BACKGROUND: Although older maternal age is a risk factor for pregnancy complications, an increasing number of women delay conception until the age of 40, and some must resort to IVF with oocyte donation. Our objective was to study the association between IVF, both with and without oocyte donation, and maternal and perinatal outcomes in a population of older women.

METHODS: This retrospective study covered all women, aged 43 or more, who gave birth between 2008 and 2010. Univariate and multivariate analyses with logistic regression models were used to compare maternal and perinatal outcomes as a function of mode of conception: without IVF, with IVF using own oocytes or with IVF and oocyte donation.

RESULTS: The study included 380 women, including 40 who had IVF without oocyte donation (10.5%) and 104 who had both (27.4%). There were 326 singleton and 54 multiple pregnancies. Overall, the complication rate was high: 8.7% pre-eclampsia, 6.1% gestational diabetes, 20.2% preterm delivery and 8.2% very preterm delivery (before 33 weeks), 44.8% Cesarean sections and 7.4% severe postpartum hemorrhage (PPH). The pre-eclampsia rate differed significantly between the groups (3.8% after no IVF, 10.0% after IVF only and 19.2% after IVF with oocyte donation, \( P, 0.001 \)). After adjustment, the risk of pre-eclampsia was significantly higher in women with donated oocytes compared with pregnant women without IVF [adjusted OR = 3.3 (1.2–8.9)]. The rate of twin pregnancy was significantly higher in women with IVF and oocyte donation (39.4 versus 15.0% with IVF only and 2.5% without IVF, \( P, 0.001 \)). Twin pregnancy was significantly associated with the risk of preterm delivery [adjusted OR = 8.9 (4.0–19.9)] and PPH [adjusted OR = 3.5 (1.3–9.5)].

CONCLUSION: In women aged 43 years or older, pregnancies obtained by IVF with oocyte donation are associated with higher rates of pre-eclampsia and twin pregnancies than those obtained without IVF or with IVF using their own oocytes.

Key words: oocyte donation / advanced maternal age / maternal and perinatal issues / pre-eclampsia

Introduction

As in most developed countries, maternal age is increasing continuously in France. According to the INSEE (Institut National de la Statistiques et des Etudes Economiques), the mean age of women at childbirth has increased in France from 28.8 years in 1994 to 30.0 years in 2010 (INSEE, 2010). In 2003, 2.7% of women giving birth were at least 40 years old (Blondel et al., 2006) and in 2010, 3.5% (Blondel and Kermarrec, 2010). This increase in maternal age is a social phenomenon that began in the late 20th century and is likely to continue in the years to come (Berkowitz et al., 1990). Its cause is probably multifactorial: longer schooling, higher career goals, later marriage, improvements in assisted reproductive technology (ART) and other social and technical factors.

Several authors have studied the excess risk of maternal and perinatal complications in pregnancy among older women and have shown an increased risk of pre-eclampsia, gestational diabetes, preterm delivery and post-partum hemorrhage (PPH) (Bianco et al., 1996; Al-Zirqi et al., 2008; Yoge et al., 2010). Older studies considered a pregnancy to be late if the mother was older than 35 years, while today late pregnancies are more likely to refer to pregnant women 40 years or older, even 45 or older. Because of their advanced age, these women often have difficulties conceiving spontaneously and therefore often resort to IVF and increasingly often to IVF with oocyte donation.
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donation. Even though the woman makes an active decision to undergo this periconceptional medical management, it is arduous for her. This mode of conception is also onerous financially. Because French regulations for IVF reimbursement set 42 years as the age limit for fertility, most IVF procedures for woman older than 42 years are performed in private institutions and are not covered by national health insurance, although any subsequent pregnancy and delivery are covered. Moreover, the legal difficulties in obtaining oocytes in France mean that most IVF procedures with oocyte donation are performed abroad, most often in other European countries. If the use of these techniques in women of very advanced maternal age entails excess maternal and perinatal risk, women must be informed of this, and physicians should adapt their practices to minimize it.

Few studies have examined the effect of mode of conception on maternal and perinatal complications in mothers of very advanced age, and those that have investigated this had small populations and no control group of spontaneous pregnancies in the same age range. The consequences of IVF without and with oocyte donation in women of these age groups appear to require specific and appropriate evaluation, for the issues are different from those of spontaneous pregnancies in women in the same age range.

