Archives of Gynecology and Obstetrics (2018) 297:1293–1299
https://doi.org/10.1007/s00404-017-4616-1

Increased incidence of preeclampsia in mothers of advanced age conceiving by oocyte donation

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Received: 18 September 2017 / Accepted: 1 December 2017 / Published online: 12 February 2018

Abstract

Purpose The aim of this study was to evaluate the risk of preeclampsia in women of advanced age who conceived through donated oocytes as compared with natural conceptions.

Methods A historical prospective study of singleton live births of parturients ≥ 45 years of age at four university hospitals was conducted. For the purpose of the study, the population was divided by the mode of conception into two groups: oocyte donation and natural conception. The main outcome variable in this study was preeclampsia. Secondary outcomes included pregnancy-induced hypertension and Small for Gestational Age.

Results Two hundred and seventy pregnancies were achieved naturally and 135 women conceived by oocyte donation. Mean age at delivery for the natural conception and oocyte donation groups was 45.7 and 47.8, respectively. Preeclampsia complicated 3 out of 270 (1.1%) natural conception pregnancies and 17 out of 135 (12.6%) oocyte donation conceptions. After adjusting for confounders, oocyte donation pregnancies were found to be associated with a 12-fold increased risk for preeclampsia ($P = 0.001$). Among oocyte donation pregnancies, the risk of preeclampsia was not affected by parity or age.

Conclusions A substantially increased risk for preeclampsia was found in oocyte donation pregnancies, suggesting that the foreign oocyte may play a specific biologic role in the development of preeclampsia after the age of 45.

Keywords Preeclampsia · Assisted reproductive technology · Oocyte donation · Hypertension in pregnancy · High-risk pregnancy

Introduction

Preeclampsia, occurring in 2–8% of pregnancies, is associated with severe adverse maternal and neonatal outcomes. Among others, preeclampsia is associated with maternal multi-organ failure [1–3], progression to eclampsia, a life-threatening event [4], intra-uterine growth restriction [5], and preterm deliveries [6]. Rising evidence further associates preeclampsia with future maternal and offspring health. Epidemiologic studies have shown a possible association between preeclampsia and long-term maternal mortality, subsequent risk of cancer [7] and metabolic morbidity [8], as well as with increased risk of morbidity and mortality for the adult offspring [9, 10]. Despite years of research invested in the study of preeclampsia and many theories that have been proposed, there is still poor understanding of the etiology; thus, efforts have been directed towards identification of populations at risk and towards studying various prophylactic measures.

Prophylactic use of low-dose aspirin is currently being investigated as a promising treatment for prevention of preeclampsia. A recent meta-analysis including five randomized controlled trials concluded that low-dose aspirin administrated at or before 16 weeks of gestation reduces mainly the risk of early preeclampsia [11]. This potential preventive treatment reinforces the importance of

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identifying specific groups that are at risk for development of preeclampsia.

Oocyte donation (OD), originally offered to women with premature ovarian failure, has now become an integral part of assisted reproductive care. Donated oocytes are currently used by women with many reproductive disorders and commonly by women in later reproductive years [12]. Over the age of 45, OD is the most applicable option for a woman desiring to achieve motherhood. Since women in this age group are at an increased risk of hypertensive complications during pregnancy [13, 14], we aimed to evaluate the risk of preeclampsia in singleton pregnancies achieved by OD as compared to natural pregnancies after the age of 45.

Materials and methods

A historical prospective study of singleton live births of parturients ≥ 45 years of age at four major hospitals in Jerusalem, Israel was conducted. For the purpose of the study, the population was divided by the mode of conception into two groups: OD and natural conception. A comparison ratio of 1:2 was used between the study group and the control group. Women who conceived by in-vitro fertilization (IVF) without OD (i.e., autologous treatment) were excluded from the study. Data were collected during the years 1995–2012. The oocyte donors ranged in age from 19 to 33 years. All donors were examined by a physician and were proven to be generally healthy, and with no ongoing medical treatment or disability.

