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Obstetrical and neonatal outcomes after single and double gamete donation

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ABSTRACT

Introduction: An increasing number of women and couples need oocyte donation to help achieve pregnancy. Several studies have found a correlation between the use of oocyte donation and adverse obstetrical outcomes such as gestational hypertension and preeclampsia when comparing with the use of autologous gametes. A possible additive risk in using double donation (oocyte and sperm donation) compared to the use solely of oocyte donation has been suggested but only sparsely investigated. The aim of this study is to investigate the differences in obstetrical and neonatal outcomes after double donation compared to oocyte donation.

Methods: This is a retrospective cohort study of 197 women, who achieved pregnancy after oocyte donation between 2015 and 2022. The primary outcomes investigated were gestational hypertension and preeclampsia. Secondary outcomes were early pregnancy loss, HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, fetal growth restriction, and gestational diabetes mellitus.

Results: No significant differences between the use of oocyte and double donation were observed when looking at the risk of developing gestational hypertension (AOR = 1.0, 95%CI = [0.33;3.09], *P* = 1.0) or preeclampsia (AOR = 2.35, 95%CI = [0.67;8.26], *P* = 0.18). We observed no significant differences between the two groups regarding any of the secondary outcomes.

Conclusion: This study did not find an increased risk of obstetrical or neonatal complications such as preeclampsia, gestational diabetes mellitus, or fetal growth restriction after double donation compared to oocyte donation.

Keywords: Gamete donation; Oocyte donation; Double donation; Preeclampsia

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INTRODUCTION

A worldwide tendency for increasing maternal age at first delivery has been observed. In Denmark, the age of first-time mothers today is nearly seven years older than in 1960 (1).

This has led to a rising need for not only assisted reproductive technologies (ART) in form of in vitro fertilization (IVF) but also oocyte donation (OD) and double donation (DD). Other indications for OD are primary ovarian failure (POF), genetic disease (e.g., Turner syndrome), prior chemotherapy, and prior ovarian surgery (2). The first case report of successful OD was described in 1984 (3), but besides egg-sharing the treatment was not legalized in Denmark until 2007. Double gamete donation was legalized in Denmark in 2018 (4).

OD is an independent risk factor for developing obstetrical complications such as gestational hypertension (GH) and preeclampsia (PE). Furthermore, studies have found an increased risk of cesarean sections (C-sections), post-partum hemorrhages (PPH), and neonatal complications like prematurity and low birth weight (LBW) in OD compared to autologous IVF pregnancies (5-7). The use of a sperm donor has also been associated with an increased risk of developing PE (8). If both sperm and oocyte donation lead to an increased risk of PE, it is plausible that the combination could lead to an additive risk in DD pregnancies.

The pathophysiological mechanisms behind the development of PE are still not fully understood. Two different explanatory hypotheses have been proposed.

One is the vascular theory, which suggests a close connection between oxidative stress and developing the inflammatory response seen in PE. The development of oxidative stress may be explained by insufficient modeling of the spiral arteries induced by trophoblasts after implantation. As a result, the placenta is in deficit of oxygen, which leads to relative ischemia (9).

The other hypothesis is based on an immunological response in the mother when exposed to allogeneic cells. This hypothesis especially links the combination of a maternal AA-genotype and a fetal HLC class II to an increased risk of PE. It has been suggested that this combination changes the function of uterine natural killer cells, altering the blood flow to the placenta, which can result in fetal growth restriction and PE (10,11). If the immunological theory is valid, a greater risk of developing PE in DD should be suspected, as the recipient is exposed to two allogenic cells compared to only one in OD or sperm donation. It is suggested that exposure to a partner's semen over longer periods of time protects against PE, which also supports the immunological hypothesis (12).

Only a few studies have investigated the risk of adverse obstetrical outcomes after DD compared to OD. Blazquez et al. conducted a retrospective cohort study in Spain (n=433), which found a higher risk of developing preterm PE after DD compared with OD (13). A French retrospective study by Preaubert et al. (n=247) found an increased risk of developing gestational diabetes mellitus (GDM) after DD compared with OD (14). The risk of adverse obstetrical outcomes when comparing DD with OD was further investigated by Augusto et al. in a systematic review and meta-analysis of four studies (n = 1.979), including the two mentioned above. The study found no significant difference in GH or PE risk between pregnancies resulting from DD and those from OD alone (15).