The objective of our study is to assess the effect of IVF with and without oocyte donation on maternal and perinatal outcomes in women giving birth after the age of 43.

Materials and Method

This retrospective study took place at Port Royal Maternity Hospital in Paris (France), a level-III university hospital center that handles ~3200 deliveries per year. It included all women who gave birth after their 43rd birthday from 1 January 2008 through 31 December 2010. Data were collected from obstetric records, and all records of such pregnancies were individually reviewed. However, we did not have access to fertility files because most of the ART procedures were performed elsewhere.

Maternal complications studied were pre-eclampsia (defined by blood pressure \( \geq 140/90 \) mmHg and proteinuria \( >0.3 \) g/24 h), gestational diabetes (defined by fasting glucose \( >0.9 \) g/l or postprandial glycaemia \( >1.20 \) g/l) and severe PPH (defined by any of the following: treatment with sulprostone (Nalador\(\text{®}\)), transfusion of packed red blood cells, embolization or a surgical procedure (ligation of the hypogastric arteries, uterine plication, emergency hysterectomy). We also studied perinatal complications: birthweight <000 g and <2500 g, preterm delivery (<37 and <33 weeks) and in utero fetal death (IUFD) after 22 weeks. Mode of delivery and any medically indicated termination of pregnancy (TOP) were also collected.

The principal factor studied was the mode of conception, classified into three categories: no IVF, IVF without oocyte donation and IVF with oocyte donation. Dual donations (sperm and oocytes) were also recorded. Because of the potential information bias due to underreporting in the medical files, we chose to combine the spontaneous pregnancies with those obtained without IVF but with other ART techniques, such as induction of ovulation by clomiphene or intrauterine insemination. The other factors studied were: maternal age, geographic origin, parity and type of pregnancy (singleton, twin or triplet).

We compared the women’s characteristics according to the mode of conception. We then used univariate and multivariate analyses to study the effect of IVF without and with oocyte donation on each maternal and perinatal complication. Comparisons with the univariate analyses were assessed with the \( \chi^2 \) test, Fisher’s exact test and the Kruskal–Wallis non-parametric test, as appropriate. Logistic regression models were used for the multivariate analyses and included all factors which were significant \( (P < 0.1) \) in the univariate analysis. We used Stata version 10.0 software (College Station, TX, USA) for the analyses.

Results

During the study period, 380 women aged 43 years or older gave birth in our maternity unit: 128 in 2008, 136 in 2009 and 116 in 2010, respectively 4.1, 4.5 and 4.0% of the annual deliveries. Overall, 236 women (62.1%) became pregnant without IVF, 40 (10.5%) had IVF without oocyte donation and 104 (27.4%) had IVF with oocyte donation, including nine who received both sperm and oocyte donations. The number of women aged 43 years or older giving birth in our unit and using oocyte donation doubled between 2008 and 2010 (Fig. 1).

Table I presents the characteristics of the population according to the mode of conception. The women who had IVF with oocyte donation were significantly older, more often nulliparous and had twin pregnancies more often. The oldest patient was 60 years old, and her pregnancy resulted from oocyte donation.

Overall, the maternal complication rates in our population were: 8.7% \((n = 33)\) for pre-eclampsia, 6.1% \((n = 23)\) for gestational diabetes and 7.4% \((n = 28)\) for severe PPHs.

The 380 women studied delivered 435 children, including 2.1% IUFD \((n = 9)\) and 1.6% TOP \((n = 7)\). Among these women, the preterm delivery rate was 20.2% \((n = 74/366, \text{IUFD and TOP excluded})\) and the very preterm birth rate (<33 weeks) was 8.2% \((n = 30/366)\). Among the children, 2.6% \((n = 11/419, \text{IUFD and TOP excluded})\) had a birthweight <1000 g and 25.8% \((n = 108/419)\) were <2500 g.

