Archives of Gynecology and Obstetrics (2019) 300:861–867
https://doi.org/10.1007/s00404-019-05291-w

REVIEW

Higher rate of early-onset preeclampsia in pregnancies following oocyte donation according to increasing maternal age

Bianca Masturzo[1] · Daniela Di Martino[2] · Federico Prefumo[3] · Paolo Cavoretto[4] · Chiara Germano[1] · Gianluca Gennarelli[1] · Enrica Roletti[5] · Elisa Bottazzoli[6] · Federica Fusè[6] · Enrico Ferrazzi[2] · Danila Morano[7] · Antonio Farina[8]

Received: 22 May 2019 / Accepted: 3 September 2019 / Published online: 14 September 2019

Abstract

Objective To assess the influence of maternal age on the incidence of early-onset preeclampsia requiring delivery before 34 weeks of gestation in pregnancies obtained after oocyte donation.

Methods We carried out a prospective cohort analysis of 431 single and twin pregnancies, admitted to 3 Tertiary Referral Hospital in Northern Italy between 2008 and 2017. The rate of early-onset PE was calculated and stratified according to maternal age (from 30 to 49 years). A reference population of 11,197 single pregnancies collected prospectively at the first trimester of pregnancy in the same geographic area of Italy and in same hospitals was used to calculate the expected incidence of early-onset PE.

Results In women who delivered after 24 weeks of gestation, the rate of early-onset PE was much higher in oocyte-donation pregnancies, reaching 6.7% (29/431), than the expected rate of 0.5% of the cohort of reference. The mean early PE rate was 4.1% (10/242) in singletons and 10.1% (19/189) in twin pregnancies. According to maternal age, the rate of early PE was 1.16% and 3.12% at 30 years, and 4.98% and 13.14% at 49 years in single and twin pregnancies obtained after oocyte donation, respectively.

Conclusion Pregnancies obtained after oocyte donation delivering after 24 weeks had a higher risk of early-onset PE requiring delivery before 34 weeks of gestation, than the general population. The risk is directly correlated with the increase of maternal age and is also higher in twin pregnancies.

Keywords Oocyte-donor pregnancy · Early-onset preeclampsia · Maternal age-related risk · Binary logistic regression

Introduction

Since the first pregnancy obtained after oocyte donation (OD) in 1984, this practice has dramatically increased [1]. Latest ESHRE data confirm this trend, since they showed 40,244 OD pregnancies in Europe in 2013, with an increase of 19.75%

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00404-019-05291-w) contains supplementary material, which is available to authorized users.

✉ Antonio Farina
antonio.farina@unibo.it

[1] Department of Surgical Sciences, OIRM S. Anna Hospital, University of Turin, Turin, EU, Italy

[2] Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, EU, Italy

[3] Department of Obstetrics and Gynecology, University of Brescia, Brescia, EU, Italy

[4] Gynecology and Obstetrics Department, IRCCS San Raffaele Hospital, Vita-Salute University, Milan, EU, Italy

[5] Gynecology and Obstetrics Department, Maggiore University Hospital, Parma, EU, Italy

[6] Department of Woman, Mother and Neonate, Buzzi Children's Hospital, University of Milan, Milan, Eu, Italy

[7] Department of Obstetrics and Gynecology, Sant'Anna University Hospital, Cona, Ferrara, EU, Italy

[8] Division of Obstetrics and Prenatal Medicine, Department of Medicine and Surgery (DIMEC) Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, EU, Italy

compared to 2012, while in 2012, OD pregnancy rate estimated at around 33,605, increased of 55,54% compared to 2009 (21,604) [2–4].

Indications for OD extended from premature ovarian failure to reduced ovarian reserve, infertility due to malignant disease, previous failed attempts of assisted reproductive technology (ART), transmittable genetic abnormalities and advanced maternal age [5]. As OD procedure has become more common, the impact of OD on potential obstetric risks raised a growing interest.

