Human Reproduction, pp. 1–9, 2020
doi:10.1093/humrep/dez275

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Maternal age and risk of low birth weight and premature birth in children conceived through medically assisted reproduction. Evidence from Finnish population registers

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Submitted on August 2, 2019; resubmitted on November 15, 2019; editorial decision on November 21, 2019

STUDY QUESTION: Does the risk of low birth weight and premature birth increase with age among mothers who conceive through medically assisted reproduction (MAR)?

SUMMARY ANSWER: Among MAR mothers, the risk of poorer birth outcomes does not increase with maternal age at birth except at very advanced maternal ages (40+).

WHAT IS KNOWN ALREADY: The use of MAR treatments has been increasing over the last few decades and is especially diffused among women who conceive at older ages. Although advanced maternal age is a well-known risk factor for adverse birth outcomes in natural pregnancies, only a few studies have directly analysed the maternal age gradient in birth outcomes for MAR mothers.

STUDY DESIGN, SIZE, DURATION: The base dataset was a 20% random sample of households with at least one child aged 0–14 at the end of 2000, drawn from the Finnish population register and other administrative registers. This study included children who were born in 1995–2000, because the information on whether a child was conceived through MAR or naturally was available only from 1995 onwards.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The outcome measures were whether the child had low birth weight (LBW, <2500 g at birth) and whether the child was delivered preterm (<37 weeks of gestation). Conceptions through MAR were identified by examining data on purchases of prescription medication from the National Prescription Register. Linear probability models were used to analyse and compare the maternal age gradients in birth outcomes of mothers who conceived through MAR or naturally before and after adjustment for maternal characteristics (i.e. whether the mother suffered from acute/chronic conditions before the pregnancy, household income and whether the mother smoked during pregnancy).

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 56 026 children, 2624 of whom were conceived through MAR treatments, were included in the study. Among the mothers who used MAR to conceive, maternal age was not associated with an increased risk of LBW (the overall prevalence was 12.6%) at ages 25–39. For example, compared to the risk of LBW at ages 30–34, the risk was 0.22 percentage points lower (95% CI: −3.2, 2.8) at ages 25–29 and was 1.34 percentage points lower (95% CI: −4.5, 1.0) at ages 35–39. The risk of LBW was increased only at maternal ages ≥40 (six percentage points, 95% CI: 0.2, 12). Adjustment for maternal characteristics only marginally attenuated these associations. In contrast, among the mothers who conceived naturally, the results showed a clear age gradient. For example,

compared to the risk of LBW (the overall prevalence was 3.3%) at maternal ages 30–34, the risk was 1.1 percentage points higher (95% CI: 0.6, 1.6) at ages 35–39 and was 1.5 percentage points higher (95% CI: 0.5, 2.6) at ages ≥40. The results were similar for preterm births.

LIMITATIONS, REASON FOR CAUTION: A limited number of confounders were included in the study because of the administrative nature of the data used. Our ability to reliably distinguish mothers based on MAR treatment type was also limited.

WIDER IMPLICATIONS OF THE FINDINGS: This is the first study to analyse the maternal age gradient in the risk of adverse birth outcomes among children conceived through MAR using data from a nationally representative sample and controlling for important maternal health and socio-economic characteristics. This topic is of considerable importance in light of the widespread and increasing use of MAR treatments.

STUDY FUNDING/COMPETING INTEREST(S): Funding for this project was provided by the European Research Council (grant no. 803959 MARTE to Alice Goisis and grant no. 336475 COSTPOST to Mikko Myrskylä). E.S. reports personal fees from Theramex, personal fees from Merck Serono, personal fees from Health Reimbursement Arrangement, non-financial support from Merck Serono and grants from Ferring, grants from Theramex, outside the submitted work. The remaining authors have no competing interests.

TRIAL REGISTRTION NUMBER: N/A

Key words: medically assisted reproduction / MAR / maternal age / birth outcomes / low birth weight / premature birth / confounding factors

Introduction

The use of medically assisted reproduction (MAR)—i.e. reproduction through treatments such as ovulation induction, intrauterine insemination, IVF and ICSI—has increased markedly over the last four decades. Since 1978, when the first IVF baby was born, more than 8 million babies have been born after MAR treatments, and the babies conceived through MAR now account for more than 7% of all births in some European countries, such as Denmark and Belgium (De Geyter *et al*., 2018).

