years had the highest rate (42%), followed by OD ≥40 years (26%), IVF ≥40 years (14%), and IVF patients <35 years (12%). In twin pregnancies, the rates of PIH remained higher in the OD groups: OD <35 years (56%), OD ≥40 years (36%), IVF ≥40 years (25%), and IVF <35 years (22%). Twin pregnancy rate was lowest in IVF patients ≥40 years (19%) and a lower preterm delivery rate (16%) reflected this difference. The cesarean section rates were 50% for singleton and 78% for twin deliveries in the OD patients <35 year; in OD patients ≥40 years, the rates were 75% and 84%, respectively.
Conclusion(s): The OD recipients are at higher risk for untoward obstetric outcomes than their IVF counterparts. Young OD recipients reported the highest rate of PIH, warranting further investigation into an association between early loss of ovarian function and PIH. (Fertil Steril® 2007;87:776–81. ©2007 by American Society for Reproductive Medicine.)

Key Words: Oocyte donation, pregnancy-induced hypertension, obstetric outcome, premature ovarian failure

Oocyte donation (OD) has become a successful means of enabling patients with diminished ovarian reserve to achieve pregnancy. In the United States, the number of treatment cycles in which donated oocytes were used to generate fresh or frozen embryos increased from 5,123 in 1996 to 13,183 in 2000 (1). Although most patients who undergo OD are of advanced maternal age, younger patients with diminished ovarian reserve may also require OD to achieve pregnancy.

Pregnancy outcomes in OD recipients have been characterized in the literature. Recipients achieving live birth are reported to be at increased risk for gestational diabetes, first and second trimester bleeding, cesarean section, preterm delivery (PTD), and pregnancy-induced hypertension (PIH) compared to patients undergoing IVF and the general population (2–8). Many of these studies have focused on women of advanced maternal age, as these patients represent the majority electing OD. To our knowledge, no investigation has specifically focused on young donor egg recipients, although this family-building technique is emerging as a popular option for younger women with premature diminished ovarian reserve.

Pregnancy-induced hypertension is likely due to factors that result in poor placentation (9). It has been shown that patients with premature ovarian failure test positive for the presence of anti-zona pellucida (ZP) antibodies, as well as antibodies against granulosa cells (GC) (10). It is plausible that this interferes with trophoblast–maternal interactions at the endometrial interface. The result may be suboptimal implantation and clinical features of PIH, as well as PTD, low birth weight, and other obstetric outcomes associated with poor placental function.

Our study was undertaken to assess the rates of select obstetric outcomes in OD recipients less than 35 years of age (<35) and recipients greater than or equal to 40 years of age (≥40) and to compare them to similarly aged women who underwent conventional IVF procedures. Based on existing literature and our clinical observations, we hypothesized that the use of donor oocytes to create pregnancy, in-and-of-itself, potentiates obstetric risks. The increased risks observed in donor oocyte cycles could not be explained solely by advanced maternal age. The known risk factors for PIH were then reviewed, and each of these factors was then assessed in the OD <35 recipients who were initially sent questionnaires.

MATERIALS AND METHODS

We conducted a retrospective questionnaire study in women who underwent OD or IVF procedures at our university-based fertility program that resulted in a fresh embryo transfer with a live birth outcome between 1999 and 2003. The

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study was approved by the NYU Institutional Board of Research Associates (IRB H10877).

Patients <35 years and ≥40 years of age who succeeded with one of these two treatments were identified in our program database. Cycles resulting in triplet pregnancies, of frozen embryo transfer cycles, or cycles monitored at Program satellite offices were not included. Also excluded were cycles in which the patient age was between 35 and 39 years. This exclusion ensured that all patients were of similar ages, given that all donated oocytes were from women <35 years. The final mailing list consisted of 1,224 patients. The data were grouped by age (<35 and ≥40 years) and by treatment type (OD and IVF), with subsequent division of the study population into four groups (OD <35, IVF <35, OD ≥40, IVF ≥40). The age range of women who anonymously donated oocytes for the OD cycles was 21–35 years with a mean age of 25.6 years.