Increased risks for many pregnancy complications have been observed in association with OD, including pregnancy-induced hypertension and preeclampsia (PE), when compared with both spontaneous pregnancies and pregnancies achieved by in vitro fertilization (IVF) with autologous oocytes [6]. Also, a much higher rate of cesarean section has been observed in OD pregnancies as reported by Ohel and Sheiner [7]. The reason of a higher risk of PE has been attributed to a potential role of the embryo obtained by OD [8]. Some Authors supposed that OD pregnancies require a more intense down-regulation of the maternal alloimmune response, since decidua invasion by trophoblastic cells, expressing fetal HLA-C, is less recognizable for mother's immunological system [9]. In fact, decidua in pregnancies obtained by OD is completely allogeneic and not partially maternal, as reviewed by van der Hoorn et al. in 2010 [10]. Aberrant HLA-C allogenicity can lead to an altered functionality of uterine natural killer cells (uNK), a cofactor, together with trophoblast, in the regulation of decidual neovascularization. The consequent abnormal maternal blood supply to the placenta, facilitates disorders such as PE and fetal growth restriction being the aetiology of PE related to a state of abnormal low tolerance to foreign antigens [11–14]. However, it must be noticed that a recent work showed that increased uterine pulsatility is uncommon in OD pregnancies, with a tendency towards lower pulsatility indexes [15].

Moreover, pregnancies obtained by OD are more common in advanced maternal age, a risk factor for hypertensive disorders.

The main aim of the study was to investigate the rate of early PE (requiring delivery before 34-week gestation), stratified according to maternal age, in a cohort of pregnancies obtained by OD. Furthermore, the study evaluated the impact of twin gestation on early PE occurrence stratified for maternal ages. The rate of early PE obtained from a large database collected prospectively of 11,197 singleton pregnancies representative of the Northern Italy was used as reference [16].

Materials and methods

The study was conducted following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement recommendations. We conducted a prospective cohort study of non-consecutive patients, including 431 pregnant women, who conceived through OD and who received prenatal care until delivery at the Departments of Obstetrics and Gynecology of 3 tertiary Referral Hospitals located in Northern Italy (Sant'Anna University Hospital in Turin, Buzzi Hospital in Milan and Spedali Civili in Brescia) between January 2008 and December 2017. All procedures of OD had been performed abroad, because the Italian law did not allow ART with donated gametes at the time of the study development.

All data were obtained from the hospital records. All data were obtained from the hospital records, after Institutional Ethics Committee approval (no 335; protocol 11,551/c28.2; 4/3/2011). Moreover, all patients, during the admission at the hospital, signed a written informed consent allowing their data to be collected and used for statistical purposes. We ensure the quality and integrity of our research and we respected the confidentiality and anonymity of our research respondents.

The eligibility criteria were: maternal age > 18 years, live fetus at 11–13 weeks of gestation and subsequently delivering a phenotypically normal live birth or stillbirth at > 24 weeks of gestation.

We selected participants with a complete available follow-up of the pregnancy (stored in Viewpoint electronic database, GE Healthcare Italia). The exclusion criteria were: lack of follow-up recorded in the electronic database, fetal congenital anomalies and pregnancies resulting in miscarriage or fetal death before 24-week gestation.

We also excluded triplet as a pathologic state per se and, also, because transfer of multiple embryos in OD programs is not common, making this event unlikely to represent a relevant issue in the future.

The early PE rate of pregnancies obtained by OD was compared with early PE rate of 11,197 spontaneous singleton pregnancies examined in the same hospitals. This large dataset was used to estimate a representative risk of early PE in Northern Italian population. Same criteria of inclusion and exclusion were adopted in reference group.

PE was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg occurred on at least two occasions 4 h apart, developed after 20 weeks of gestation in previously normotensive women. There should also be proteinuria ≥ 300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24 h collection was available. PE superimposed on chronic hypertension was defined as significant proteinuria, developing after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at booking before 20 weeks of gestation without trophoblastic disease) [17].

