Original Article

What are the Predictive Factors for Preeclampsia in Oocyte Recipients?

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Abstract

Objectives: Oocyte donation pregnancies are more frequently complicated by preeclampsia (PE), which cause significant fetal-maternal morbidity and mortality. Our objective was to determine risk factors for PE in oocyte recipients (OR). Our secondary objective was to describe the course of pregnancy and the neonatal outcome in this group. **Methods:** This was a historical-prospective study. One hundred and fifty OR who gave birth to children at over 22 weeks of amenorrhea between January 2010 and June 2018 were included in the study. **Results:** Risk factors for PE in OR found in univariate analysis were as follows: primiparity, primipaternity, body mass index (BMI), and anti-Müllerian hormone (AMH) of the OR and age and AMH of the oocyte donors (OD). In multivariate analysis, the BMI of the OR (odds ratio [OR]: 1.2, 95% confidence interval [CI]: [1.1–1.4], $P = 0.0474$) and the AMH of the OD (OR: 1.2, 95% CI: [1.2–1.4], $P = 0.0481$) were found to be statistically significant risk factors for PE. In addition, we observed an increase in the rate of prematurity in the OR that were not associated with fetal growth retardation, despite the occurrence of PE. **Conclusion:** In OR, the allogeneic nature of pregnancy induces an increased risk of PE, the pathophysiology of which seems different from that in other methods of conception. Thus, risk factors for PE should be reconsidered to take into account the impact of certain characteristics of OD such as age and AMH.

Keywords: *Allogeneic, oocyte donation pregnancies, oocyte recipients, preeclampsia, risk factors*

Introduction

Preeclampsia (PE) affects 1%–8% of all pregnancies worldwide. It is the second leading cause of maternal deaths and is responsible for 8%–10% of premature deliveries.[1-4] It is secondary to an early placentation disorder, the pathophysiological mechanisms of which are still not fully understood.

In oocyte recipients (OR), the risk of developing PE more than quadruples compared to spontaneous conceptions.[5-9]

The main objective of this study was to identify the specific risk factors to the development of PE in oocyte recipients. Our secondary objective was to describe the course of pregnancy and the neonatal outcome in this group.

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Methods

It is an analytical, historical-prospective, and bicentric epidemiological study.

All patients of legal age with a pregnancy resulting from oocyte donation at over 22 weeks of amenorrhea (WA) in one of the study centers who delivered between January 2010 and June 2018 and with no objection to participating in the study were included.

All pregnancies resulting from foreign oocyte donation, persons of legal age under legal protection, and persons deprived of their liberty were excluded.

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After obtaining the agreement of the National Commission for the Protection of Persons and Informatics and Liberty, the data were collected in each center by accessing the electronic medical data. In cases where data were missing, a telephone interview with the patients was carried out.

We sought to determine whether the risk factors for PE usually considered for the general population were relevant in the context of OR: primiparity, patient history of PE, chronic hypertension, diabetes, chronic renal failure, autoimmune disease, thrombophilia, obesity, and polycystic ovary syndrome, family history of PE in first-degree relatives and maternal age (under 18 or over 40 years of age), multiple pregnancies, an interval of more than 10 years between pregnancies, primipaternity, insufficient duration of exposure to sperm, or the occurrence of PE in a previous spouse.[10,11]

We also identified potential risk factors that are more specific to the context of oocyte donation: the age of the OD and the anti-Müllerian hormone (AMH) of the recipients and the OD.

According to the literature, evaluating the risk factors associated with an event, in this case PE, must enable observation of 5–10 occurrences of this event per candidate variable.[12] Based on an average rate of 14% PE in OR[7,8] and a patient population of 150 patients, we predicted observing 21 cases of PE. Such a sample would make it possible to conduct a multivariate analysis of the combination of four risk factors for PE among the set of candidate factors.

Quantitative variables are expressed as means and standard deviations and qualitative variables as numbers and percentages. The evaluation of the primary endpoint is based on a binary logistic regression analysis. Potential risk factors are first studied in univariate analysis. Factors with $P < 0.20$ are included in the multivariate analysis.