Data on demographic and obstetric characteristics, as well as neonatal data, were retrieved from the delivery room management software. Data concerning fertility treatments were further confirmed through the infertility outpatient clinic of each participating hospital. The study protocol was approved on January 1st 2013 by the institutional review board, approval number 0064-13-HMO.

Clinical characteristics that were collected and analyzed included maternal age, gravidity and parity, mode of conception, antepartum course, and neonatal weight.

The main outcome variable in this study was preeclampsia. The main exposure variable was oocyte donation pregnancies. Secondary outcomes included pregnancy-induced hypertension and Small for Gestational Age (SGA).

Diagnosis of preeclampsia and pregnancy-induced hypertension was made according to the criteria of the International Society for the Study of Hypertension in Pregnancy [15]. Pregnancy-induced hypertension was defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions, 4 h apart, developing after 20 weeks' gestation in previously normotensive women in the absence of proteinuria. Preeclampsia was defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg with proteinuria of ≥ 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. Birth weight percentiles were determined from the gender-specific charts of Poon et al. [16] and SGA was defined as a birth weight < 10th percentile.

Statistical analysis

Women who received OD and delivered were compared to those who conceived naturally. Univariate comparisons used the *t* test or the χ^2 test, as appropriate. Multivariate logistic regression models were performed to examine the association between the use of OD and preeclampsia, pregnancy-induced hypertension, and SGA, controlling for possible confounders: maternal age and parity. A P value < 0.05 was considered statistically significant. We report odds ratios (OR), 95% confidence interval, and two-sided P values. The statistical software package SPSS 23.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

Results

During the study period, 135 women ≥ 45 years of age conceived by OD and carried and delivered a singleton pregnancy. As mentioned earlier, a 1:2 comparison ratio was used to compare these conceptions to randomly chosen 270 women who conceived spontaneously during this period and had their most recent delivery after the age of 45 years.

Data on demographic and obstetric characteristics, as well as information regarding background diseases, are presented in Table 1. The mean maternal age of oocyte recipients was 2 years older than natural conception controls ($P < 0.01$). Mean gravidity and parity for the OD and natural conception groups were 2.6 vs. 11.1 and 0.5 vs. 8.2, respectively. Whereas only three of the women in the natural conceptions group were nulliparous, 68.9% of women in the OD group were nulliparous. OD conceptions were more likely to have gestational diabetes mellitus than natural conceptions. There was no significant difference between the groups in rates of chronic hypertension.

Three out of 270 (1.1%) naturally conceived pregnancies and 17 out of 135 (12.6%) OD pregnancies were complicated with preeclampsia. After controlling for parity and age at delivery, OD pregnancies were found to be associated with a 12-fold increased risk for preeclampsia (95% CI 2.69–52.73, $P < 0.001$) (Table 2). Controlling also for chronic hypertension did not change the results. Since primiparity is associated with an increased risk of preeclampsia by itself, we performed an additional risk analysis within the group of the OD pregnancies, comparing between primiparous and

Table 1 Maternal demographic characteristics of study population

	Oocyte donation ($n = 135$)	Spontaneous conception ($n = 270$)	P value
Maternal age [years, mean ± SD, (range)]	47.8 ± 2.6 (45–58)	45.7 ± 0.94 (45–49)	< 0.01
Gravidity [mean ± SD, (range)]	2.6 ± 1.7 (1–10)	11.1 ± 4.5 (2–26)	< 0.01
Parity[a] [mean ± SD, (range)]	0.5 ± 1.0 (0–8)	8.2 ± 4.0 (1–20)	< 0.01
Chronic hypertension (*N*, %)	11, 8.1%	15, 5.6%	0.21
Gestational diabetes mellitus (*N*, %)	22, 16.3%	26, 9.6%	0.04