Women who conceive through MAR are, on average, older than women who conceive naturally, as fertility treatments are often used in response to age-related infertility or subfertility problems (Luke and Brown 2007). Moreover, the average age of women who conceive through MAR has been increasing over time (author's elaboration of data from the Finnish Medical Birth Register). For example, in Finland, the average age of women who conceived through MAR rose from around 33 in 1991 to over 35 in 2017. This trend might raise concerns, as an advanced maternal age at birth (usually defined as a maternal age of 35 or older at the time of birth), is a well-known risk factor for adverse birth outcomes. Older mothers were shown to be at higher risks of low birth weight, preterm birth, perinatal mortality and more likely to use special care or respiratory care (Hemminki and Gissler, 1996; Aldous and Edmonson, 1993; Jolly *et al*., 2000; Carolan and Frankowska, 2011; Klemetti *et al*., 2013). As the existing evidence on the link between advanced maternal age and adverse birth outcomes largely reflects the patterns among mothers who conceive naturally, the extent to which these findings can be applied to the patterns among MAR mothers is unclear. The meaning of an advanced maternal age could differ depending on the mode of conception, especially given the distinct health and subfertility conditions among women who conceive through MAR treatments at all ages (Pinborg *et al*., 2013; Wennberg *et al*., 2016).

The maternal age gradient in adverse birth outcomes in MAR pregnancies has received limited attention in the literature. The only two existing studies that have directly analysed the age gradient in adverse birth outcomes of MAR-conceived children (Tough *et al*., 2000; Wennberg *et al*., 2016) showed that an advanced maternal age was not associated with worse birth outcomes among MAR-conceived children. However, a limitation of these studies is that they were unable to control for the health and socio-economic characteristics of the mothers. These are important to consider because older MAR mothers might represent a selected group of highly educated, higher income and healthier women compared to younger MAR mother and mothers conceiving naturally. This might confound the results, contributing to the absence of excess risk observed in older MAR mothers (Wennberg *et al*., 2016; Barbuscia and Mills, 2017). Therefore, more evidence on the maternal age gradient in the risk of poorer birth outcomes among MAR-conceived children is needed.

Exploring the relationship between maternal age and birth outcomes in MAR pregnancies is especially relevant, as studies that have examined this association have consistently shown that children conceived through MAR are at increased risk of adverse birth outcomes, such as low birth weight (LBW) or preterm birth (Hansen *et al*., 2005; Sutcliffe and Ludwig, 2007; Wilson *et al*., 2011; Pandey *et al*., 2012; Hart and Norman, 2013). Although a complete explanation of the mechanisms underlying the association between the use of MAR and birth outcomes is still lacking, the existing research has identified certain risk factors. These include high rates of multiple births (Kalra and Barnhart, 2011), the MAR treatment techniques themselves (Pinborg *et al*., 2013), and parental characteristics that might predispose the parents to undergo MAR and that are known risk factors for adverse birth outcomes, including subfertility and advanced maternal age (Basso and Baird, 2003; Romundstad *et al*., 2008; Roseboom, 2018; Goisis *et al*., 2019).

Preterm birth and LBW are associated with lower cognitive ability in childhood as well as other negative outcomes later in life, such as poor health and cognitive development (Black, *et al*. 2007; Saigal and Doyle, 2008). It is, therefore, essential that we improve our understanding of the relevant risk factors for poorer birth outcomes among MAR children, as this knowledge can help women who are considering undergoing MAR treatments make better-informed choices. Addressing the question of whether and, if so, to what extent giving birth at an advanced maternal age is associated with an increased risk of LBW or preterm birth among women who conceive through MAR is of considerable importance in light of the widespread and increasing

use of MAR treatments, and of the increasing ages of the women who conceive through MAR (Ferraretti *et al*., 2017).

In this study, we compare the association between maternal age and the risk of adverse birth outcomes among mothers who conceived thorough MAR and among mothers who conceived naturally using large-scale and representative population-based data from Finland. We analyse the maternal age gradient in poorer birth outcomes before and after adjustment for child and maternal characteristics, such as twin status, parity and the health condition of the mother before the pregnancy.