A selection using backward stepwise elimination procedure and cross-validation is used to determine the final model chosen according to the Akaike information criterion. Possible interactions are also studied. The results will be expressed as odds ratios (ORs) with their corresponding 95% confidence interval (CI).

The missing data are included by multiple imputation. $P < 0.05$ is considered statistically significant.

Results

Between January 2010 and June 2018, 158 OR gave birth to a child at over 22 WA. To complete the missing data, 72% of the patients were reached by telephone.

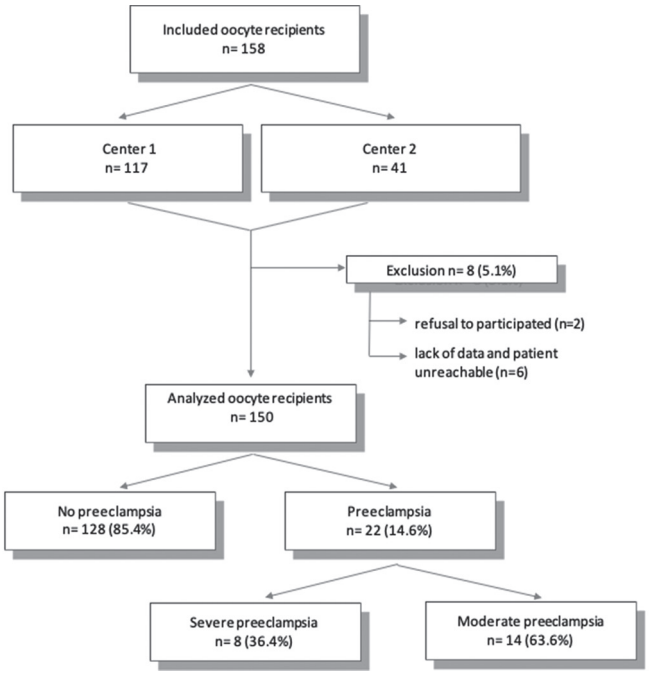

Figure 1: Flowchart

Two patients were excluded from the study for refusal to participate. Six unreachable patients were not studied due to a lack of medical data. Of the 150 patients studied, 22 had PE, which is 14.6% of all patients [Figure 1].

The average age of the OR was 37 years (±4.5 years), and 26% of the patients were over 40 years old on the day of the embryo transfer.

Oocyte donation was being used due to ovarian failure in 102 patients (68%), including 4 with radiotherapy-induced ovarian failure and 12 associated with Turner's syndrome. Referral for oocyte donation took place in 39 couples (26%) after failure of intraconjugal Assisted Reproduction Techniques (ART). A genetic indication for the donation was present in seven couples (4.6%).

OR' AMH levels averaged 1.3 ng/mL (±2.1), and 55% were <1.1 ng/mL.

The primiparity rate was 77% (n = 116), and among multipara women, 31% of previous births were spontaneous conceptions (n = 11), 27% were from *in vitro* fertilization (IVF) (n = 9), and 42% were from a first oocyte donation (n = 14).

The average age of OD was 32 years (±3.2), and 25% of them were over 35 years old. The average parity rate was 1.9, and they had all given birth to at least one child. None of them reported a history of PE. Their average AMH level was 5.3 (±4.7). One donor enabled an average of 2.3 children (±0.6) to be born [Table 1].

Of the 150 patients included, 14.6% (n = 22) presented with PE. The risk factors selected for PE in univariate analysis (P < 0.2) are primiparity (OR: 2.7, 95% CI: [0.59–13], P = 0.197), primipaternity (OR: 3.1, 95% CI: [0.68–14], P = 0.142), OR' body mass index (BMI) (OR: 1.2, 95% CI: [1.1–1.4], P = 0.0388), OR' AMH (OR: 1.1, 95% CI: [0.93–1.4], P = 0.193), donors' age (OR: 1.1, 95% CI: [0.95–1.3], P = 0.197), and the OD' AMH (OR: 1.2, 95% CI: [1–1.2], P = 0.154).