N number, *SD* standard deviation

[a]Not including current pregnancy

Table 2 Study outcomes by mode of conception

	Oocyte donation ($n = 135$)		Spontaneous conception ($n = 270$)		Univariate model		Multivariate model	
	N	%	*N*	%	OR[a]	95% CI	aOR[a]	95% CI
Preeclampsia[b]	17	12.6	3	1.1	12.82	3.69–44.60	11.90	2.69–52.73
Pregnancy-induced hypertension[b]	13	9.6	15	5.5	1.81	0.84–3.93	1.23	0.33–4.51
Birth weight < 3rd percentile[c]	6	4.4	17	6.3	0.69	0.27–1.80	0.68	0.22–2. 06
Birth weight < 10th percentile[c]	32	23.7	36	13.3	2.02	1.19–3.43	1.37	0.72–2.60

N number, *OR* odds ratio, *aOR* adjusted odds ratio, *CI* Confidence interval

[a]Risk for event for oocyte donation/Risk for event for spontaneous conception

[b]Adjusted for: age at delivery, parity

[c]Adjusted for: age at delivery, parity, hypertensive disorders, gestational and non-gestational diabetes mellitus

multiparous women. The rate of preeclampsia in nulliparous and multiparous pregnancies following OD was 16.7 and 10.8%, respectively ($P = 0.40$), and remained non-significant also after controlling for age. In addition, we found no significant risk of preeclampsia related to the maternal age in this group after the age of 45 years (data not shown; age analyzed as a continuous variable or dichotomized by the median).

While there were no cases of early preeclampsia (< 34 gestation weeks) in the natural conception group, there were five cases of early preeclampsia in the OD group. Rates of pregnancy-induced hypertension of naturally conceived and oocyte donation pregnancies were 5.5 and 9.6%, respectively ($P = 0.22$). This difference remained non-significant also after controlling for age at delivery and parity.

Mean gestational week at delivery was 37.4 weeks (range 25-42) for the OD group and 39.4 weeks (range 32–43) for the natural conception group. Data regarding mode of delivery was available for 88.1% of patients. Rates of caesarean section for the OD and the naturally conception groups were 58.5 and 21.9%, respectively.

The rate of SGA (birth weight under 10th percentile for the specific gestational age) was higher for the OD group as compared to natural conception pregnancies (23.7 vs. 13.3%). However, a multivariate analysis, controlling for age, parity, hypertensive disorders, gestational and non-gestational diabetes mellitus, and gestational age, revealed a non-significant association.

Discussion

The present study shows that after the age of 45, OD pregnancies are associated with a 12-fold increased risk of preeclampsia as compared to pregnancies following natural conception. Previous studies reported an elevated risk of various obstetrical adverse outcomes, including preeclampsia, for women conceiving by OD [17]. However, in most cases, the risk was assessed as compared to autologous oocyte in-vitro fertilization (IVF) pregnancies rather than to natural conception pregnancies, and multiple pregnancies were not excluded.

Our study and control groups are unique in their composition. The study group is unique in the fact that it includes multiparous mothers who conceived via OD. Women conceiving naturally at extremely advanced maternal age characterize the control group. This group of women encourages natural conception, discourages contraceptive use, and views fecundity as a blessing; therefore, they continue to challenge

their reproductive system until menopause. Those unique populations enabled us to isolate the effect of the donated oocyte.

Natural conceptions were chosen in our study as the control group due to their biological neutrality. The main drawback of choosing natural conceptions as the reference group is the possible selection bias due to their medical background that enabled them to extend their fertility up to this age. Choosing IVF autologous pregnancies as the reference group also has its limitations, including their medical background, the hormones used for ovarian stimulation and the fact that in our country, IVF is not allowed after the age of 45. Hence, we sought to choose natural conceptions as the control group and controlling for possible confounders.

We excluded multiple gestation pregnancies from our study. Multiple gestations are related to distinct maternal physiologic adaptation mechanisms as well as to increased risk for specific pregnancy complications, particularly preeclampsia [14]. Including multiple gestations, even if controlling for them, can bias the results and they were, therefore, excluded.

Previous studies assessing adverse obstetric outcomes in elderly parturients reported rates of preeclampsia of 2.7–28.4% (Table 3) [13, 18–30]. Of note, as the mother's age rose, the rate of preeclampsia increased. However, most of these studies included multiple gestations and did not assess different modes of conception.