Power analysis

A power analysis was carried out using Power Analysis Sample Size (PASS) software (Kaysville, UT, USA). We calculated that, using a binary logistic regression on a dichotomous independent variable (spontaneous pregnancies vs. pregnancies obtained by OD), we would need 8974 cases drawn for the population to achieve 80% power at a 5% significance level to detect a change in the rate of early PE from the expected value of 0.5% to 5%. In sample size calculation, an adjustment was made assuming a McFadden coefficient of determination (R^2) < 0.15 obtained in a regression of the independent variable of interest (pregnancies by OD) on the other independent variables in the logistic regression (including maternal age, parity, BMI, family history of PE, chronic hypertension, known congenital thrombophilia, history of SLE or APLS autoimmune disease, type I and II diabetes).

Statistical analysis

The Student's *t* test and χ^2 test were carried out to make univariable comparisons of quantitative and qualitative variables, respectively, between subgroups.

Binary logistic regression was used to calculate the rate of early-onset PE stratified according to maternal age, number of fetuses (one or two) and adjusted for BMI. Further potential predictors were also examined in the statistical model. IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY, USA) IBM Corp. was used for all analyses.

Results

Between January 2008 and December 2017, 431 Caucasian women who had reported conception using donor oocyte (OD cohort) met the criteria of inclusion of the present study; 242 (56.1%) were singletons, whereas 189 (43.9%) were twin pregnancies.

Table 1 reports the demographic and clinical variables available for the cohort of pregnancies obtained by OD and for the cohort of pregnancies enrolled as reference group. As expected, the populations are not homogenous regarding maternal age, BMI, rate of nulliparae, rate of known congenital thrombophilia, family history of PE, history of chronic hypertension, history of SLE or APLS autoimmune disease and history of type 1 or 2 diabetes mellitus. History of type 1 or 2 diabetes mellitus was the only risk factor for PE that resulted higher in the reference cohort.

The unadjusted rate of early PE requiring delivery < 34 weeks was much higher in OD pregnancies, reaching 6.7% (29/431), than the expected rate of 0.5% of the reference cohort.

Table 1 Descriptive and clinical variables for the pregnancies obtained after oocyte donation and in the cohort of spontaneous pregnancies

	Pregnancies obtained after oocyte donation			Spontaneous pregnancies			
	Total (n = 431)	Early PE (n = 29)	No early PE (n = 402)	Total (n = 11,197)	Early PE (n = 54)	No early PE (n = 11,143)	P value[a]
Age (years)	43 ± 4.14	42 ± 4.14	44 ± 3.62	32.3 ± 4.62	34.5 ± 4.15	32.3 ± 4.62	< 0.001
BMI (Kg/m^2)	24.77 ± 3.9	26.11 ± 3.6	24.67 ± 3.94	22.66 ± 3.98	22.66 ± 3.98	23.74 ± 3.51	< 0.001
Nulliparous (%)	89.3	86.2	89.6	65.1	53.7	65.2	< 0.001
Gestational age at delivery (weeks)	36.5 ± 3.66	31.5 ± 3.10	36.2 ± 3.46	38.6 ± 2.67	31.4 ± 2.03	38.6 ± 2.62	< 0.001
Known congenital thrombophilia (%)	4.6	6.9	4.5	2.1	1.9	2.1	0.003
Family history of PE (%)	7.4	10.3	7.2	3.6	3.7	3.6	< 0.001
History of chronic hypertension (%)	3.2	6.9	3.0	0.7	13	0.7	< 0.001
History of SLE or APLS autoimmune disease (%)	1.1	1.2	0	0.3	1.9	0.3	0.069
History of type 1 or 2 diabetes mellitus (%)	0.5	3.4	0.2	3.3	14.8	3.3	< 0.001

SLE systemic lupus erythematosus

APSL antiphospholipid syndrome

[a]Student's *t* test or χ^2. Comparisons performed on the total cases (431 vs. 11,197)

In the final logistic regression model, we entered only significant covariates including maternal age, twin pregnancy, chronic hypertension and type 1 or 2 diabetes mellitus. The associated McFadden R^2 was 0.11 in line with the hypothesis of the sample size calculation.