The questionnaire was a one-page, anonymous survey developed to assess the prevalence of select obstetric outcomes based on previous literature reporting untoward events in these patient groups. The questionnaire briefly described the objective of the study. There were two versions of the questionnaire depending on patient age, which differed only in the explanation as to why one's specific age group was relevant to the study. The questionnaire inquired whether the cycle was OD or IVF, the gestational age at time of preterm delivery, if the birth was singleton or twin, and the respective birth weight of the infant. The remaining items were presented in checklist format in laymen's terms including: PTD "less than 37 weeks of gestational age," PIH "high blood pressure during your pregnancy," gestational diabetes mellitus, placenta previa "placenta covering the opening of the uterus," placental abruption "premature separation of the placenta," cerclage placement "a suture about your cervix," uterine infection, antepartum hospitalization, bed rest, blood transfusion, and hysterectomy "removal of your uterus."

Questionnaires were mailed to patients with self-addressed stamped envelopes to facilitate their return. It was stated that by returning the questionnaire, patients would be giving consent for inclusion in the study. The patients were also given the option to identify themselves on the questionnaire if they chose.

The validity of the questionnaire was not evaluated. Categorical data were entered into a Microsoft Excel database (Microsoft, Redmond, WA) and statistical analyses were performed using χ^2, Fischer's exact, Mann-Whitney rank sum, and Student's *t*-tests where appropriate with significance at $P<.05$.

We reviewed the literature for known risk factors for PIH. These included nulliparity, multiple gestation, prior or family history of PIH, chronic medical conditions such as hypertension and diabetes, and extremes of age (9, 11). We then reviewed the charts of the initial patients who were sent questionnaires in the OD <35 (n = 28) group to determine whether they had any preexisting risk factors for the development of PIH. No statistical analysis was conducted on these observations. The inclusion of this information is meant to serve as a descriptor for the study group of interest, namely the young OD recipients.

RESULTS

The overall questionnaire response rate was 60% ranging from 52%–68% by group. There were no differences in the rate of response among the four groups. Patient demographics and outcomes are shown in Table 1. Mean ages of the patients did not differ when young OD versus IVF patients were compared. The IVF ≥40 patients were 2.5 years younger than OD ≥40 patients. The IVF ≥40 patients reported the highest mean birth weight, which was significant when compared to all three other groups. There were significant rate differences reported between the four study groups for the following outcomes: twin gestation, PTD, cesarean section, and PIH. There were no significant differences in rates of elective reduction, gestational diabetes mellitus, placenta previa, placental abruption, blood transfusion, cerclage placement, uterine infection, antepartum hospitalization, bed rest, and hysterectomy. Less than one-third of patients in all groups required antepartum bed rest or hospitalization. The following detail the significant findings.

Twin Gestation Rate

The twin gestation rate was significantly lower in the IVF ≥40 group (19%, $P<.001$) compared to the other three groups (OD <35 [47%], IVF <35 [42%], OD ≥40 [40%]). The twin rates were not statistically different among the OD <35, IVF <35, and OD ≥40 groups (Fig. 1).

Preterm Delivery Rate

The PTD rate reflected the twinning rate such that IVF ≥40 patients with the oldest oocytes and fewest twins also reported the lowest rate of PTD (16%) overall (Table 2). When the groups were compared by order of gestation, there were no significant differences in the rates of PTD for any group, although there was a trend toward higher rates of PTD in the OD groups. There was no difference in the overall PTD rate between the three groups with similarly aged oocytes and same twinning rate (OD <35, IVF <35, OD ≥40).

Cesarean Section Rate

Overall, OD <35 patients reported a 63% cesarean section rate compared to a 47% rate in the IVF <35 group (P = not significant [NS]). However, the cesarean section rates of OD ≥40 patients (78%) and IVF ≥40 patients (55%) were significantly different ($P\leq.001$), and this was largely attributable to the higher cesarean section rate in OD ≥40 singletons (75%). There were no significant differences in rates when comparing the older to younger groups within each type of treatment (Table 3).

TABLE 1

Patient demographics and outcomes.