Higher maternal age and primigravidity, which are common characteristics of women receiving OD, are independent risk factors for several obstetrical complications. Additionally, high maternal age can be associated with comorbidities such as hypertension and diabetes mellitus, which also contribute to an increased risk of developing PE (16,17). It has been suggested that patients undergoing a programmed FET cycle compared to one without hormone substitution prior to the transfer of the embryo, may have an increased risk of developing PE (18). Furthermore, one study found circulating autoantibodies against zona pellucida and granulosa cells in women receiving OD, suggesting a predisposition to developing PE (19).

The aim of this study is to investigate the differences in obstetrical and neonatal outcomes after DD compared with OD. Uni- and multivariate statistical analyses were performed on these outcomes to compare the two treatment forms. Our

study adds valuable data by providing a comprehensive investigation of both obstetrical and neonatal outcomes in a relatively understudied area.

MATERIALS AND METHODS

Study design and population

This is a retrospective cohort study of 197 women aged 27 to 46 who achieved pregnancy after OD in either a Danish public fertility clinic (Herlev Hospital) or one of three private fertility clinics (Trianglen, TFP STORK clinic, Dansk Fertilitetsklinik) in Denmark between 2015 and 2022. The study included women who became pregnant after OD with fresh or frozen embryo transfer (FET). The pregnancies were obtained in either substituted cycles, where the women received hormone medication (estradiol and progesterone), or modified natural cycles, where the women were given Human Chorionic Gonadotropin (hCG) to trigger ovulation, with or without progesterone. The women were classified into two groups: one receiving OD using a partner's sperm, and one receiving both oocyte and sperm donation.

The data on ART-treatment cycles were extracted from the database Danish Medical Data Center (DMDC), Formatex, used by the four Danish fertility clinics. Data regarding pregnancy and delivery outcomes were collected from the obstetrical records in Epic/Sundhedsplatformen through review of records.

Women with a known diagnosis of essential hypertension or diabetes mellitus were excluded from the study. Furthermore, the study excluded women who gave birth in hospitals located outside the Capital Region and Region Zealand in Denmark, as illustrated in Figure 1.

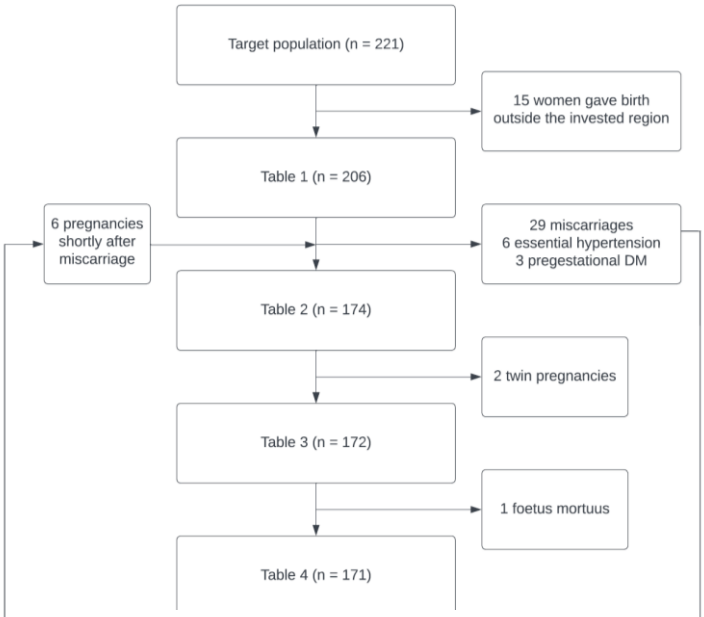

Figure 1: Flowchart for included patients.

Outcomes

The primary outcomes investigated were GH and PE. GH was defined as the development of hypertension (repeated measurements showing BP ≥ 140/90 mmHg) without proteinuria after 20 weeks of gestation for a previously healthy pregnant woman. PE was defined as GH with proteinuria (≥0,3 g/24 hours). Furthermore, PE was classified as either preterm (< 37 weeks of pregnancy) or term (≥ 37 weeks of pregnancy) (20).

Secondary obstetrical outcomes included early pregnancy loss, HELLP syndrome, abruptio placenta, and GDM. HELPP syndrome was defined as hemolysis, elevated liver enzymes (ALAT/ASAT > 100 U/l), and low platelets (< 100 x 10^9/l) (21). The international association of diabetes and pregnancy study group guidelines were used to define GDM as having hyperglycemia with onset or first recognition during pregnancy discovered after the Oral Glucose Tolerance Test (75 g glucose) (22). Delivery outcomes investigated were gestational age at delivery, preterm delivery (classified according to WHO's guidelines into extremely: < 28 weeks, very: 28-32 weeks, and moderate to late: 32-37 weeks) (23), cesarean or vaginal delivery, PPH (classified as bleeding > 500 ml) and the umbilical cord pH.