Table 2 reports risks of early PE and relative 95% confidence intervals (95%CI) in the reference and OD groups, the latter according also to a single or a twin pregnancy. The risks are adjusted for the effect of significant covariates. As shown, data were truncated to include data between 30 and 49 years, representing maternal age range available for both the cohorts. The maternal age, in fact, ranged between 18 and 49 in the cohort of spontaneous pregnancies and from 30 to 54 in the cohort of pregnancies obtained after OD. According to maternal age, the adjusted rate of early PE in the reference group at 30 years was 0.30%, while it was 1.16% and 3.12% at the same age in singleton and twin pregnancies obtained by OD, respectively. The risk of PE, at 49 years, in the reference cohort was 1.40%, and 4.98% and 13.14% in singleton and twin OD pregnancies, respectively. The addition of chronic hypertension would increase the risk of early PE, as average, approximately of nine-, 7.5- and fivefold, respectively, in normal pregnancies, single OD pregnancies and twin OD pregnancies. Likewise, type 1 or 2 diabetes mellitus would increase the risk of early PE of five-, four- and threefold in the 3 groups (see Table 1S).

Figure 1 reports the risks of early PE according to maternal age in single and twin pregnancies obtained by OD and in the reference cohort. As shown, in both the groups, there is a rise of the risk of early PE with increasing maternal age. The risk trajectories are not parallel and, in twin pregnancies, a higher risk of early PE at paired maternal ages can be observed.

Discussion

This was the first Italian study which evaluated the rate of early PE (requiring delivery < 34 weeks) stratified for maternal age, in a population of single and twin pregnancies obtained by OD and it gave a strong comparison with a reference population representative of the Northern Italy.

Table 2 Risk of early PE requiring delivery < 34 weeks of gestation according to the type of pregnancy. Values were adjusted for chronic hypertension and history of type 1 or 2 diabetes mellitus

Maternal age (years)	Reference cohort			Pregnancy obtained by oocyte donation (single)			Pregnancy obtained by oocyte donation (twin)		
	Lower 95% bound	Mean risk	Higher 95% bound	Lower 95% bound	Mean risk	Higher 95% bound	Lower 95% bound	Mean risk	Higher 95% bound
30	0.21	**0.30**	0.43	0.44	**1.16**	2.86	1.36	**3.12**	6.96
31	0.23	**0.33**	0.46	0.47	**1.19**	2.99	1.40	**3.50**	7.28
32	0.26	**0.35**	0.49	0.53	**1.29**	3.13	1.73	**3.65**	7.52
33	0.28	**0.38**	0.52	0.59	**1.40**	3.27	1.95	**3.95**	7.83
34	0.31	**0.42**	0.56	0.66	**1.52**	3.44	2.18	**4.27**	8.17
35	0.34	**0.45**	0.61	0.74	**1.65**	3.61	2.44	**4.61**	8.53
36	0.36	**0.49**	0.67	0.83	**1.78**	3.80	2.73	**4.98**	8.93
37	0.38	**0.53**	0.74	0.92	**1.93**	4.02	3.04	**5.38**	9.36
38	0.40	**0.58**	0.82	1.02	**2.09**	4.25	3.37	**5.81**	9.84
39	0.43	**0.63**	0.92	1.13	**2.27**	4.51	3.73	**6.28**	10.38
40	0.45	**0.68**	1.02	1.24	**2.45**	4.79	4.11	**6.77**	10.97
41	0.47	**0.73**	1.15	1.36	**2.66**	5.11	4.50	**7.31**	11.64
42	0.48	**0.79**	1.29	1.49	**2.88**	5.47	4.91	**7.88**	12.40
43	0.50	**0.85**	1.45	1.63	**3.11**	5.87	5.34	**8.49**	13.25
44	0.53	**0.93**	1.65	1.77	**3.37**	6.33	5.76	**9.15**	14.22
45	0.55	**1.01**	1.88	1.91	**3.64**	6.84	6.19	**9.85**	15.30
46	0.57	**1.11**	2.18	2.06	**3.94**	7.41	6.62	**10.59**	16.53
47	0.59	**1.20**	2.44	2.21	**4.26**	8.05	7.05	**11.39**	17.89
48	0.61	**1.29**	2.73	2.37	**4.61**	8.78	7.47	**12.24**	19.41
49	0.63	**1.40**	3.09	2.52	**4.98**	9.59	7.89	**13.14**	21.09
Untruncated mean risk	0.27	**0.39**	0.56	1.72	**3.36**	6.45	5.25	**8.57**	13.68