Studies assessing adverse obstetric outcomes in pregnancies achieved by OD demonstrated a high risk of preeclampsia in this group (Table 4) [17, 31–34]. Yet, these studies compared the results to pregnancies achieved by IVF and did not limit their analysis to a specific range of age or to singleton pregnancies.

The pathophysiology of preeclampsia likely involves both maternal and fetal/placental factors. Some researchers have postulated shallow trophoblast invasion and defective placental vasculature early in pregnancy, resulting in placental underperfusion, hypoxia, and ischemia, which then lead to release of antiangiogenic factors into the maternal circulation that alter maternal systemic endothelial function, leading to hypertension and other multisystemic manifestations of the disease [35, 36].

In addition, it is speculated that immunologic factors may contribute substantially to the underlying defective placentation in terms of rejection of the fetoplacental unit as an allograft or aberrant immunological response directed against tissue of organ-specific antigens associated with the placenta [37, 38]. This hypothesis is supported by higher rates of preeclampsia in cases in which there was no prior exposure to paternal/fetal antigens, such as in nulliparous gestations [14] and in conceptions following sperm donation [39]. Based on a similar rational process, in OD pregnancies, the foreign oocyte may play a role in the immunologic cascade and contribute to an abnormal placentation, thus accounting for the markedly higher rate of preeclampsia in oocyte donation pregnancies, as compared to conceptions with an autologous oocyte. Our study may support this hypothesis, since trophoblasts of pregnancies following OD carry 100% "foreign" tissue for the mother host as compared with only 50% in autologous oocyte IVF and naturally conceived

Table 3 Summary of the previous studies of preeclampsia in advanced aged gravidas

	Location	Age	*N*	*N* singleton	Preeclampsia (%)	PIH (%)	Preterm delivery < 37 weeks (%)	SGA (%)
Dildy, 1996	USA	≥ 45	79	77	10.1	N/A	15.2	N/A
Dulitzki, 1998	Israel	≥ 44	109	109	12.8	N/A	18.3	11.9
Gilbert, 1999	USA	≥ 40	24,032	N/A	5.4 (nulliparous) 2.7 (multiparous)	N/A	14.1 (nulliparous) 13.7 (multiparous)	N/A
Ziadeh, 2001	Jordan	≥ 40	468	N/A	6.6 (nulliparous) 5.2 (multiparous)	N/A	6.0	N/A
Salihu, 2003	USA	≥ 50	539	341	8.5	N/A	~21	N/A
Jacobsson, 2004	USA	≥ 45	1205	1167	2.2	3.4	9.38	5.03
Callaway, 2005	Australia	≥ 45	76	75	12.9	N/A		10.5
Goldman, 2005	USA	≥ 40	1364	1364	3.0	5.5	11.8	N/A
Simchen, 2006	Israel	≥ 45	123	95	28.4	N/A	N/A	30
Hoffman, 2006	USA	≥ 40	3953	3953	9.3	N/A	N/A	N/A
Tabcharoen, 2009	Thailand	≥ 40	789	775	N/A	3.7	13.7	N/A
Yogev, 2010	Israel	≥ 45	177	165	10.7	9.0	21.5	11.3
Laskov, 2012	Israel	≥ 45	278	278	7.9 (severe only)	N/A	18.7	N/A
Khalil, 2013	UK	≥ 40	4061	4061	3.4	3.0	2.3 (< 34 weeks)	5.9 (< 5th percentile)

N number, *PIH* pregnancy-induced hypertension, *SGA* small for gestational age (i.e., < 10th percentile), *N/A* not available, ~ numbers extracted from graphs

Table 4 Summary of the previous studies of preeclampsia in pregnancies following oocyte donation