Materials and Methods

Study population

The study utilises data from the Finnish population register and other administrative registers. The base dataset is a 20% random sample of households with at least one child aged 0–14 at the end of 2000, with individual-level information on all household members. The linkages between different registers were carried out by Statistics Finland using unique personal identification numbers (however, data remains anonymous). In this study, we restricted the data to children who were born in 1995–2000 because the information (described below) on whether the child was conceived through MAR or naturally was only available from 1995 onwards. We excluded cases in which fertility drugs were used to treat other diagnosed medical conditions, such as cancer (as indicated by prescription medication purchases in the special refund category). We excluded births to mothers younger than age 25 ($n = 11\,041$) or older than age 45 ($n = 267$) because the utilisation of MAR among women younger than age 25 was rare, and because women in both of these age groups might have used the drugs for purposes other than the treatment of infertility. We dropped families with triplets ($n = 44$). Our final sample consisted of 54 623 children, 2624 (4.9%) of whom were conceived through MAR treatments.

Medically assisted reproduction

We identified children who were conceived through MAR from purchases of prescription medication, which we retrieved from the National Prescription Register maintained by the Social Insurance Institution. The Prescription Register provides information on the day of purchase, the name and the class of the drug, and the size and the quantity of the packages. By combining information on each woman's purchases of fertility drugs with her child's date of birth, which was retrieved from the Finnish Medical Birth Register (MBR), we were able to identify children conceived through MAR. Four main kinds of treatments (ovulation induction, artificial insemination, IVF and ICSI) can be identified through a common pattern of fertility drugs. We followed the method developed by Hemminki *et al*. (2003), which has been found to be reliable, and has been applied by Goisis *et al*. (2019). Detailed information on the data linkage can be found in the appendix of Hemminki's paper (Hemminki *et al*., 2003).

Birth outcomes

Information on birth outcomes was extracted from the Finnish MBR.

We used two dependent variables: whether the child had LBW (<2500 g at birth) and whether the child was delivered preterm (<37 weeks of gestation).

Maternal age

The key explanatory variable was maternal age at the birth of the child, which was also extracted from the MBR. Maternal age was divided into the following categories: 25–29, 30–34, 35–39 and 40+ years. The age group 30–34 was the reference category in our analyses, since most of the MAR births were to women in this age group.

Control variables

We controlled for the child's characteristics: sex, twin status and birth order (first, second, third or higher). We controlled for a set of the mother's characteristics, which include the mother's health before pregnancy (whether the mother had any diagnosed chronic or acute health conditions, and her number of miscarriages before the pregnancy), the mother's socio-economic status (deciles of family income) and whether the mother smoked during pregnancy. To identify the presence of diagnosed chronic or acute health conditions in the mother before the pregnancy, we retrieved information from the Social Insurance Institution on the granting of the right to special reimbursement for drugs that are used to treat severe long-term illnesses. Among these illnesses, we considered the conditions that could be associated with pregnancy outcomes and/or infertility or subfertility problems. These conditions were hypertension, thyroid dysfunction, epilepsy, diabetes, thrombosis, obesity, heart disease, arthritis, dialysis, transplants, behavioural disorders, coagulation disorders, psychoses and anaemia. We constructed a binary variable that takes a value of one if the woman had any of these chronic or acute health conditions before the pregnancy.

Statistical analysis

To analyse the association between maternal age and birth outcomes, we estimated linear probability models because of its ease of interpretation of the results. Coefficients are interpretable as marginal effects which means that the coefficient of an age group indicates the percentage-point increase in the probability of poor birth outcome associated to giving birth in that age group compared to the baseline (Wooldridge, 2012). Equivalent logistic models provided similar results, and the odds ratios are shown, for comparison, in Supplementary Tables SI and SII. We estimated separate models for the two birth outcomes, and for mothers who conceived either through MAR or naturally. For each outcome, we estimated four sets of models. Model 1 introduced controls for the child's characteristics. Model 2 controlled for the child's characteristics while also introducing controls for the woman's health before pregnancy. Model 3 controlled for the child's characteristics while also introducing controls for family income and maternal smoking during pregnancy. Model 4 included all of the control variables. Table I shows mothers' and infants' characteristics by the way of conception. The maternal age coefficients resulting from the linear probability models with LBW or pre-term birth as the outcome variable are presented in Table II and Table III, respectively. The coefficients for the control variables included in the different model specifications are presented in Supplementary Tables SIII and SIV.