Risks are expressed as percent. Risks were truncated so to include only age between 30 and 49 years. Untruncated mean risks were calculated from 18 to 49 years for the spontaneous pregnancies and from 30 to 54 years for the pregnancies obtained after oocyte donation

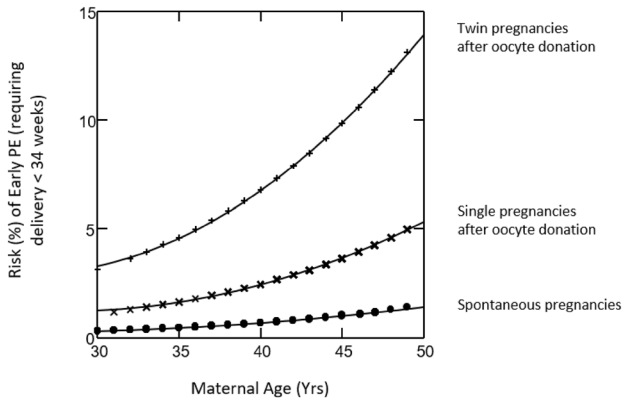

Fig. 1 Adjusted risk (%) for early PE requiring delivery < 34 weeks in the reference pregnancy cohort (filled circle) and in cohort of pregnancies obtained after oocyte donation (x = single, + twin) from 30 to 49 years

According to the previous literature, we observed that the rate of early PE was higher than the expected for the general population with an average of almost tenfold. We also found that in pregnancies obtained by OD, at increasing maternal ages, the risk of early PE rises with a divergent trajectory. Moreover, the number of fetuses affects the risk of early PE, with a 20-fold greater rate in twin pregnancies.

Even if many papers found quite similar results, no data seem to exist in the medical literature about the multivariable quantification of the risk of early PE associated with pregnancies obtained by OD. This kind of analysis is the most indicated in this case, since etiological relationship between pregnancies obtained by OD and PE is multifactorial. At least, three major risk factors are simultaneously present, including advanced maternal age, IVF and completely HLA-C allogenicity of the fetus to the mother. Recently, a systematic review by Giannakou et al. 2018, concluded that OD itself can act as an extra-independent risk factor for the development of PE with an associated odds ratio (OR) of 4.33 when compared with spontaneous conception [16]. To confirm the strength of this finding, same results (OR 4.34 and 4.50) were reported, independently, also by Masoudian et al. 2016 and Schwarze et al. 2018, respectively [18, 19].

Regardless of how the pregnancy was obtained, PE is more common in women with advanced maternal age [20–25]. Maternal age is also considered a major risk factor responsible of variations in PE prevalence among Countries [26]. The PE risk is directly correlated with increasing maternal age and several studies consider 40 years of age as an outstanding cut-off to define higher risk women [20].

In a Finnish study by Lamminpää et al., women over 35 years revealed a 9.4% of PE risk compared to 6.4% of younger women [23]. Ben-David et al. found, among primiparae at very advanced maternal age (>45 years), a rate of PE 2.45-fold higher than primiparae aged 30–35 [27]. In a recent study by Kahveci et al., where a more detailed age stratification has been performed, in women over 40 years, the PE incidence was 9.2%, while between 35 and 39, a 7.7% was quoted; instead, in women under 35 years, a 4.6% was estimated [28].

In a Japanese study, by Ogawa et al. conducted on a mixed population of spontaneous (80%) and assisted conception (20%) in pregnancies with very advanced maternal age (>45), a 1.86 relative risk (RR) of PE was calculated in comparison with women of 30–34 years [24]. Besides, RR for severe PE in the advanced age group was even higher (2.03), showing a more specific higher effect of maternal age on severe PE forms. Similar results were also reported by Jacobsson et al. with a 1.86 OR for severe PE in women > 45 years [22]. Furthermore, maternal age is also considered a major risk factor responsible for variations in PE prevalence among Countries [26].