	Location	Control group	*N*		*N* Singleton		Mean age		Preeclampsia OD (%)	PIH, OD (%)	Preterm delivery OD (%)	SGA OD (%)
			OD	Control	OD	Control	OD	Control				
Anttila, 1998	Finland	IVF	51	97	41	68	33.5	33.4	41.1[b]	11.8[b]	25.4[a]	9.8[a]
Wiggins, 2005	USA	IVF	50	50	35	37	41.9	37.7	12.0[b]	26.0[b]	N/A	N/A
Krieg, 2008	USA	IVF	71	108	41	81	42.7	41.3	~ 7.3[a]	N/A	~ 13.6[a]	~ 4.5[a]
Klatsky, 2010	USA	IVF	77	81	54	61	40.2	39.8	17.0[b]	N/A	34[b]	N/A
Stoop, 2012	Belgium	IVF-ICSI	205	205	148	148	36.3	36.2	17.0[a]	10.2[a]	14.2[a]	N/A

N number, *PIH* pregnancy-induced hypertension, *SGA* small for gestational age (i.e., < 10th percentile), *OD* oocyte donation, *IVF* in-vitro fertilization, *N/A* not available, ~ numbers extracted from graphs

[a]Singletons only

[b]Singletons and multiple gestations (no data for singletons only)

pregnancies. Our findings of non-significant, different rates of preeclampsia among different parity and age groups of OD parturients lend further support to this theory, predisposing for significantly higher rates of preeclampsia when conception is through a foreign oocyte.

In our study, we found no significant association between the mode of conception and SGA. Prior studies have shown an association between oocyte donation and birth weight [31]. However, this may be due to a definition bias, since the outcome reported in some studies was low birth weight (≤ 2500 g), rather than the specific birth weight percentile in accordance with the gestational age. We decided not to use low birth weight as it does not reflect any biological mechanism due to its disconnection to gestational age. Our findings of a significant association of oocyte donation conceptions with preeclampsia but not with SGA may reflect the dominance of the immunologic preeclampsia pathway, rather the vascular theories.

In a recent meta-analysis, a comparison between elective delivery and expectant management for preeclampsia was presented. For women with preeclampsia beyond 34 weeks, gestation elective delivery was shown to decrease the incidence of complications, severe hypertension and need for antihypertensive medical therapy. Before 34 weeks gestation, elective delivery was shown to decrease the risk of placental abruption in women suffering from severe preeclampsia, but this reduction may come at the cost of increased risk of neonatal complications [40].

The role of the male partner in preeclampsia and SGA is yet to be fully understood [41]. We did not have access to data regarding the male partner and whether all pregnancies were achieved with the same partner or not. However, the control group is comprised mainly of multiparous women who are likely to have a more religious background. In those communities, the divorce rate is extremely low, and hence, it can be assumed that most of those women had conceived by the same male partner. We were not able to retrieve data regarding Body Mass Index and gestational weight gain. We recognize this as a limitation of our study. However, as the risk of preeclampsia in the OD group was increased 12-fold as compared to the natural conception group, it is unlikely that this data would have had a significant impact on the results.

OD is an effective method of achieving pregnancy for women of advanced aged who seek motherhood. In the United States, from 2000 to 2010, there was an increase in the number of donor oocyte cycles from 10,801 to 18,306 per year [42]. This significant growth should encourage clinicians to become familiar with the specific risk factors of this unique population.

During the last decade, guidelines on routine antenatal care were published by national and international bodies. Some of those have recommended that a woman's risk for preeclampsia should be evaluated early in pregnancy. There are now certain guidelines that advocate in favor of daily low-dose aspirin for women who are at high risk [43–45]. One of the new ways in which clinicians address antenatal care consists of an integrated approach in which at 11–13 weeks, maternal characteristics and history, along with biophysical and biochemical markers, are used to evaluate the risk of developing various complications later in pregnancy [46]. In the context of preeclampsia, the main goal of such a combined approach would be to detect the patients who could benefit from prophylactic interventions.

Our study showing a significant increased risk for preeclampsia in this group of women may encourage clinicians to implement this approach and perform a first-trimester screening test for preeclampsia as part of the routine follow-up in those pregnancies.

Author contributions UPD: project development, data collection, analysis, and writing of the manuscript. NL: project development, editing of the manuscript, and supervision. HHC: manuscript writing and

editing and data analysis. SGG: project development, data analysis, and manuscript editing. HY: data collection and editing of manuscript. YG: project development, data collection, and manuscript editing.