Table I Background characteristics of mothers and infants born in 1995–2000 in Finland, by whether the child was conceived through MAR[1] or naturally.

	MAR					Natural conception				
	25–29	30–34	35–39	40+	Total	25–29	30–34	35–39	40+	Total
Multiple births (%)	14.8	24.3	20.5	18.7	20.4	1.6	2.6	2.9	2.1	2.3
Girl (%)	46.3	48.9	50.9	47.2	48.6	48.8	49.0	48.8	50.9	48.9
First parity (%)	73.8	62.1	47.2	44.0	60.4	44.5	27.6	18.9	15.6	32.5
Smoking during pregnancy (%)	8.9	4.1	6.5	4.4	6.0	13.5	11.5	12.2	12.1	12
Income deciles (mean)	5.5	6.7	6.8	6.4	6.4	5.1	5.9	6.1	6.0	5.6
Number of miscarriages (mean)	0.2	0.3	0.5	0.6	0.4	0.2	0.3	0.4	0.6	0.3
Diagnosed chronic or acute health condition (%)	2.9	4.1	5.7	11.5	4.7	3.2	3.8	4.8	5.9	3.8
%	27	42	24	7	100	41	39	17	3	100
N	717	1091	634	182	2624	21 120	20 089	8989	1801	51 999

[1]MAR, medically assisted reproduction.

Table II Proportion of and % change in the predicted probability of low birth weight for children conceived through MAR (*n* = 2624) or naturally (*n* = 51 999).

	Proportion	Model 1: birth order + multiple birth + child's sex		Model 2: Model 1+ mother's health before pregnancy		Model 3: Model 1 + income + smoking during pregnancy		Model 4: fully adjusted	
					MAR (*n* = 2624)				
Maternal age	**%**	***B*[1]**	**95% CI**	***B***	**95% CI**	***B***	**95% CI**	***B***	**95% CI**
25–29	10.7	−0.22	(−3.2 to 2.8)	−0.17	(−3.2 to 2.9)	−0.49	(−3.6 to 2.6)	−0.34	(−3.4 to 2.8)
30–34 (ref[1])	13.9	0.0		0.0		0.0		0.0	
35–39	10.9	−1.34	(−4.5 to 1.8)	−1.4	(−4.5 to 1.7)	−1.35	(−4.5 to 1.8)	−1.54	(−4.7 to 1.6)
40+	17.6	5.99	(0.49 to 2.57)	5.73	(0.0 to 11.5)	5.99	(0.2 to 11.8)	5.47	(−0.2 to 11.2)
					Natural conception (*n* = 51 999)				
25–29	3.0	−0.55	(−0.91 to −0.19)	−0.54	(−0.89 to −0.18)	−0.7	(−1.06 to −0.33)	−0.65	(−1.02 to −0.29)
30–34 (ref)	3.4	0.0		0.0		0.0		0.0	
35–39	4.3	1.08	(0.58 to 1.58)	1.06	(0.55 to 1.56)	1.09	(0.59 to 1.60)	1.02	(0.52 to 1.52)
40+	4.4	1.53	(0.49 to 2.57)	1.47	(0.43 to 2.51)	1.55	(0.52 to 2.59)	1.34	(0.29 to 2.38)

Results from linear probability models. Coefficients denote percentage point changes in the predicted probability of low birth weight.
[1]Reference groups for all models is maternal age between 30 and 34 years.

Results

The mothers' characteristics and the infants' characteristics and outcomes differed considerably depending on whether the birth was after MAR or was naturally conceived (Table I). First, higher proportions of mothers who conceived through MAR gave birth at older ages than of mothers who conceived naturally: among the MAR mothers, 24% gave birth at ages 35–39 and 7% gave birth at ages 40 and older, while among the mothers who conceived naturally, the corresponding shares were 17 and 3%. Second, in line with findings reported in the literature, the MAR children were more likely to be twins and were more likely to be first born. Third, in terms of maternal socio-economic characteristics, the MAR mothers had a higher average income and were less likely to have smoked during pregnancy than the mothers who conceived naturally. The MAR mothers were also more likely to have experienced a miscarriage and to have suffered from a chronic disease than the mothers who conceived naturally.