The following complications were significantly associated with IVF with oocyte donation in the univariate analysis: pre-eclampsia, preterm delivery, birthweight <2500 g and PPH (Table II). The pre-

Figure 1 Number of pregnancies according to the mode of conception: Trends in women aged 43 years or older from 1 January 2008 through 31 December 2010.
Eclampsia rates were 3.8% without IVF, 10% with IVF but without oocyte donation and 19.2% with both IVF and oocyte donation ($P < 0.001$). Among the women who had IVF with oocyte donation, the pre-eclampsia rate did not differ significantly between those with oocyte donation alone and those using dual donation (19.2 versus 22.2%, $P = 0.824$). Of the 33 women who developed pre-eclampsia, eight required delivery before 34 weeks. The rate of pre-eclampsia associated with preterm birth before 34 weeks varied according to the mode of conception, but not significantly (1.3% without IVF, 0% with IVF and without oocyte donation and 4.8% with both IVF and oocyte donation, $P = 0.107$). Among twin pregnancies, all women with IVF with oocyte donation developed pre-eclampsia, compared with none in the other groups ($P < 0.001$). Among the singleton pregnancies, the pre-eclampsia rate was 3.9% for those with no IVF, 11.8% for IVF without oocyte donation and 12.9% ($P = 0.011$) for IVF with oocyte donation.

The association between IVF with oocyte donation and pre-eclampsia remained significant after adjustment: the risk of pre-
eclampsia was 3.3 times higher in pregnancies obtained by IVF with oocyte donation compared with those from spontaneous pregnancies (adjusted OR = 3.3 (1.2–8.9)) (Table III).

IVF with oocyte donation did not remain significantly associated with the risk of preterm delivery after multivariate analysis. Indeed, the only factor significantly associated with preterm delivery was twin pregnancy (adjusted OR = 8.9, 95% CI (4.0–19.9)). Nor did the association between PPH and mode of conception persist after adjustment for mode of delivery, type of pregnancy, parity and birthweight. On the other hand, Cesarean delivery doubled (adjusted OR = 2.4, 95% CI (1.0–5.5)), and twin pregnancy tripled (adjusted OR 3.5, 95% CI: (1.3–9.5)), the risk of PPH.

In our series, 44.8% of the women (n = 164/366, IUFD and TOP excluded) had Cesarean deliveries. The Cesarean rate among women with both IVF and oocyte donation was 61.4%, significantly higher than among women who did not use IVF or did use it, but without oocyte donation (P = 0.001; Table II). In a selected population of uncomplicated pregnancies (after exclusion of multiple pregnancies, premature deliveries and pre-eclampsia), the Cesarean rate was still significantly associated with mode of conception (33.9% for pregnancies without IVF, 33.3% for IVF without oocyte donation and 57.8% for both IVF and oocyte donation (P = 0.011)).

### Table III Maternal and obstetric factors associated with the risk of pre-eclampsia: univariate analyses and final multivariate model.

<table>
<thead>
<tr>
<th></th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>44 years</td>
<td>0.7 (0.2–2.5)</td>
<td></td>
</tr>
<tr>
<td>45 years</td>
<td>1.0 (0.3–3.6)</td>
<td></td>
</tr>
<tr>
<td>46 years</td>
<td>1.2 (0.2–5.6)</td>
<td></td>
</tr>
<tr>
<td>47 years and older</td>
<td>2.4 (0.7–8.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Geographic origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other European countries</td>
<td>0.6 (0.1–2.8)</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>1.1 (0.4–2.5)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>1.0 (0.1–8.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.9 (0.2–3.1)</td>
<td></td>
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<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>3.4 (1.5–7.5)</td>
<td>2.1 (0.9–5.0)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Type of pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Twin</td>
<td>4.3 (1.9–9.3)</td>
<td>2.1 (0.9–5.1)</td>
</tr>
<tr>
<td><strong>Mode of conception</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IVF</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IVF without oocyte donation</td>
<td>2.8 (0.8–9.6)</td>
<td>2.3 (0.7–8.3)</td>
</tr>
<tr>
<td>IVF with oocyte donation</td>
<td>6.0 (2.6–13.7)</td>
<td>3.3 (1.2–8.9)</td>
</tr>
</tbody>
</table>

*Adjustment for parity, type of pregnancy and mode of conception.