	OD <35 N = 19	IVF <35 N = 296	OD ≥40 N = 171	IVF ≥40 N = 192
Mean age ± SEM (y)	31.7 ± 0.4	31.0 ± 0.2	43.9 ± 0.2[a]	41.4 ± 0.1[b]
Mean gestational age of preterm delivery ± SEM (weeks)	36.3 ± 0.4	35.4 ± 0.2	35.3 ± 0.4	35.6 ± 0.5
Mean birth weight ± SEM (g)	2,864 ± 89[c]	2,909 ± 42[d]	2,801 ± 49[e]	3,030 ± 49[f]
Response rate (%)	68	52	52	65
Elective reduction n (%)	0	17 (6)	10 (6)	11 (6)
Placenta previa n (%)	2 (11)	12 (4)	14 (8)	11 (6)
Placental abruption n (%)	0	2 (0.6)	1 (0.6)	6 (3)
Gestational diabetes n (%)	4 (21)	22 (7)	16 (9)	25 (13)
Cerclage placement n (%)	0	13 (4)	5 (3)	6 (3)
Uterine infection n (%)	2 (11)	0	1 (0.6)	0
Hysterectomy n (%)	0	0	1 (0.6)	0
Blood transfusion n (%)	0	9 (3)	3 (2)	0
Antepartum bed rest n (%)	3 (16)	88 (30)	39 (23)	33 (17)
Antepartum hospitalization n (%)	1 (5)	66 (22)	34 (20)	26 (14)
Twin gestation n (%)	9 (47)[g]	125 (42)[h]	69 (40)[i]	36 (19)[j]

[a,b] $P<.001$; [f–c,d,e] $P<.05$, Mann-Whitney rank sum test.
[j–g,h,i] $P<.001$, χ^2 test.

Keegan. Young donor egg recipients' risk for PIH. Fertil Steril 2007.

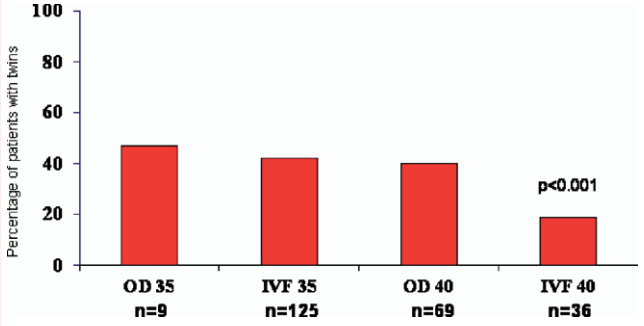
Pregnancy-Induced Hypertension Rate

The OD <35 recipients had the highest overall reported rate of PIH (42%). This rate was significantly higher when compared to IVF <35 (12%, $P<.001$) and IVF ≥40 (14%, $P=.004$) patients. The PIH rate of OD ≥40 recipients (26%) was also significantly higher than that of younger (IVF <35: 12%, $P<.001$) and older (IVF ≥40: 14%, $P=.003$) conventional IVF patients (Table 4). Hence, regardless of age, OD recipients had significantly higher rates of PIH when compared to their conventional IVF counterparts. Interestingly, there were no significant differences in the rate of PIH when comparing older to younger patients undergoing the same treatment type.

When singleton and twin pregnancies were analyzed separately, a higher rate of PIH was reported in twin than in singleton deliveries for all groups. However, this comparison was significant only in the IVF <35, OD ≥40 and IVF ≥40 groups (Fig. 2). Again, OD <35 recipients demonstrated the highest rate of PIH of the four treatment groups, even when comparing different orders of gestation, but these comparisons only approached significance. Power was likely lost when the groups were broken down.

FIGURE 1

Twin gestation rate. OD 35/OD 40 = oocyte donation recipients less than 35 years/≥40 years; IVF 35/IVF 40 = IVF recipients less than 35 years/ ≥40 years.



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OD <35 Risk Factor Review for Pregnancy-Induced Hypertension

The mean age of OD <35 patients initially contacted was 31.7 ± 0.4 years, 97% were white, 48% were multigravid, and 19% were multiparous. Diagnoses leading to the use of donor eggs were as follows: premature ovarian failure (50%), poor responder to conventional IVF treatment (32%), personal history of chemotherapy (11%), or genetic disease (7%). There was no evidence of prior history of PIH in any multiparous patient. One patient, who had identified herself on the questionnaire, had a medical history of preexisting hypertension, and did not develop superimposed preeclamp-

TABLE 2

Preterm delivery rates.