Neonatal outcomes included birth weight, weight deviation (divided into SGA and LGA), weight restriction (weight < 10^{th} percentile for estimated fetal weight at a given gestational age) (24), APGAR score (Appearance, Pulse, Grimace, Activity, and Respiration at 1, 5, and 10 minutes) (25), transfer to a neonatal care unit in the continuation of the hospitalization right after

Table 1: Baseline characteristics of women with pregnancies obtained after oocyte and double gamate donation.

Characteristics	Overall (n = 206)	OD (n = 152)	DD (n = 54)	p-value
*Maternal age, mean (± SD)**	39.86 (4.66)	39.4 (4.92)	41.1 (3.65)	0.01
*Pregestational BMI, mean (± SD)**	24.3 (4.25)	24.2 (4.42)	24.7 (3.76)	0.45
▪ *< 18,5*	6 (3.17)	6 (4.29)	0 (0)	
▪ *18,5-24,9*	118 (62.4)	87 (62.1)	31 (63.3)	
▪ *25-29,9*	46 (24.3)	32 (22.9)	14 (28.6)	
▪ *30-34,9*	15 (7.94)	12 (8.57)	3 (6.12)	
▪ *35-39,9*	3 (1.59)	2 (1.43)	1 (2.04)	
▪ *>40*	1 (0.53)	1 (0.71)	0 (0)	
Primigravidity, n (%)	82 (41.6)	61 (42.1)	21 (40.4)	0.87
Fertilization method, n (%)				
▪ *IVF*	13 (6.6)	13 (8.97)	0 (0)	0.02
▪ *ICSI*	184 (93.4)	132 (91.0)	52 (100)	
Smoking status, n (%)				
▪ *Smoker*	8 (4.62)	7 (5.51)	1 (2.17)	0.68
▪ *Nonsmoker*	165 (95.4)	120 (94.5)	45 (97.8)	
Essential hypertension, n (%)	6 (2.91)	4 (2.63)	2 (3.7)	0.65
Pregestational diabetes mellitus, n (%)	3 (1.46)	3 (1.97)	0 (0)	0.57

OD: Oocyte donation

DD: Double donation (oocyte and sperm)

IVF: In vitro fertilization

ICSI: Intracytoplasmic sperm injection

Fisher's exact test was used as statistical analysis, unless otherwise specified

**Student's t-test was used*

birth, malformations, and asphyxia (based on low APGAR score at one minute and pH < 7 in umbilical artery blood) (26).

The data is based on the patients' first cycle achieving pregnancy resulting in birth after OD in one of the four clinics.

Covariates

Maternal age was registered at the start of the treatment cycle in which the women achieved pregnancy. The Body Mass Index (BMI) is defined as a person's weight (kg) divided by the square of their height (meter). This study divided the BMIs into six groups: Underweight (< 18.5 kg/m^2), normal weight (18.5 kg/m^2-<25 kg/m^2), overweight (25 kg/m^2-<30 kg/m^2), obese (30 kg/m^2-<35 kg/m^2), severely obese (35 kg/m^2-<40 kg/m^2), and extremely obese (>40 kg/m^2) (27). Lastly, the gravidity was classified as either primigravida (first pregnancy) or as multigravida. These covariates were all considered possible confounders regarding the obstetrical outcomes.

Statistics

Data analyses were performed with the statistical software R, version 2022.02.2, build 485. Student's t-test and Fisher's exact test were used for univariate analysis for each study outcome, where OD and DD outcomes were compared. P-values < 0.05 were considered statistically significant. Furthermore, multivariable analyses were performed by logistic regression for the two primary outcomes. These outcomes were calculated as adjusted odds ratios (AOR) with associated confidence intervals (95%, CI) and p-values. The outcomes were adjusted for possible confounders such as maternal age, BMI, and gravidity.

Due to the skewed distribution of smokers in the two groups, as well as the small proportion of smokers, the results became improbable and imprecise, which was evident in the adjusted analyses including this as a confounding factor.

Table 2: Obstetrical outcomes in pregnancies obtained after oocyte and double gamete donation.