A higher rate of PE in pregnancies obtained by OD is widely accepted. According to Blázquez et al., the overall prevalence of PE in pregnancies obtained by OD was 17.2%, ranging from 9 to 29% [29]. Similar data were also reported in the literature where the rate of PE ranged from 9.3 to 24% [8, 9, 13, 30–33]. In Preaubert et al., a PE rate of 18% was achieved regardless pregnancy was obtained by double gamete donations or one-oocyte donations [30].

Twin pregnancy is a risk factor for PE. According to recent reviews, the rate of PE is significantly increased among spontaneous twins compared to singletons with an overall rate of 9.5% and an associated OR of 3.00 when compared to singletons [34, 35]. In fact, PE develops earlier in twin pregnancies with an increased severity [34, 36]. In 5 studies, based on 24–77 twin pregnancies obtained by OD, the overall rate of PE was 35.2% [8, 13, 31, 33, 37]. Therefore, the associated OR of PE in twin pregnancies obtained by OD could be estimated as about 10. It is quite interesting that we obtained a very similar result even if we considered only early PE cases.

Despite the early PE is associated with a higher fetal neonatal and maternal morbidity, few studies evaluated the rate of early PE < 34 weeks at delivery. Blázquez et al. reported a 3.4% of early PE risk in pregnancies obtained by OD [29]. The same authors, in a wider dataset, described a rate of 4.9% of early PE including the 58.3% of the forms of PE, showing a very unbalanced ratio between early and late PE, with early PE the 50% of all PE forms [38]. In fact, in general population, the expected percentage of early PE < 34 weeks is 14% of all the PE forms [39].

In conclusion, it is quite evident that maternal age, allogenic embryo-transfer and twin pregnancies are three important risk factors that must be considered simultaneously in the management of pregnancies obtained by OD. Until now, specific risks according to all these factors together had never been calculated and no proper stratification for

maternal age seems to be ever performed. Risk analysis, designed in this way, could have an important clinical impact for the management of these pregnancies.

Limitations of the study

Our study had certainly some limitations. No data about the ovulatory status of recipient women were available. In particular, we were not able to know how many patients suffered from premature ovarian failure as a possible extra risk factor for PE [40].

Since all OD treatments had been performed abroad, data on the ART procedure and on donor characteristics were not available. Also, in the reference population, we had very few cases of advanced maternal age (>46 years), therefore, the risk estimation afterwards could not be properly assessed. Moreover, no twin pregnancies were available in reference group and possible differences in the PE risk in spontaneous twin pregnancies vs. twin pregnancies obtained by OD can not be evaluated.

Strengths of the study

This is the first study that calculates the risk of early PE requiring delivery < 34 weeks stratified for maternal age and single or twin pregnancy in a population of OD pregnancies and evaluates the power of the results by a sample size analysis.

Conclusions

In pregnancies obtained by OD, several risk factors occur at the same time, including increasing maternal age, fully allogenic embryo transfer and twin gestation. We provided, for the first time, simultaneous evaluation of all these factors in the management of OD pregnancies. Our results could be used for a better clinical management of pregnancies obtained by OD.