	OD <35 cases/n (%)	IVF <35 cases/n (%)	*P* value	OD ≥40 cases/n (%)	IVF ≥40 cases/n (%)	*P* value
Singletons	2/10 (20)	16/171 (9)	0.58	16/102 (16)	14/156 (9)	.15
Twins	4/9 (44)	59/125 (47)	0.85	37/69 (54)	17/36 (47)	.68
Total population	6/19 (32)	75/296 (25)	0.74	53/171 (31)	31/192 (16)	.001

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sia. Two patients had thyroid disease and three had undergone chemotherapy in the past.

DISCUSSION

Our findings suggest that recipients of OD may be at higher risk for untoward obstetric outcomes than their IVF counterparts. The twin gestation rate was higher in both the younger and older OD recipients (both groups using <35-year-old oocytes) when compared with cycles of older IVF (IVF ≥40) patients. This finding is expected given the older age of oocytes in the IVF ≥40 group. The higher mean birth weight in the IVF ≥40 group likely reflects the lower twinning rate observed in this group. Similarly, the PTD rate reflects the twinning rate such that IVF ≥40 patients with the oldest oocytes and fewest twins reported the lowest rate of PTD (16%).

The cesarean section rate was higher in OD recipients, significantly so when older OD recipients were compared to age-matched conventional IVF patients. Although this may be an effect of multiple gestation in OD recipients, obstetrician and patient preference may also contribute.

Although the advanced maternal age of oocyte recipients has been purportedly implicated as the reason for multiple untoward obstetric outcomes (2–7), our data show that younger oocyte recipients (<35 years) are not spared from these risks, and may in fact be at higher risk. Oocyte recipients of both age groups had a higher rate of PIH compared to IVF patients, with the rate overwhelmingly high (42%) in the young OD recipients. Surprisingly, there was no difference in the rate of PIH between younger and older patients within each treatment type. These observations suggest that [1] multiple gestation alone does not account for this difference, as there was more PIH in both OD groups compared to the IVF<35 group who had the same twinning rate, and [2] advanced maternal age alone as a factor also cannot account for this difference, as the youngest OD patients had the highest rate of PIH. Furthermore, the chart review for preexisting risk factors in the OD <35 group did not suggest a higher a priori risk for the development of PIH.

These preliminary data indicate that, among a heterogeneous population of women undergoing both OD and IVF, young patients with diminished ovarian reserve may have the highest risk for PIH. The overall observed rate of 42% is approximately five times that expected in the general population, and also higher than that previously reported for older OD and IVF patients (2, 5, 11). These higher rates are also seen when singleton and twin gestations are considered separately. From our findings, we speculate a relationship may exist between diminished ovarian function at a young age and the development of PIH. We suggest that the unique reproductive pathophysiology associated with non-age–related loss of ovarian function might enhance the risk for PIH in pregnancy.

Pados et al. (7) reported on the outcomes of 52 OD pregnancies and suggested that women with ovarian failure may be at a higher risk for PIH than women with functioning ovaries (38% vs. 22%, P = NS). Aside from this study, this relationship has not been formally considered in the literature. We thus reviewed the mechanism of PIH to determine

TABLE 3

Cesarean section rates.

	OD <35 cases/n (%)	IVF <35 cases/n (%)	P-value	OD ≥40 cases/n (%)	IVF ≥40 cases/n (%)	P-value
Singletons	5/10 (50)	57/171 (33)	0.46	76/102 (75)	79/156 (51)	<.001
Twins	7/9 (78)	82/125 (66)	0.70	58/69 (84)	27/36 (75)	.39
Total population	12/19 (63)	139/296 (47)	0.26	134/171 (78)	106/192 (55)	<.001

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TABLE 4

Pregnancy-induced hypertension rates.