Outcomes	Overall (n = 174)	OD (n = 129)	DD (n = 45)	OR (95%CI)	p-value
Gestational hypertension	20 (11.6)	15 (11.8)	5 (11.1)	0.93 (0.32;2.78)	1.0
Preeclampsia	13 (7.56)	8 (6.3)	5 (11.1)	1.86 (0.58;6.11)	0.33
▪ *Preterm < week 37*	*5 (38.46)*	*4 (50)*	*1 (20)*	0.4 (0.03;4.68)	0.56
▪ *Term ≥ week 37*	*8 (61.54)*	*4 (50)*	*4 (80)*	1.6 (0.27;9.49)	
Twin pregnancy	2 (1.15)	2 (1.55)	0 (0)		1.0
HELPP syndrome	2 (1.16)	1 (0.79)	1 (2.22)	2.9 (0.18;47.5)	0.45
Gestational diabetes mellitus	22 (12.8)	20 (15.7)	2 (4.44)	0.25 (0.06:1.13)	0.07
Abruptio placenta	1 (0.58)	1 (0.79)	0 (0)		1.0
*Miscarriage**	29 (14.9)	22 (15.4)	7 (13.5)	0.86 (0.35;2.91)	0.82

OD: Oocyte donation

DD: Double donation (oocyte and sperm)

HELLP: Hemolysis, elevated liver enzymes, and low platelets

n (%), preterm (% within preeclampsia)

Fisher's exact test was used as statistical analysis

**Miscarriage cohort, n = 195*

For that reason, smoking was excluded from the multivariate analyses. The same applies to the fertilization method since IVF treatments were not used in DD in our study cohort, and thereby skewing the data.

Statistical analyses were made with pairwise deletions to correct for missing data. The pairwise deletion is based on the assumption that those with missing information are no different from those without it.

Ethical approval

The study was based on register data, for which the Danish legislation does not require approval from the ethics committee. The Center for regional development granted permission to perform the study in accordance with the law of the Data Protection Act and access to electronic heath records (case number: R-2203161). As the study is an observational research study it is structured after the STROBE criteria.

Table 3: Logistic regression analysis for odds ratio between OD and DD, before and after adjusting for potential confounders

	OR	p-value	AOR
Risk of gestational hypertension	0.93 [0.29;2.56]	0.89	1.00 [0.33;3.09]
Risk of preeclampsia	1.84 [0.53;5.86]	0.31	2.35 [0.67;8.26]

OD: Oocyte donation

DD: Double donation (oocyte and sperm)

AOR: Adjusted odds ratio

**Adjusted for maternal age, pregestational BMI and primigraviity*

Table 4 Delivery outcomes of pregnancies obtained after oocyte and double gamete donation

Outcome	Overall (n = 172)	OD (n = 127)	DD (n = 45)	OR (MD), (95% CI)	p-value
Type of labor					
▪ *Vaginal*	91 (53.2)	65 (51.6)	26 (57.8)	1.3 (0.66;2.59)	0.49
▪ *C-section*	80 (46.8)	61 (48.4)	19 (42.2)	0.79 (0.4;1.57)	
*Gestational age at birth, mean (SD)**	39.2 ±1.72	39.2 ± 1.74	39.3 ±1.67	0.1 (-0.49;0.69)	0.75
▪ *Extremely preterm (<28 weeks)*	0 (0)	0 (0)	0 (0)		
▪ *Very preterm (28-32 weeks)*	1 (0.59)	1 (0.79)	0 (0)		1.0
▪ *Moderate to late preterm (32-37 weeks)*	11 (6.93)	7 (5.56)	4 (8.89)	1.67 (0.47;6.0)	0.51
*PPH**	100 (58.5)	73 (57.9)	27 (60)	1.11 (0.56;2.22)	1.0
Umbilical cord					
▪ *Arterial pH, mean (± SD)*	7.22 (0.09)	7.22 (0.09)	7.23 (0.07)	0.01 (-0.02;0.04)	0.33
▪ *Venous pH, mean (± SD)*	7.25 (0.58)	7.22 (0.69)	7.33 (0.05)	0.11 (-0.09;0.31)	0.13
Fetal asphyxia	10 (5.8)	8 (6.35)	2 (4.65)	0.69 (0.14;3.88)	0.69
Foetus mortuus	1 (0.58)	1 (0.79)	0 (0)		1.0

OD: Oocyte donation

DD: Double donation (oocyte and sperm)