In multivariate analysis, the OR' BMI (OR: 1.2, 95% CI: [1.1–1.4], P = 0.0474) and the OD' AMH (OR: 1.2; 95% CI: [1.1–1.4], P = 0.0481) were found to be statistically significant risk factors for PE. The age of the OD approaches significant with P = 0.0724 (OR: 1.2, 95% CI: [0.98–1.4], P = 0.0724) [Table 2].

We studied 171 births, 21 of which were twins (14%). The rate of prematurity in our patient sample was 14.8% (n = 21). Patients with PE gave birth on average at 36 WA (252 days ±39) versus 39 WA +1 day (274 days ±16) for OR with no PE (P = 0.02).

Table 1: Description of the population

	OR (n=150)	OD (n=63)
Age (years old)	37±4.5	32±3.2
Age >40	39 (26)	NA
Age >35	100 (67)	16 (25)
Age <35	52 (35)	47 (75)
BMI (kg/m^2)	23±4.7	24±3.8
BMI >30	15 (10)	8 (12.7)
Antecedent of PE	1 (0.7)	0 (0)
Antecedent of diabetes	1 (0.7)	0 (0)
Antecedent of chronic nephropathy	2 (1.3)	0 (0)
Antecedent of thrombophilia	3 (2)	0 (0)
Antecedent of autoimmune disease	8 (5.3)	0 (0)
Turner syndrome	12 (8)	0 (0)
AMH	1.3±2.1	5.3±4.7
AMH <1.1 ng/mL	83 (55)	3 (4.8)
Ovarian failure	102 (68)	4 (6.3)
Age of onset of ovarian failure	30±4.8	
PCOS	10 (6.7)	
Endometriosis	20 (13)	
Twins	21 (14)	
Primiparity	116 (77)	
Primipaternity	115 (76)	
Antecedent of PE in a previous spouse	0 (0)	

Results expressed as mean±SD or sample size (%).
OR=Oocyte recipients, OD=Oocyte donors, BMI=Body mass index, PE=Preeclampsia, AMH=Anti-Mullerian hormone, PCOS=Polycystic ovary syndrome, NA=Not applicable, SD=Standard deviation

The preterm birth rate in the PE group was 47.6% versus 9.1% in the group with no PE (P < 0.001).

The mean birth weight of OR' children was 3013 g (±679). Children in the OR with PE group had a lower birth weight than those in the OR with no PE group: 2531 g (±862) versus 3092 g (±607) (P = 0.003). There was no more small for gestational age (SGA), defined by birth weight below the tenth percentile, in the OR with PE group than in the non-PE group, which was calculated with the anthropometric data of the mother or OD.

We found no significant difference in adaptation to ectopic life between the two groups. Apgar scores at birth and the rate of neonatal resuscitation involvement were comparable between the two groups despite the higher rate of prematurity in the OR with PE [Table 3].

Discussion

In our study, 14.8% of the OR presented with PE. This rate is in line with the data from the literature.

The risk factors for PE found in univariate analysis are primiparity and primipaternity, the BMI and AMH of the OR, the age and AMH of the OD. In multivariate analysis, only the OR' BMI and the OD' AMH are statistically significant.

Many authors have hypothesized that the pathophysiology of PE in oocyte donation was different from that of pregnancies with autologous gametes.[13-17] Indeed, in the context of pregnancies in the OR, the fetal genome is completely allogeneic to the mother. Complex immunological adaptation reactions take place to allow these pregnancies to progress.[14,18,19] Thus, specifically in the OR, there are dense deposits of fibrin on the basal plate of the placenta with chronic involvement of the decidua and site of a high level of T-helper lymphocytes and natural killer cells. This immune reaction phenomenon would result in early placentation disorder causing PE.[14,19]

In addition, in a 2005 study, Kim *et al*.[20] discovered a decrease in the rate of PE where oocytes are donated by a relative. Similarly, Lashley *et al*. in 2015 demonstrated that there is a better human leukocyte antigen compatibility in the group of OR with no PE than in those with PE. Thus, PE in OR would be more related to an immunological than vascular mechanism and initiated by a maternal-fetal immune conflict with a "graft-versus-host" response.[21]

Given that the pathophysiological mechanism of PE seems to be particular in the context of OR, we can assume that the risk factors are also different from those in pregnancies with autologous gametes.