Compliance with ethical standards

Funding This study did not receive any funding.

Research involving human and animal participants All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional research committee at Hadassah Medical Center, Hebrew University Medical School and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

References

1. Cunningham FG, Fernandez CO, Hernandez C (1995) Blindness associated with preeclampsia and eclampsia. Am J Obstet Gynecol 172:1291–1298
2. Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B (2011) Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. Hypertension 57:85–93
3. Rafik Hamad R, Larsson A, Pernow J, Bremme K, Eriksson MJ (2009) Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens 27:2257–2264
4. MacKay AP, Berg CJ, Atrash HK (2001) Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol 97:533–538
5. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R (2000) Preeclampsia and fetal growth. Obstet Gynecol 96:950–955
6. Sibai BM (2006) Preeclampsia as a cause of preterm and late preterm (near-term) births. Semin Perinatol 30:16–19
7. Calderon-Margalit R, Friedlander Y, Yanetz R, Deutsch L, Perrin MC, Kleinhaus K et al (2009) Preeclampsia and subsequent risk of cancer: update from the Jerusalem perinatal study. Am J Obstet Gynecol 200(63):e61–e65
8. Stekkinger E, Zandstra M, Peeters LL, Spaanderman ME (2009) Early-onset preeclampsia and the prevalence of postpartum metabolic syndrome. Obstet Gynecol 114:1076–1084
9. Washburn L, Nixon P, Russell G, Snively BM, O'Shea TM (2013) Adiposity in adolescent offspring born prematurely to mothers with preeclampsia. J Pediatr 162(912–917):e911
10. Oglaend B, Forman MR, Romundstad PR, Nilsen ST, Vatten LJ (2009) Blood pressure in early adolescence in the offspring of preeclamptic and normotensive pregnancies. J Hypertens 27:2051–2054
11. Roberge S, Giguere Y, Villa P, Nicolaides K, Vainio M, Forest JC et al (2012) Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. Am J Perinatol 29:551–556
12. Sauer MV, Kavic SM (2006) Oocyte and embryo donation 2006: reviewing two decades of innovation and controversy. Reprod Biomed Online 12:153–162
13. Callaway LK, Lust K, McIntyre HD (2005) Pregnancy outcomes in women of very advanced maternal age. Aust N Z J Obstet Gynaecol 45:12–16
14. Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 330:565
15. 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
16. Poon LC, Volpe N, Muto B, Syngelaki A, Nicolaides KH (2012) Birthweight with gestation and maternal characteristics in live births and stillbirths. Fetal Diagn Ther 32:156–165
17. Krieg SA, Henne MB, Westphal LM (2008) Obstetric outcomes in donor oocyte pregnancies compared with advanced maternal age in in vitro fertilization pregnancies. Fertil Steril 90:65–70
18. Dildy GA, Jackson GM, Fowers GK, Oshiro BT, Varner MW, Clark SL (1996) Very advanced maternal age: pregnancy after age 45. Am J Obstet Gynecol 175:668–674
19. Dulitzki M, Soriano D, Schiff E, Chetrit A, Mashiach S, Seidman DS (1998) Effect of very advanced maternal age on pregnancy outcome and rate of cesarean delivery. Obstet Gynecol 92:935–939
20. Gilbert WM, Nesbitt TS, Danielsen B (1999) Childbearing beyond age 40: pregnancy outcome in 24,032 cases. Obstet Gynecol 93:9–14
21. Ziadeh S, Yahaya A (2001) Pregnancy outcome at age 40 and older. Arch Gynecol Obstet 265:30–33
22. Salihu HM, Shumpert MN, Slay M, Kirby RS, Alexander GR (2003) Childbearing beyond maternal age 50 and fetal outcomes in the united states. Obstet Gynecol 102:1006–1014
23. Jacobsson B, Ladfors L, Milsom I (2004) Advanced maternal age and adverse perinatal outcome. Obstet Gynecol 104:727–733
24. Cleary-Goldman J, Malone FD, Vidaver J, Ball RH, Nyberg DA, Comstock CH et al (2005) Impact of maternal age on obstetric outcome. Obstet Gynecol 105:983–990
25. Simchen MJ, Yinon Y, Moran O, Schiff E, Sivan E (2006) Pregnancy outcome after age 50. Obstet Gynecol 108:1084–1088
26. Hoffman MC, Jeffers S, Carter J, Duthely L, Cotter A, Gonzalez-Quintero VH (2007) Pregnancy at or beyond age 40 years is associated with an increased risk of fetal death and other adverse outcomes. Am J Obstet Gynecol 196:e11–e13
27. Tabcharoen C, Pinjaroen S, Suwanrath C, Krisanapan O (2009) Pregnancy outcome after age 40 and risk of low birth weight. J Obstet Gynaecol 29:378–383
28. Yogev Y, Melamed N, Bardin R, Tenenbaum-Gavish K, Ben-Shitrit G, Ben-Haroush A (2010) Pregnancy outcome at extremely advanced maternal age. Am J Obstet Gynecol 203(558):e551–e557
29. Laskov I, Birnbaum R, Maslovitz S, Kupferminc M, Lessing J, Many A (2012) Outcome of singleton pregnancy in women ≥ 45 years old: a retrospective cohort study. J Matern fetal Neonatal 25:2190–2193
30. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH (2013) Maternal age and adverse pregnancy outcomes: a cohort study. Ultrasound Obstet Gynecol 42:634–643
31. Soderstrom-Anttila V, Tiitinen A, Foudila T, Hovatta O (1998) Obstetric and perinatal outcome after oocyte donation: comparison with in vitro fertilization pregnancies. Hum Reprod 13:483–490
32. Wiggins DA, Main E (2005) Outcomes of pregnancies achieved by donor egg in vitro fertilization—a comparison with standard in vitro fertilization pregnancies. Am J Obstet Gynecol 192:2002–2006 **(discussion 2006–2008)**
33. 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