MD: Mean difference

PPH: Postpartum hemorrhage > 500 mL

Fisher's exact test was used as statistical analysis, unless otherwise specified

**Student's t-test was used*

RESULTS

Demographic characteristics

This study initially included 221 patients, of which 54 were pregnant after DD and 152 after OD using the partner's sperm. Nine women were excluded from the study due to either essential hypertension (OD: 4 vs. DD: 2) or pregestational diabetes (OD: 3 vs. DD: 0). Fifteen women gave birth outside the region and were excluded due to inaccessible data (Figure 1). A total of 197 women were included in the study. Patient demographics and baseline characteristics are shown in Table 1. Women in the DD group were significantly older than the women in the OD group (41.1 years ± 3.7 vs. 39.4 years ± 4.9, *P* = 0.01). Furthermore, a significantly higher prevalence of pregnancies obtained with IVF contra ICSI was observed in the OD group compared to the DD group (*P* = 0.02). Pregestational BMI, primigravidity, and smoking status did not differ between the two groups (Table 1).

Obstetrical outcomes

Data on obstetrical outcomes after OD and DD are shown in Table 2. The investigated study cohort consists of 174 women, as 29 miscarriages were subtracted from these analyses. We found no significant difference in the prevalence of developing GDM between the two groups (OD: 15.7% vs. DD: 4.4%, *P* = 0.07). Overall, 20 cases of GH were observed, this accounted for 11.6% of the pregnancies. The prevalence was similar in the two groups (OD: 11.8% vs. DD: 11.1%, *P* = 1.0). The same applied for PE, which had an overall prevalence of 7.6% (OD: 6.3% vs. DD: 11.1%, *P* = 0.33). Only two of the women with GH were diagnosed with PE. None of the women with PE developed eclampsia. However, both women observed with HELPP syndrome were diagnosed with PE prior to HELLP syndrome. We found the risk of developing GH and PE associated with DD nonsignificant (GH: OR 1.0 [0.33;3.09], *P* = 1.0, PE: OR 2.35 [0.67;8.26], *P* = 0.18), (Table 3).

Delivery and neonatal outcomes

One *foetus mortuus* was observed in the OD group. It was excluded for both delivery and neonatal analyses to avoid skewing the data. The *foetus mortuus* was unexplained. As Table 4 displays, the prevalence of C-sections was similar in the two groups (OD: 48.4% vs. DD: 42.2%, *P* = 0.49). Likewise, no significant difference was found in PPH between the two groups (OD: 57.9% vs. DD: 60%,

Table 5: Neonatal outcomes of pregnancies obtained after oocyte and double gamete donation

Outcome	Overall (n = 175)	OD (n = 130)	DD (n = 45)	OR (MD), (95% CI)	p-value
*Birth weight, mean (± SD)**	3374.8 (±569.79)	3396 (±573)	3316 (±563)	-80 (-275.6;115.6)	0.4
Weight deviation					
▪ *SGA*	3 (1.8)	2 (1.59)	1 (2.22)	1.41 (0.12;15.93)	1.0
▪ *LGA*	18 (10.5)	14 (11.1)	4 (8.89)	0.78 (0.24;2.51)	0.78
Fetal growth restriction (FGR)	12 (7.0)	9 (7.14)	3 (6.67)	0.93 (0.24;3.6)	1.0
APGAR					
▪ *≤ 7 after 1 min*	16 (9.36)	14 (11.1)	2 (4.54)	0.37 (0.08;1.7)	0.24
▪ *≤ 7 after 5 min*	4 (2.34)	3 (2.38)	1 (2.27)	0.93 (0.09;9.19)	1.0
▪ *≤ 7 after 10 min*	1 (0.58)	1 (0.79)	0 (0)		1.0
NICU	24 (14.0)	20 (15.9)	4 (8.89)	0.52 (0.17;1.6)	0.33
Malformations	3 (1.8)	3 (2.38)	0 (0)		0.57

OD: Oocyte donation
DD: Double donation (oocyte and sperm)
MD: Mean difference
NICU: Neonatal intensive care unit
SGA: Small for gestational age (fetus, which has not achieved biometric measurements equivalent to its gestational age)
LGA: Large for gestational age
APGAR: The Appearance, Pulse, Grimace, Activity, and Respiration of the newborn
Fisher's exact test was used as statistical analysis, unless otherwise specified
**Student's t-test was used, the result displayed in this row is MD and not OR*

P = 1.0). None of the children were born extremely preterm, and only one was born very preterm in the OD group. There were no differences in the delivery outcomes such as type of delivery, gestational age at delivery, or PPH between the two groups (Table 4).