Table 2: Univariate and multivariate analysis of preeclampsia risk factors

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Age of the OR	0.97	0.87-1.1	0.528	-	-	-
BMI	1.2	1.1-1.4	0.0388	1.2	1.1-1.4	0.0474
Antecedent of PE	<0.01	0.15-Inf	0.15			
Antecedent of diabetes	<0.01	0-Inf	0.99	-	-	-
Antecedent of chronic nephropathy	6	0.35-102	0.214	-	-	-
Antecedent of thrombophilia	<0.01	0-Inf	0.991	-	-	-
Antecedent of autoimmune disease	2	0.37-11	0.412	-	-	-
Turner syndrome	2.4	0.56-9.8	0.238	-	-	-
AMH of the OR	1.1	1-1.4	0.193	-	-	-
Ovarian failure	1.7	0.53-5.5	0.375	-	-	-
Age of onset of ovarian failure	1	0.93-1.2	0.482	-	-	-
PCOS	1.5	0.29-7.7	0.633	-	-	-
Endometriosis	1	0.27-3.9	0.977	-	-	-
Twins	2.1	0.65-6.4	0.216	-	-	-
Primiparity	2.7	0.59-13	0.197	-	-	-
Primipaternity	3.1	0.68-14	0.142	-	-	-
Age of the OD	1.1	0.95-1.3	0.197	1.2	0.98-1.4	0.0724
AMH of the OD	1.2	1-1.2	0.154	1.2	1.1-1.4	0.0481

OR=Odds ratio, 95% CI=95% confidence interval, OR=Oocyte recipients, OD=Oocyte donors, BMI=Body mass index, PE=Preeclampsia, AMH=Anti-Mullerian hormone, PCOS=Polycystic ovary syndrome

Table 3: Obstetric and neonatal outcomes

	OR with PE (*n*=22)	OR without PE (*n*=128)	*P** <0.001
Gestational diabetes	2 (9.5)	12 (9.4)	1
Twin pregnancy	5 (23.8)	17 (13.3)	0.03
Term of pregnancy (day)	252±39	274±16	0.02
Prolonged pregnancy	1 (4.8)	25 (19.5)	0.002
Premature delivery	10 (47.6)	11 (8.6)	<0.001
Delivery route			
Vaginal delivery	5 (22.7)	70 (54.7)	<0.001
Cesarean section outside of labor	13 (59.1)	33 (25.8)	<0.001
In emergencies	11 (50)	5 (3.9)	<0.001
Scheduled	2 (9.1)	28 (21.9)	0.02
Cesarean section during labor	4 (18.2)	25 (19.5)	0.86
Way of getting into labor			
Spontaneous	2 (9.1)	63 (49.2)	<0.001
Triggered	11 (50)	32 (25)	0.35
Birth weight (g)	2531±862	3092±607	0.003
SGA relative to OR data	5 (22.7)	43 (33.6)	0.12
<10th percentile	4 (18.2)	30 (23.4)	0.48
<5th percentile	1 (4.5)	13 (10.2)	0.16
SGA relative to OD data	7 (31.9)	59 (46.1)	0.06
<10th percentile	5 (22.7)	35 (27.3)	0.62
<5th percentile	2 (9.1)	24 (18.8)	0.07
Apgar score <7-1 min	2 (9.1)	7 (5.5)	0.59
Apgar score <7-5 min	2 (9.1)	4 (3.1)	0.13
Neonatal resuscitation	1 (4.5)	4 (3.1)	1

