ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Hypertensive pathologies and egg donation pregnancies: Results of a large comparative cohort study

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Objective: To determine whether egg donation (ED) pregnancies are at higher risk of pregnancy-induced hypertension (PIH) than those achieved by autologous assisted reproductive technology (ART; controls).
Design: Anonymous comparative observational matched cohort study.
Setting: Assisted reproductive technology centers.
Patient(s): Two hundred seventeen ED and 363 control singleton pregnancies matched at 7–8 weeks (pregnancy date, parity, cycle type [fresh/frozen] and women's age). According to French practice, all women were under 45.
Intervention(s): None.
Main Outcome Measure(s): Percentage of PIH for ED versus controls.
Result(s): The groups were comparable (mean age, 34.5). PIH was more frequent during ED pregnancies (17.8% vs. 5.3%), as was preeclampsia (11.2% vs. 2.8%) and eclampsia (1.8% vs. 0.0%). In multivariate analyses, PIH risk increased with ED (odds ratio [OR], 3.92; 95% confidence interval [CI], 1.93–7.97) and women's age (OR, 1.08; 95% CI, 1.00–1.16). No significant effect of previous pregnancies or cycle rank/type was observed.
Conclusion(s): This study had sufficient power to detect doubling of the PIH rate. It was demonstrated that the risk of PIH was tripled for ED versus controls. Even in young women, ED is a risk factor for PIH. An immunological explanation seems most likely, that is, the fetus is fully allogeneic to its mother. This risk must be acknowledged to inform couples and provide careful pregnancy monitoring. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Hypertensive pathologies, pregnancy induced hypertension, preeclampsia, eclampsia, egg donation

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Assisted reproductive technology (ART) with egg donation (ED) has become widely used since the first ED pregnancy reported in 1984 by Lutjen et al. (1). Initially reserved for couples in which the woman had premature ovarian failure or a genetic disease transmittable to her child with a risk of notable severity (2), its indications have been broadened, mostly extended to women with pathologically or physiologically (age-linked) ovarian status.

Consequently, ED management now concerns an increasing number of couples, with the number of ED cycles in Europe rising from 15,028 in 2007 to 30,198 in 2011, according to the European Society of Human Reproduction and Embryology Registry (3). At the same time, numerous publications reported the marked increase of certain pathologies, particularly hypertension and especially severe forms, during ED pregnancies compared with

Received January 12, 2016; revised March 4, 2016; accepted March 16, 2016.
H.L. has nothing to disclose. M.P. has nothing to disclose. J.O. has nothing to disclose. I.C.-D. has nothing to disclose. E.M.-D. has nothing to disclose. F.S. has nothing to disclose. V.G.-M. has nothing to disclose. J.d.M. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.03.031

the risks expected in the general population or during the course of intraconjugal assisted ART pregnancies (4–15).

However, most studies had interpretation difficulties: they often did not distinguish among "older" women whether their pregnancies were achieved with their own oocytes or through ED; or they did not analyze the role of some important confounders, such as women's age, nulliparity, multiple pregnancies, and ovarian failure (4, 6, 10, 14–16). Indeed, it is well known that the mother's older age is associated with a certain number of pathologies, for example, gestational diabetes and hypertension. Finally, most of those retrospective studies were small, had no control group or had a control group that was not matched, or did not consider the main confounders, such age, number of fetuses, and ART procedure (IVF or intracytoplasmic sperm injection [ICSI], "fresh" or cryopreserved and thawed ET, etc.) (7, 11, 16). Notably, several investigations taking the mother's age into account showed an enhanced risk of hypertensive disorders during ED pregnancies (7–9, 11, 13, 15), whereas others did not (16, 17). Taking these confounding factors into account, by incorporating a control group with intraconjugal autologous ART pregnancies matched for them, seems essential because infertility itself and ART could be sources of more high-risk pregnancies than natural conception (18).

Should more ED cycles and the increased risk of hypertension during their ensuing pregnancies be confirmed, they constitute a public health warning. Hence, our study on a large cohort was undertaken to verify, as the primary endpoint, whether ED pregnancies carry a higher risk of hypertensive disorders than intraconjugal (autologous) ART pregnancies.

MATERIALS AND METHODS

Patients and Controls

Seven French centers participated in this prospective and retrospective, anonymous observational cohort study conducted from February 2005 to September 2012.

The study group consisted of all ED singleton pregnancies (n = 217), diagnosed on first trimester (7–8 weeks of gestational age) ultrasound, in the participating centers. Multiple pregnancies were excluded because of their small number and increased associated pathological risks. Likewise, this study did not include pregnancies originating from EDs performed abroad, because most of them were not registered in a French ART center and the risk of bias could be high.

The control group was made up of singleton pregnancies achieved at the same center, diagnosed on first trimester ultrasound, and originating from ART (IVF or ICSI) with the couple's own oocytes, henceforth referred to as autologous (n = 363). For each ED pregnancy, the first two subsequent pregnancies obtained with the couples' gametes were retained as controls, with matching for mother's age (±1 year), parity (nulli- or multiparous), ET date, and whether the embryos were fresh or frozen/thawed.

Each center's coordinator consulted each woman's medical chart to collect data on demographics, medical/obstetrical history, ED indication, pregnancy-associated pathologies, delivery information, and health status of the newborn. This information was then entered anonymously on a designated form and transmitted to the study group.

Pregnancy-induced hypertension (PIH) occurring after 20 weeks of gestation was classified into three categories according to classical definitions: isolated gestational hypertension—blood pressure (BP) ≥140/90 mmHg at least twice, separated by more than 6 hours, and no proteinuria; preeclampsia—repeated BP readings of ≥140/90 mmHg, with proteinuria ≥0.3 g/day; and eclampsia—generalized seizures in a context of severe preeclampsia (repeated BP readings ≥160/110 mmHg, with proteinuria ≥3 g/day).

Statistical Analyses

The study was designed to demonstrate doubling of PIH frequency (from 10% to 20%), with 80% power and a 5% alpha risk with two controls per case. The numbers of required patients were 170 ED pregnancies and 340 controls. At the outset, the women's and cycle characteristics and pregnancy outcomes were compared between the two groups (217 ED and 363 controls). Then hypertensive disorders were analyzed after excluding miscarriages, abortions, ectopic pregnancies, intrauterine fetal deaths, and unknown outcomes (48 ED and 79 controls in total), and matching characteristics were reassessed.

Qualitative variables were compared with χ^2-tests, using a correction or Fisher's exact test for small numbers. Quantitative variables were compared with Student's *t*-test or analysis of variance, as appropriate. $P < .05$ was considered statistically significant. Then multivariate logistic regression models were used to analyze the risk of PIH taking into account the main confounders: women's age and body mass index (BMI), previous pregnancy, cycle rank, number of transferred embryos, pregnancy origin (frozen embryo replacements [FERs] or not). Odds ratios (OR) with their 95% confidence intervals (95% CIs) are given. Statistical analyses were computed using the SAS statistical package version 9.3. (SAS Institute).

Subjects' Approvals

According to French law, our study did not require a specific patient's approval since it was totally anonymous and noninterventional (observational). No personal identifying data (patient's surname or first name, identification number, address, birth date [only year was given], ED date [only month and year were given]) were transmitted from participating centers to the study group. There was no specific physical, biological, or verbal intervention. Only the information included in the anonymous files completed by the center coordinators was considered.

The study was approved by the French study group on egg donation scientific board and executive board, both acting as an Institutional Review Board.

RESULTS

The initial sample comprised 217 ED singleton pregnancies and 363 singleton pregnancies achieved by autologous ART