The 197 women gave birth to 175 children, 130 after OD and 45 after DD. Two twin pregnancies were observed in the study, both being in the OD group. These were excluded for further analysis to minimize potential bias. The mean birthweight did not differ significantly between the two groups (OD: 3396 g vs. DD: 3316 g, *P* = 0.4). Three malformations were observed in the OD group: hypospadias, clubfoot, and spina bifida. No statistically significant difference was found in the study regarding any of the neonatal outcomes (Table 5).

DISCUSSION

Women, who conceive after the use of OD, are known to have an increased risk of developing various obstetrical complications compared to women who conceive naturally or with the use of autologous gametes in IVF/ICSI (5-7). A previous Danish study found a two- to three-fold higher risk for developing GH and PE after the use of OD compared to autologous gametes (28). It is still unclear whether the use of both an oocyte and a sperm donor leads to an additive risk of adverse obstetrical and neonatal outcomes.

In this retrospective study of 197 women, who achieved pregnancy after OD or DD, we found a prevalence of GH of 11.6% and PE of 7.6%, which is in accordance with previous findings (15). In the background population, the risk of developing GH is up to 7%, and the risk of developing PE is about 3% of all pregnancies (29). Furthermore, our study observed a GDM prevalence of 12,8%, which is up to four times higher than the reported prevalence of 3-4% in the background population (20,30). This result is consistent with the findings of the study by Preaubert et al., which reported a similar GDM prevalence of 12,9% in pregnancies conceived after OD, yet a higher one (26,4%) for the DD-group (14).

Our study found no differences in delivery method or neonatal outcomes between the OD and DD groups, which is in accordance with the findings by both Blazquez et al. (13) and Preaubert et al. (14). However, our study observed a higher prevalence of c-sections (46.8%) compared to the background

population, which have a prevalence of 20.3% (31). This is in line with the high rates reported in the study by Preaubert et al., which found c-sections rates of 50,9% in the OD group and 61,7% in the DD group, as well as in the study by Blazquez et al., which reported an overall c-section rate of 64,3%. Considering the investigated pregnancies were achieved by fertility treatment, and the women had a high maternal age at first-time delivery, these pregnancies can be considered high risk, and therefore more prone to c-sections.

In our study, we found no increased risk of developing GH or PE after DD compared to OD. These results are not in accordance with the findings of the study by Blazquez et al., who reported an increased risk of developing preterm PE after DD compared with OD. This incongruence may be explained by inadequate power in our study or differences in study designs regarding the collection of data. In the study by Blazquez data was collected from questionnaires filled in by the patients and their clinicians, whereas the data in our study was obtained from the regional register, where data were collected and registered throughout the pregnancy.

The study by Preaubert et al. reported an increased risk of developing GDM when using DD compared with OD. Our study results did not support these findings, as there were no differences in the development of GDM between the two study groups. The discrepant results between the studies may be due to lack of statistical power caused by the small cohort sizes and limited number of individuals with the investigated outcomes.

In summary, our results did not show any significant difference in GH or PE risk between pregnancies resulting from DD and those from OD alone. Our results coincide with the findings of the recent meta-analysis by Augusto et al., which also found no significant differences in the distribution of GH and PE between the two groups (15). While the meta-analysis represents the largest and most comprehensive research conducted on the subject to date, there was great heterogeneity in the included studies. Therefore, further research with larger studies should be made to confirm the findings of this meta-analysis and provide more precise estimates of the differences in outcomes when comparing OD and DD.

Strengths and limitations of the study

This is a retrospective study based on data registration made by clinicians all over the region of Zealand, Denmark. Registration bias and underreporting of outcomes cannot be completely excluded in register studies. However, Denmark has a great focus on precise and true-to-time registration in both public and private clinics leading to detailed records. This enables variables and outcomes to be included in the study with only a few missing data. Furthermore, the data was extracted from both private and public clinics and hospitals, giving the study a broader perspective.

We performed a multivariate analysis in order to adjust for possible confounders. One being higher maternal age, as several studies have found a strong link between maternal age and the development of adverse obstetrical outcomes such as GH and PE (16,17). Another confounder is pregestational BMI, which is a known risk factor for developing several adverse obstetrical outcomes such as GDM, GH, and PE (29).

Previous studies have investigated obstetrical outcomes after fresh compared to frozen embryo transfer (FET) in autologous treatment cycles. The results in the literature are conflicting, as some found FET to be protective factor (32), and others as being a risk factor (33). The effect of FET vs. fresh embryo transfer on obstetrical and neonatal outcomes in OD cycles has not been investigated. In our study, the patients underwent both fresh and frozen embryo transfers and there was no distinction between the two transfer methods since this data was unavailable. However, there is no reason to suspect any differences in distribution between the two groups.