Author contributions BM: protocol/project development, data collection, manuscript writing. DDM: protocol/project development. FP: data collection. PC: data collection. CG: protocol/project development, data collection, manuscript writing. GG: Protocol/project development, data collection. ER: protocol/project development, data collection. EB: data collection. FF: data collection. EF: protocol/project development. DM: protocol/project development, manuscript writing. AF: protocol/project development, data collection, manuscript writing, data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The committee for this study is Professor Antonio Farina.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Bustillo M, Buster JE, Cohen SW, Hamilton F, Thorneycroft IH, Simon JA et al (1984) Delivery of a healthy infant following non-surgical ovum transfer. JAMA 251:889
2. European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction, and Embryology (ESHRE), Calhaz-Jorge C, de Geyter C, Kupka MS, de Mouzon J, Erb K, Mocanu E, Motrenko T, Scaravelli G, Wyns C, Goossens V (2017) Assisted reproductive technology in Europe 2013: results generated from European registers by ESHRE. Hum Reprod 2017(32):1957–1973
3. European IVF-Monitoring Consortium (EIM) for the European Society of Human Reproduction, and Embryology (ESHRE), Calhaz-Jorge C, de Geyter C, Kupka MS, de Mouzon J, Erb K, Mocanu E, Motrenko T, Scaravelli G, Wyns C, Goossens V (2016) Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. Hum Reprod 2016(31):1638–1652
4. Ferraretti AP, Goossens V, Kupka M, Bhattacharya S, de Mouzon J, Castilla JA, et al. (2013) European IVF-Monitoring (EIM) Consortium for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. Hum Reprod 28:2318–2331.
5. Sauer MV, Kavic SM (2006) Oocyte and embryo donation 2006: reviewing two decades of innovation and controversy. Reprod Biomed Online 12:153–162
6. Letur H, Peigné M, Ohl J, Cédrin-Durnerin I, Mathieu-D'Argent E, Scheffler F et al (2016) Hypertensive pathologies and egg donation pregnancies: Results of a large comparative cohort study. Fertil Steril 106:284–290
7. Ohel I, Sheiner E (2009) Does oocyte donation equal cesarean delivery? J Matern Fetal Neonatal Med 22(9):776–779
8. Klatsky PC, Delaney SS, Caughey AB, Tran ND, Schattman GL, Rosenwaks Z (2010) The role of embryonic origin in preeclampsia: a comparison of autologous in vitro fertilization and ovum donor pregnancies. Obstet Gynecol 116:1387–1392
9. Levron Y, Dviri M, Segol I, Yerushalmi GM, Hourvitz A, Orvieto R et al (2014) The 'immunologic theory' of preeclampsia revisited: a lesson from donor oocyte gestations. Am J Obstet Gynecol 211(383):e381–385
10. van der Hoorn ML, Lashley EE, Bianchi DW, Claas FH, Schonkeren CM, Scherjon SA (2010) Clinical and immunologic aspects of egg donation pregnancies: a systematic review. Hum Reprod Update 16:704–712
11. Madeja Z, Yadi H, Apps R, Boulenouar S, Roper SJ, Gardner L et al (2011) PaternalMHC expression onmouse trophoblast affects uterine vascularization and fetal growth. Proc Natl Acad Sci U S A 108:4012–4017
12. Hiby SE, Walker JJ, O'Shaughnessy KM, Redman CW, Carrington M, Trowsdale J et al (2004) Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. J Exp Med 200:957–965