### Discussion

For women giving birth at or after the age of 43 years, the risk of pre-eclampsia tripled for those having used IVF with oocyte donation, compared with women in the same age group whose pregnancy did not result from IVF. The risk of preterm delivery was also especially high in this population of women of very advanced maternal age, due mainly to the multiple pregnancies induced by IVF.

Women in their 40s currently account for a substantial proportion of parturients in France. They resort increasingly often to IVF techniques, especially IVF with oocyte donation. This periconceptional medical management is arduous for them. If it also increases maternal and perinatal risks in these women already at a higher risk than younger women of pregnancy-related complications, they must be carefully informed and counseled, and fertility specialists must adapt their practices to minimize these risks. It is therefore important to assess the maternal and perinatal consequences of IVF with oocyte donation in this ‘very advanced maternal age’ group.

We chose a threshold of 43 years to define ‘very advanced age’, consistent with French regulations for IVF reimbursement that set 42 years as the age limit for fertility. The rates of maternal and perinatal complications in our population of women aged 43 years or older were certainly high, but not substantially different from data in the literature. Recently, Yogev et al. assessed maternal and perinatal outcomes as a function of maternal age and found, among women aged 45 years or older, rates of 10.7% for pre-eclampsia, 21.5% for preterm delivery, 78.5% for Cesarean deliveries, 4% for PPH and 11.3% for birthweight below the 10th percentile, with all modes of conception combined (Yogev et al., 2010).

High rates of maternal complications have been reported in several small series of pregnancies after oocyte donation (Sauer et al., 1996; Sheffer-Mimouni et al., 2002; Keegan et al., 2007). But the heterogeneity of these series, which included young women with no ovarian reserves and older women on the borderline of fertility, has prevented a specific analysis of complications in older women using donor oocytes.

In our population, 19.2% of the women who had IVF with oocyte donation developed pre-eclampsia. This risk is not only very high compared with the risk of pre-eclampsia reported in the overall French population, which ranges from 0.5 to 2% according to the woman’s characteristics (Pottecher, 2001), but it is also three times higher in women aged 43 years and older with IVF and oocyte donation than among those of the same age not using IVF. This association between pre-eclampsia and oocyte donation has previously been reported in the literature. In a series of 69 women with oocyte donations and between 36 and 55 years compared with 681 women older than 38 years with autologous oocytes, Henne et al. found a significant increase in the risk of pre-eclampsia, after adjustment for maternal age and twins (Henne et al., 2007). In a small series of 27 women with oocyte donation, matched for age and parity with controls with spontaneous pregnancies, Salha et al. found a pre-eclampsia rate of 16% compared with 3.7% in the control group (P < 0.05) (Salha et al., 1999). In the same study, the pre-eclampsia rate was also high for in-semination with donor sperm (18.2%) and embryo donations (25%). These results tend to support the hypothesis of immunological maladaptation as a cause of pre-eclampsia. That is, in pregnancies with donor oocytes, the fetus may be considered schematically as a...
totally allogenic graft for the woman and no longer a semi-allogenic graft. This may have increased the risk of pre-eclampsia in our study. The risk of severe pre-eclampsia, associated with birth before 34 weeks, also appeared to be higher in women who had IVF with oocyte donation, compared with no IVF. Thus, this maternal complication was also accompanied by the neonatal complications associated with preterm birth.

In our study, the rate of preterm delivery—in particular, the rate of very preterm birth (<33 weeks), an important source of severe neonatal complications—was high among these women much older than the general population of mothers. The 2003 French national perinatal survey found an overall preterm delivery rate of 7.2% and a very preterm birth rate of 2.0 versus 20.2% and 8.2%, respectively, in our study (Blondel et al., 2006). As our results show, ART tends to increase the incidence of twin pregnancies. Twinning was the only risk factor in our study that remained significantly associated with the risk of preterm delivery after adjustment, and the women pregnant following IVF, both with and without oocyte donation, had significantly more of these multiple pregnancies that are associated with preterm delivery. However, even with singletons, there is a significant relationship between IVF and preterm delivery. In a meta-analysis published in 2004, Jackson et al. (2004) found a risk of preterm delivery twice as high in singletons from IVF as in spontaneous pregnancies. To reduce the risk, the option of transferring a single high-quality embryo should always be favored, especially for older women with oocytes donated by young women. The critical factor for implantation is oocyte quality. The quality of oocytes from young donors is usually high, and the chances of implantation are better than with oocytes from older women (Centers For Disease Control and Prevention, 2008). Transferring multiple high-quality embryos increases the risk of multiple pregnancies among these older women.