*Statistically highly significant as $P < 0.001$. Results expressed as mean±SD or sample size (%). OR=Oocyte recipients, OD=Oocyte donors, PE=Preeclampsia, SGA=Small for gestational age, SD=Standard deviation

Unlike spontaneous pregnancies or pregnancies resulting from ART using autologous gametes, the majority of couples on the path toward oocyte donation want to conceive their first child. Thus, risk factors for PE that have been validated in the literature such as primiparity, primipaternity, and a history of PE are less discriminating in this population. In our study, we find that primiparity and primipaternity are significant risk factors for PE in univariate analysis, but these are not replicated in the multivariate analysis because of the low prevalence of couples with children. Similarly, the history of chronic vascular-renal diseases, autoimmune diseases, and thrombophilia is rare and therefore poorly represented in our population of 150 patients. There is no evidence in the literature to suggest that OR are not subjected to these risk factors in the same way as other parturient women.

The patients in the oocyte donation process are on average older than the other parturient women. However, we know that, in patients over 40 years, there is an increased risk of developing PE.[22] However, studies comparing pregnancies from oocyte donation to spontaneous pregnancies or resulting from IVF without oocyte donation find a persistently increased risk of PE in the OR group despite adjustment by age.[23-25] Thus, Le Ray *et al.*[26] who focused on patients over 43 years of age, showed a significant difference in the rate of PE according to the conception mode: spontaneous (3.8%), using IVF without oocyte donation (10%) and with oocyte donation (19.2%) ($P < 0.001$). After adjusting for

parity and twinning, it found a significant difference in PE between OR and spontaneous pregnancy (adjusted OR: 3.3, 95% CI: [1.2–8.9]). In our study, the average patient age is 37 (±4.5), and 26% of the OR are over 40 years old. We found no significant difference in age between the group of OR with PE (36.3 years ± 3.98) or with no PE (36.9 years ± 4.6) (P = 0.5). These results support the hypothesis of Levron *et al*.[27] on the existence of an immune disorder independent of the OR' age as a cause of PE. Moreover, we identify for the first time that the age of the OD could be related to the occurrence of PE for the pregnancy resulting from this donation (OR: 1.2, 95% CI: [0.98–1], P = 0.0724). As for calculating the trisomy 21 combined risk, it would, therefore, be the age of the OD that should be taken into account to establish the risk of PE.

While, to our knowledge, no other study has investigated the correlation between OD' AMH and the occurrence of PE in OR, we have demonstrated that OD' AMH is a risk independent of PE (OR: 1.2, 95% CI: [1.1–1.4], P = 0.0481). It appears that ovarian failure is associated with the presence of circulating autoantibodies against the granulosa and zona pellucida cells.[28] These antibodies would increase the risk of disrupting the invasion of trophoblastic cells into the endometrium and would be a factor in causing PE.[29,30] In the context of pregnancies resulting from oocyte donation, this autoimmunity is likely to be present not only in the recipients but also in the OD since they are not disqualified because of a weak AMH. Thus, in our population, 4.8% of the OD had an AMH lower than 1.1 ng/mL.

Some studies have shown an increased risk of PE in the event of a fall in ovarian reserve in the context of spontaneous pregnancies or after IVF/intracytoplasmic sperm injection with autologous gametes.[31-33] Shand *et al*.[34] studied 331 patients, with spontaneous pregnancies or pregnancies resulting from conventional IVF, looking for a correlation between the rate of toxemia of pregnancy and the AMH level. After adjusting for BMI, parity, and age, the study found that in women with AMH below the tenth percentile, the risk of developing hypertensive disorders during pregnancy increased by 3.3. We found in a univariate analysis that the OR' AMH was indeed a risk factor for PE (OR: 1.1, 95% CI: [0.93–1.4], P = 0.193). On the other hand, because of a large amount of missing data, this result is not significant in multivariate analysis.