34. 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
35. Lindheimer MD, Katz AI (1989) Preeclampsia: pathophysiology, diagnosis, and management. Annu Rev Med 40:233–250
36. Karumanchi SA, Lindheimer MD (2008) Preeclampsia pathogenesis: "Triple a rating"-autoantibodies and antiangiogenic factors. Hypertension 51:991–992
37. Laresgoiti-Servitje E (2013) A leading role for the immune system in the pathophysiology of preeclampsia. J Leukoc Biol 94:247–257
38. Sharma S, Norris WE, Kalkunte S (2010) Beyond the threshold: an etiological bridge between hypoxia and immunity in preeclampsia. J Reprod Immunol 85:112–116
39. Smith GN, Walker M, Tessier JL, Millar KG (1997) Increased incidence of preeclampsia in women conceiving by intrauterine insemination with donor versus partner sperm for treatment of primary infertility. Am J Obstet Gynecol 177:455–458
40. Wang Y, Hao M, Sampson S, Xia J (2017) Elective delivery versus expectant management for pre-eclampsia: a meta-analysis of RCTs. Arch Gynecol Obstet 295(3):607–622
41. González-Comadran M, Urresta Avila J, Saavedra Tascón A, Jimenéz R, Solà I, Brassesco M et al (2014) The impact of donor insemination on the risk of preeclampsia: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 182:160–166
42. Kawwass JF, Monsour M, Crawford S, Kissin DM, Session DR, Kulkarni AD et al (2013) Trends and outcomes for donor oocyte cycles in the United States, 2000–2010. JAMA 310:2426–2434
43. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. RCOG Press; 2010. National Institute for Health and Clinical Excellence: Guidance
44. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy (2013) Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol 122:1122–1131
45. World Health Organization, Department of Reproductive Health and Research, Department of Maternal, Newborn, Child and Adolescent Health, and Department of Nutrition for Health and Development, WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia, World Health Organization, 2011
46. Nicolaides KH (2011) Turning the pyramid of prenatal care. Fetal Diagn Ther 29:183–196