A limitation of the study is, that it does not distinguish between the two treatment forms: Substituted (estradiol and progesterone) and modified natural (hCG with/without progesterone). Unfortunately, the data on the medication used was inaccessible. An overweight of substituted treatments is expected in both groups, as POI and anovulation are among the main reasons for needing OD. Previous studies have shown an association between hormone-substituted treatments prior to embryo transfer and an increased risk of developing hypertensive disorders in pregnancy (34,35). It has been suggested that the increased

risk of developing PE after a substituted FET cycle may be due to the lack of the corpus luteum producing several essential hormones during early pregnancy. These hormones may prevent the development of PE (19). Although some countries transfer multiple blastocysts, in Denmark, it is recommended to only transfer one blastocyte per cycle according to guidelines.

Studies suggest that aspirin protects fetal growth and development while decreasing the risk of PE and its associated complications, such as prematurity and neonatal care unit admission. In Denmark, pregnant women who have conceived through OD or DD are recommended to take 150 mg aspirin from gestational week 10-37 (36-37). This may have an impact on the prevalence of several obstetrical outcomes, but the treatment has been recommended for both study groups and is therefore not expected to affect the prevalence of adverse obstetrical outcomes between the groups.

Our study included OD cases from 2015 and DD cases from the treatment's legalization in 2018. Although this could be viewed as a limitation, we decided to include the OD cases as there have been no major changes in the treatment regime during that period, and therefore it is not expected to affect the investigated outcomes.

It has not been possible to obtain information on the indications for ART treatments for all women and couples due to a lack of record keeping. It was therefore not possible to adjust for confounding by indication.

To our knowledge, this is the first Scandinavian study investigating obstetrical outcomes after DD compared with OD. In Denmark, around 1.000 oocyte donations are performed annually, and the number seems to be increasing. A potential limitation of this study is the relatively small sample size, which could lead to a lack of statistical power to detect significant differences in the outcome measures. However, with the legalization of DD in 2018, the data on obstetrical outcomes are still sparse, and our study equals the size of previous studies made on the subject. The treatments can have severe short- and long-term implications for the mother as well as the child. Therefore, it is crucial to register and evaluate all complications associated with the treatments we offer the patients.

CONCLUSION

This study does not find double gamete donation to be associated with a greater risk of developing obstetrical or neonatal complications compared to oocyte donation. However, given the small sample size in the study, it is important to acknowledge the possibility of a type 2 error occurring. As the usage of oocyte and double donation seems to be increasing, there is a need for larger prospective studies to evaluate the risk factors, which may be associated with these treatments, and perhaps gain more knowledge about the pathophysiological mechanisms involved in the development of preeclampsia.

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REFERENCES

1. Danmarks statistik: Gennemsnitsalder for fødende kvinder og nybagte fædre efter alder og tid. Gennemsnitsalder for førstegangsfødende kvinder og gennemsnitsalder for samtlige fødende kvinder fra 1960-2021. https://www.statistikbanken.dk/FOD11.

2. Blázquez, A., Vassena, R., Rodríguez, A., Figueras, F. & Vernaeve, V. Characteristics and clinical outcomes of patients undergoing fertility treatment by double gamete donation. Hum Fertil 19, 180–185 (2016).

3. Lutjen, P. et al. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. Nature 307, 174–175 (1984).

4. LOV nr 1688 af 26/12/2017: dobbeltdonation blev lovligt i Danmark. Loven trådte i kraft den 1. januar 2018. Preprint at https://www.retsinformation.dk/eli/lta/2017/1688.

5. Rizzello, F. et al. Comorbidities, risk factors and maternal/perinatal outcomes in oocyte donation pregnancies. Reprod Biomed Online 41, 309–315 (2020).

6. Storgaard, M. et al. Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis. BJOG 124, 561–572 (2017).

7. Berntsen, S., Larsen, E. C., la Cour Freiesleben, N. & Pinborg, A. Pregnancy outcomes following oocyte donation. Best Practice and Research: Clinical Obstetrics and Gynaecology vol. 70 81–91 Preprint at https://doi.org/10.1016/j.bpobgyn.2020.07.008 (2021).

8. Pohjonen, E.-M. et al. Obstetric and perinatal risks after the use of donor sperm: A systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology 274, 210–228 (2022).

9. Tenório, M. B. et al. Cross-Talk between Oxidative Stress and Inflammation in Preeclampsia. Oxid Med Cell Longev 2019, 1–26 (2019).