Keegan *et al*.[29] compared PE in four groups of patients: OR under the age of 35, OR over the age of 40, and patients under the age of 35 and over the age of 40 using conventional IVF. The study found that OR under the age of 35 are significantly more at risk of developing PE with a rate of 42%, followed by OR over the age of 40 years (26% PE), then women with conventional IVF over the age of 40 years (14%), and finally, those under the age of 35 years (12%). Although these PE rates appear to be particularly high and probably related to a different meaning, this study is the first to suggest that the early onset of ovarian failure could play a role in the origin of PE in OR. We do not find these data in our results.

Our study shows, in multivariate analysis, an increased risk of PE associated with a BMI above 30 kg/m^2 (OR: 1.2, 95% CI: [1.1–1.4], P = 0.0474). These data are shared with spontaneous pregnancies in which the risk of PE increases with the patient's BMI.[35] Obesity, associated with hyperlipidemia, would encourage the production of peroxides that would lead to endothelial damage and vasoconstriction.[36,37] In our population, almost 10% of the patients were obese, and the average BMI was 25.5 (±4.8) in the group of OR with PE versus 23.1 (±4.6) in the group of OR with no PE (P = 0.04).

In our population of OR, there was a 14% rate of premature deliveries, which is more than twice the rate found in the general population.[38] These rates of prematurity in the population of OR are comparable to those from another recent study in the United States.[39] When comparing our OR group with or without PE, we note that there is an increased risk of preterm birth in cases of PE (P < 0.001). However, the high rate of prematurity is not only explained by the increased rate of PE in the OR. Malchau *et al*.[40] showed that after adjustment for PE, there is a continued risk of prematurity in the OR group compared to spontaneous pregnancies and those resulting from IVF with autologous oocytes.

As in other previously published studies, we note the lack of association between PE and SGA in pregnancies resulting from oocyte donation.[27,41-43] We note in our study that although birth weight is lower in OR with PE (2531g +/- 862) than in those without PE (3092g +/- 607) (P = 0.003), there is no increase in the SGA rate whether data are weighted with the maternal characteristics or with those of the OD. The low birth weight observed in cases of PE is related to the increased rate of prematurity present with this disease.

Although the numbers are small, Lashley *et al*.[42] found no cases of SGA in nine OR patients with PE, while 30% of children born with autologous oocytes from a preeclamptic mother were SGA (P < 0.0001). They suggested that this discrepancy was explained by the difference in the pathophysiological mechanism of PE between the two types of conception. It was also mentioned that the use of frozen embryos could

increase the birth weight of children resulting from oocyte donation.[44] However, in our study, the majority of pregnancies (n = 112) are derived from fresh embryo transfer.

To our knowledge, there are no other studies on the specific risk factors for PE in OR. We have found that some characteristics of OD such as age and AMH can influence the onset of PE. Of course, due to small numbers, our results are at the limit of significance, and large-scale studies should be performed to confirm our data.

We also confirm the lack of impact on fetal growth of the onset of PE in oocyte donation pregnancies supporting the hypothesis of a pathophysiology different from PE in OR.

Some proven risk factors in the general population such as duration of exposure to sperm or change of partner and interval between pregnancies could not be studied. Similarly, while tobacco appears to have a protective effect against PE,[45] we have not been able to analyze its effect in oocyte donation due to unreliable data and too small group.

To compile the maximum number of births resulting from OD, we selected all patients regardless of the place of delivery. This may have led to disparities in the management of pregnancy and the delivery process. In addition, to complete the medical information, we contacted several patients by telephone which could lead to recall bias.

Conclusion

In OR, PE seems to be more of an expression of immune conflict in response to the presence of a totally allogeneic embryo than that of a primitive vascular dysfunction. This results in a need to weigh the risk factors for PE agreed by common accord and the considered specific factors such as the AMH level and the age of the OD. This new information, if confirmed by large-scale studies, would optimize the match between OR and OD by limiting the combination of PE risk factors.

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Conflicts of interest

There are no conflicts of interest.

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