13. Le Ray C, Scherier S, Anselem O, Marszalek A, Tsatsaris V, Cabrol D et al (2012) Association between oocyte donation and maternal and perinatal outcomes in women aged 43 years or older. Hum Reprod 27:896–901
14. Redman CW, Sargent IL (2010) Immunology of pre-eclampsia. Am J Reprod Immunol 63:534–543
15. Inversetti A, Mandia L, Candiani M, Cetin I, Larcher A, Savasi V et al (2018) Uterine artery Doppler pulsatility index at 11–38 weeks in ICSI pregnancies with egg donation. J Perinat Med 46:21–27
16. Di Martino D, Masturzo B, Paracchini S et al (2019) Comparison of two "a priori" risk assessment algorithms for preeclampsia in Italy: a prospective multicenter study. Arch Gynecol Obstet 299(6):1587–1596
17. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM (2001) The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 20:IX–XIV
18. Masoudian P, Nasr A, de Nanassy J, Fung-Kee-Fung K, Bainbridge SA, El Demellawy D (2016) Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis. Am J Obstet Gynecol 214:328–339
19. Schwarze JE, Borda P, Vásquez P, Ortega C, Villa S, Crosby JA et al (2018) Is the risk of preeclampsia higher in donor oocyte pregnancies? A systematic review and meta-analysis. JBRA Assist Reprod 22:15–19
20. Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 330:565 **(Epub 2005 Mar 2)**
21. Ortiz C, Rondeau NU, Moore LE, Mulla ZD (2018) Parental age and the risk of gestational hypertension and preeclampsia. South Med J 111:544–548
22. Jacobsson B (2004) Advanced maternal age and adverse perinatal outcome. Obstet Gynecol 104:727–733
23. Lamminpää R, Vehviläinen-Julkunen K, Gissler M, Heinonen S (2012) Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997–2008. BMC Pregnancy Childbirth 47:1–5
24. Ogawa K, Urayama KY, Tanigaki S, Sago H, Sato S, Saito S et al (2017) Association between very advanced maternal age and adverse pregnancy outcomes: a cross sectional Japanese study. BMC Pregnancy Childbirth 17:349
25. Ananth CV, Keyes KM, Wapner RJ (2013) Pre-eclampsia rates in the United States, 1980–2010: age-period-cohort analysis. BMJ 347:f6564
26. Hutcheon JA, Lisonkova S, Joseph KS (2011) Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol 25:391–403
27. Ben-David A, Glasser S, Schiff E, Zahav AS, Boyko V, Lerner-Geva L (2016) Pregnancy and birth outcomes among primiparae at very advanced maternal age: at what price? Matern Child Health J 20:833–842
28. Kahveci B, Melekoglu R, Evruke IC, Cetin C (2018) The effect of advanced maternal age on perinatal outcomes in nulliparous singleton pregnancies. BMC Pregnancy Childbirth 18:343
29. Blázquez A, García D, Rodríguez A, Vassena R, Figueras F, Vernaeve V (2016) Is oocyte donation a risk factor for preeclampsia? A systematic review and meta-analysis. J Assist Reprod Genet 33:855–863
30. Preaubert L, Vincent-Rohfritsch A, Santulli P, Gayet V, Goffinet F, Le Ray C (2018) Outcomes of pregnancies achieved by double gamete donation: A comparison with pregnancies obtained by oocyte donation alone. Eur J Obstet Gynecol Reprod Biol 222:1–6
31. Stoop D, Baumgarten M, Haentjens P, Polyzos NP, De Vos M, Verheyen G et al (2012) Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis. Reprod Biol Endocrinol 10:42
32. Boria F, de la Calle M, Cuerva M, Sainz A, Bartha JL (2018) Impact of oocyte donation on obstetric and perinatal complications in twin pregnancies. J Matern Fetal Neonatal Med 21:1–4
33. Van Dorp W, Rietveld AM, Laven JS, van den Heuvel-Eibrink MM, Hukkelhoven CW, Schipper I (2014) Pregnancy outcome of non-anonymous oocyte donation: a case-control study. Eur J Obstet Gynecol Reprod Biol 182:107–112
34. Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides K (2017) Hidden high rate of preeclampsia in twin compared to singleton pregnancies. Ultrasound Obstet Gynecol 50:88–92
35. Krotz S, Fajardo J, Ghandi S, Patel A, Keith LG (2002) Hypertensive disease in twin pregnancies: a review. Twin Res 5:8–14
36. Suzuki S, Igarashi M (2009) Risk factors for preeclampsia in Japanese twin pregnancies: comparison with those in singleton pregnancies. Arch Gynecol Obstet 280:389–393
37. Sekhon LH, Gerber RS, Rebarber A, Saltzman DH, Klauser CK, Gupta S et al (2014) Effect of oocyte donation on pregnancy outcomes in in vitro fertilization twin gestations. Fertil Steril 101:1326–1330
38. Blazquez A, García D, Vassena R, Figueras F, Rodriguez A (2018) Risk of pre-eclampsia after fresh or frozen embryo transfer in patients undergoing oocyte donation. Eur J Obstet Gynecol Reprod Biol 227:27–31
39. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH (2015) Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol 213(62):e1–10
40. Pados G, Camus M, Van Steirteghem A, Bonduelle M, Devroey P (1994) The evolution and outcome of pregnancies from oocyte donation. Hum Reprod 1994(9):538–542