Our Cesarean rate for women aged 43 years or older may also appear high, almost 45 overall and 61% for IVF with oocyte donation, compared with the national French data (20% Cesarean rate in 2003 in France) and with the 25% Cesarean rate in our maternity centre (Blondel et al., 2006). It is nonetheless similar to, or even lower than, some published data, including, for example, a Cesarean rate of 78% among women with both IVF and oocyte donation (Keegan et al., 2007). After adjustment for the mothers’ characteristics and twin status, mode of conception remained associated with the risk of Cesarean, which may suggest that obstetricians are perhaps more inclined to perform cesareans in these older women who had IVF with oocyte donation. We did not study the post-operative complications, such as thromboembolic or infectious complications, associated with cesareans, and our series includes no maternal deaths. These complications fortunately occur only rarely, and our population may have been too small to study the risk of severe maternal complications. It has now been clearly demonstrated that maternal mortality and morbidity are significantly higher with Cesarean compared with vaginal deliveries. Accordingly, vaginal deliveries should be favored, regardless of the patient’s age or mode of conception (Deneux-Tharaux et al., 2006; Villar et al., 2007).

Our study nonetheless has several limitations. First, our population includes only women managed and delivered in a level-III maternity unit, and may not be representative of women aged 43 years or older in France. Our data are nonetheless relevant for studying the association between IVF and without oocyte donation, and maternal and neonatal complications. Moreover, although our series is one of the largest published thus far, with 104 pregnancies obtained by IVF with oocyte donation in 3 years, some categories, especially women who had IVF without oocyte donation, have limited numbers of subjects. A lack of power, as shown by wide confidence intervals, may limit the interpretation of some results. Moreover, the grouping into one category pregnancies obtained spontaneously and those obtained after ovulation induction and/or intrauterine insemination might have led to a misclassification bias. According to the available data reported in the obstetric records, which may be incomplete, 7% of the pregnancies classified as ‘no IVF’ were obtained with other ART techniques. This bias, however, tends to support our results for it increases, for example, the number of twin pregnancies in the group without IVF. Finally, due to the retrospective design of our study and because information about infertility is often unreported in obstetric records, we unfortunately cannot determine the percentage of women with a history of infertility in the control group or the etiology of infertility in the IVF groups, with or without oocyte donation, or the fertility treatment other than IVF with or without oocyte donation.

The originality of our study lies in the homogeneity of the study population. That is, we studied only women aged 43 years or older, rather than women of all ages who used oocyte donations. Most studies also include young women without any ovarian reserve (Sheffer-Mimouni et al., 2002; Wiggins and Main, 2005). Moreover, our study is the only one that compares three modes of conception: no IVF, IVF without oocyte donation and IVF with oocyte donation.

Currently, ever more women are deciding late that they want a child, sometimes above and beyond the natural limits of fertility. They account for the apparent increase in the use of IVF with oocyte donation in recent years. This study has a 3-fold interest: (i) to inform women who are considering IVF with oocyte donation of the risks involved, (ii) to encourage physicians performing IVF with oocyte donation in older women to transfer a single embryo, at least when the donor is young, to avoid multiple pregnancies and (iii) to inform obstetricians caring for these patients during pregnancy of the increased risk of pre-eclampsia so that they can conduct a maternal assessment before pregnancy and set up heightened monitoring during pregnancy.

Authors’ roles

C.L.R. conceived and designed the experiments, performed the analysis, interpreted the data, drafted the article and approved the final version. S.S. conceived and designed the experiments, acquired the data, drafted the article and approved the final version. O.A., A.M., V.T., D.C. contributed to conception and design, revised the article and approved the final version. F.G. conceived and designed the experiments, interpreted the data, drafted the article and approved the final version.

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Conflict of interest

None declared.
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