	OD <35 cases/n (%)	IVF <35 cases/n (%)	*P* value	OD ≥40 cases/n (%)	IVF ≥40 cases/n (%)	*P* value
Singletons	3/10 (30)	9/171 (5)	0.02	20/102 (20)	17/156 (11)	.08
Twins	5/9 (56)	27/125 (22)	0.06	25/69 (36)	9/36 (25)	.34
Total population	8/19 (42)	36/296 (12)	<0.001	45/171 (26)	26/192 (14)	.003

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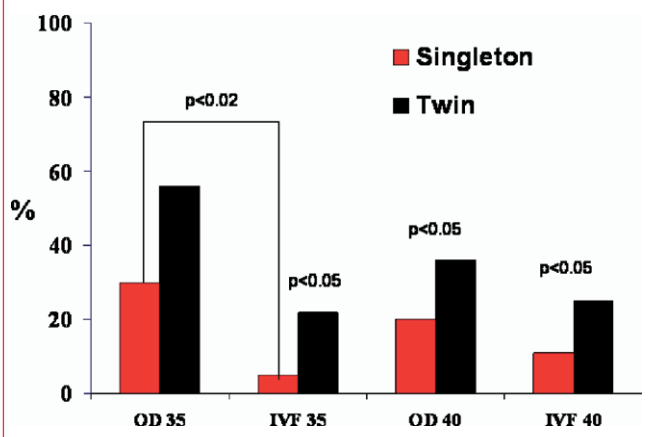
whether a biologic plausibility exists, placing these women at higher risk for PIH.

Redman and Sargent (9) succinctly summarized the events associated with the development of PIH. It is proposed that clinical signs of preeclampsia result from the combination of dysfunctional maternal endothelium and the maternal systemic inflammatory response, both causing an oxidatively stressed placenta. This placenta then elaborates sFlt-1 and syncytiotrophoblast debris. Most PIH investigations in the literature focus on these areas that the researcher labeled stage 2; the onus is thus on "stage 1," poor placentation. Less is known about the mechanism of how and why poor placentation occurs, or that which precedes this stage 1.

We propose a "stage 0" in which embryonic–maternal interactions determine the pattern of endometrial invasion through as yet, unknown factors. Secretory products of the maternal endometrium and the embryo's trophectoderm likely play a role in these interactions. In OD recipients, these interactions may be altered by the genetic incompatibilities of the mother and embryo, leading to successful yet suboptimal invasion of the maternal endometrium. This, in turn, may lead to poor placentation and eventually oxidative stress on the placenta and PIH by these mechanisms. Furthermore, other immunologic factors in young patients with ovarian failure may amplify the risk. Studies designed to investigate the embryo's role the early placentation may provide important information about the genesis of PIH.

FIGURE 2

Pregnancy-induced hypertension in singleton and twin gestations.



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We appreciate the limitations of our study and therefore cautiously interpret our data. Because a questionnaire study relies on patient responses for data collection, recall bias, selection bias, ascertainment bias, and loss of validity cannot be avoided. We chose a questionnaire for data collection as a way to screen our population because our referral base is nationwide and worldwide, overwhelming our ability to obtain obstetric records for these patients. Although obstetric delivery information is readily available from the Society of Assisted Reproductive Technology (SART), obstetric course and complications are not.

The presence of these biases introduces the problem of not having a strict and consistent definition of PIH. It is possible, that from the questionnaire, PIH was inconsistently interpreted by respondents, perhaps leading to an overestimation of the true prevalence of PIH in the study population. Furthermore, potential confounders for PIH were only reviewed in the OD <35 group, and not in the control groups. Therefore, we cannot be completely certain that the OD group did not have a greater baseline risk for the observed outcomes.

Another limitation is the low number of patients in the OD <35 group. This is likely due to the low incidence of diminished ovarian reserve in women at a young age, reduced further by the percentage of these women that pursue alternative means of family building. Thus, treatment of these patients with OD is relatively less common than for those in other age groups.

Regardless of the limitations, our data come from a diverse population of women seeking infertility treatment during a 5-year period. Based on our findings and existing literature, we believe OD recipients, particularly young women, may be at higher risk for PIH. In addition to PIH, any woman electing oocyte donation as a means to family building should be counseled regarding the potential risks of twin delivery, cesarean section, and PTD. We offer our findings as observation only, which nonetheless serve as a hypothesis generator. That is, loss of ovarian function at a young age and its biologic underpin-

nings may be associated with the development of PIH in OD pregnancies. We are currently designing a retrospective cohort study to assess further the obstetric courses experienced by these young women and provide additional data to confirm our hypothesis.

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