10. van Bentem, K. et al. The development of preeclampsia in oocyte donation pregnancies is related to the number of fetal-maternal HLA class II mismatches. J Reprod Immunol 137, 103074 (2020).

11. Burton, G. J., Redman, C. W., Roberts, J. M. & Moffett, A. Pre-eclampsia: pathophysiology and clinical implications. BMJ l2381 (2019) doi:10.1136/bmj.l2381.

12. Di Mascio, D., Saccone, G., Bellussi, F., Vitagliano, A. & Berghella, V. Type of paternal sperm exposure before pregnancy and the risk of preeclampsia: A systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology 251, 246–253 (2020).

13. Blazquez, A., García, D., Vassena, R., Figueras, F. & Rodriguez, A. Risk of preeclampsia in pregnancies resulting from double gamete donation and from oocyte donation alone. Pregnancy Hypertens 13, 133–137 (2018).

14. Preaubert, L. et al. Outcomes of pregnancies achieved by double gamete donation: A comparison with pregnancies obtained by oocyte donation alone. European Journal of Obstetrics and Gynecology and Reproductive Biology 222, 1–6 (2018).

15. Augusto, J. & Margarida Póvoa, A. Preeclampsia risk in oocyte donation versus double gamete donation pregnancies: A systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology 276, 219–227 (2022).

16. Rana, S., Lemoine, E., Granger, J. P. & Karumanchi, S. A. Preeclampsia. Circ Res 124, 1094–1112 (2019).

17. Khader, Y. S., Batieha, A., Al-njadat, R. A. & Hijazi, S. S. Preeclampsia in Jordan: incidence, risk factors, and its associated maternal and neonatal outcomes. The Journal of Maternal-Fetal & Neonatal Medicine 31, 770–776 (2018).

18. Busnelli, A., Schirripa, I., Fedele, F., Bulfoni, A. & Levi-Setti, P. E. Obstetric and perinatal outcomes following programmed compared to natural frozen-thawed embryo transfer cycles: a systematic review and meta-analysis. Human Reproduction 37, 1619–1641 (2022).

19. Pereira, M. M., Mainigi, M. & Strauss, J. F. Secretory products of the corpus luteum and preeclampsia. Hum Reprod Update 27, 651–672 (2021).

20. DSOG. Hypertension og præeklampsi. Obstetrisk Guideline. (2018).

21. Woudstra, D. M., Chandra, S., Hofmeyr, G. J. & Dowswell, T. Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy. Cochrane Database of Systematic Reviews (2010) doi:10.1002/14651858.CD008148.pub2.

22. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care 33, 676–682 (2010).

23. Blencowe, H. et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet 379, 2162–2172 (2012).

24. Savchev, S. et al. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound in Obstetrics & Gynecology 39, 299–303 (2012).

25. Apgar, V. The Newborn (APGAR) Scoring System: Reflections and Advice. Pediatr Clin North Am 13, 645–650 (1966).

26. DSOG Obstetriske guidelines. Intrapartal acidose – asfyksi 2010.

27. World Health Organization. The Surveillance of Risk Factors Report Series (SuRF). (2005).

28. Malchau, S. S. et al. Perinatal outcomes in 375 children born after oocyte donation: a Danish national cohort study. Fertil Steril 99, 1637-1643.e3 (2013).

29. Yang, Y. et al. Preeclampsia Prevalence, Risk Factors, and Pregnancy Outcomes in Sweden and China. JAMA Netw Open 4, e218401 (2021).

30. Gestationel diabetes mellitus: Screening og diagnose. DSOG obstetrisk guideline 2014.

31. Wiley. European perinatal health report 2019. (2019).

32. Maheshwari, A. et al. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? Hum Reprod Update 24, 35–58 (2018).

33. Wertheimer, A. et al. Frozen-thawed embryo transfer is an independent risk factor for third stage of labor complications. Arch Gynecol Obstet 304, 531–537 (2021).

34. Ginström Ernstad, E., Wennerholm, U.-B., Khatibi, A., Petzold, M. & Bergh, C. Neonatal and maternal outcome after frozen embryo transfer: Increased risks in programmed cycles. Am J Obstet Gynecol 221, 126.e1-126.e18 (2019).

35. von Versen-Höynck, F. et al. Increased Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum. Hypertension 73, 640–649 (2019).

36. Roberge, S., Bujold, E. & Nicolaides, K. H. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol 218, 287-293.e1 (2018).

37. Wright, D. et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol 218, 612.e1-612.e6 (2018).