The incidence of both LBW and preterm was consistently higher among MAR-conceived children than among naturally conceived children higher (overall 12.6% LBW among MAR children compared to 3.4% among NC children; 14.2% preterm birth among MAR children compared to 4.9% among NC children) at all maternal ages. However, while it increased with the age of the mother among the naturally conceived children, the pattern was less clear among the MAR-conceived children (Tables II and III).

Linear probability models

The results from the linear probability models suggest that, despite the older maternal ages and the higher prevalence of poor birth

Table III Proportion of and % change in the predicted probability of preterm birth for children conceived through MAR ($n = 2624$) or naturally ($n = 51\,999$).

	Proportion	Model 1: birth order + multiple birth + child's sex		Model 2: Model 1 + mother's health before pregnancy		Model 3: Model 1 + income + smoking during pregnancy		Model 4: fully adjusted	
					MAR ($n = 2624$)				
Maternal age	**%**	***B***	**95% CI**	***B***	**95% CI**	***B***	**95% CI**	***B***	**95% CI**
25–29	12.5	−0.32	(−3.91 to 3.27)	−0.26	(−3.85 to 3.33)	−0.44	(−4.10 to 3.22)	−0.27	(−3.94 to 3.40)
30–34 (ref)	15.6	0.0		0.0		0.0		0.0	
35–39	13.2	−0.57	(−4.39 to 8.94)	−0.65	(−4.47 to 3.17)	−0.66	(−4.47 to 3.16)	−0.86	(−4.69 to 2.97)
40+	15.9	2.59	(−3.76 to 8.94)	2.24	(−4.09 to 8.56)	2.61	(−3.75 to 8.97)	2.02	(−4.30 to 8.33)
					Natural conception ($n = 51\,999$)				
25–29	4.5	−0.27	(−0.70 to 1.16)	−0.24	(−0.67 to 0.19)	−0.43	(−0.87 to 0.01)	−0.35	(−0.79 to 0.09)
30–34 (ref)	4.6	0.0		0.0		0.0		0.0	
35–39	5.8	1.30	(0.71 to 1.90)	1.26	(0.66 to 1.85)	1.33	(0.74 to 1.93)	1.21	(0.62 to 1.81)
40+	6.1	1.91	(0.71 to 3.11)	1.81	(0.61 to 3.00)	1.95	(0.75 to 3.15)	1.61	(0.41 to 2.81)

Results from linear probability models.

outcomes observed among the MAR pregnancies, maternal age was not associated with the probability of LBW or preterm birth among the MAR births (Tables II and III and Figs 1 and 2).

Among the mothers who conceived through MAR, those at both younger maternal ages (25–29) and at maternal ages between 35 and 39 had a lower risk of giving birth to a LBW child than those in the reference age group (30–34). However, these associations were small in magnitude, and the differences in the risk ranged from slightly positive to negative associations (respectively $\beta = -0.22$, 95% CI = −3.2 to 2.8 and $\beta = -1.34$, 95% CI = −4.5 to 1.8; Table II). The coefficients did not change with the inclusion of maternal characteristics in Models 2 through 4. On the contrary, the risk of LBW was substantially increased for mothers aged 40 or older ($\beta = 5.99$, 95% CI = 0.2 to 11.8). The association was only slightly attenuated after adjustment for the mother's health before pregnancy and socio-economic indicators: in the fully adjusted model, the probability of giving birth to a LBW child after MAR was 5.47 (95% CI = −0.2 to 11.2) percentage points higher at maternal ages 40+ than at ages 30–34.

By contrast, among mothers who conceived naturally, the results showed a clear age gradient in the probability of giving birth to a LBW child. The probability of giving birth to a LBW child was 0.55 (95% CI = −0.91 to −0.19) percentage points lower at maternal ages 25–29 than at the reference group ages, while the probability of giving birth to a LBW child was higher at maternal ages older than at the reference category ages ($\beta = 1.08$, 95% CI = 0.58 to 1.58 for ages 35–39 and $\beta = 1.53$, 95% CI = 0.49 to 2.57 for ages 40 or older in Model 1). The association was only slightly attenuated on adjustment for the mothers' health conditions and socio-economic indicators (for example, to $\beta = 1.02$, CI = 0.52 to 1.52 for the 35–39 age group).

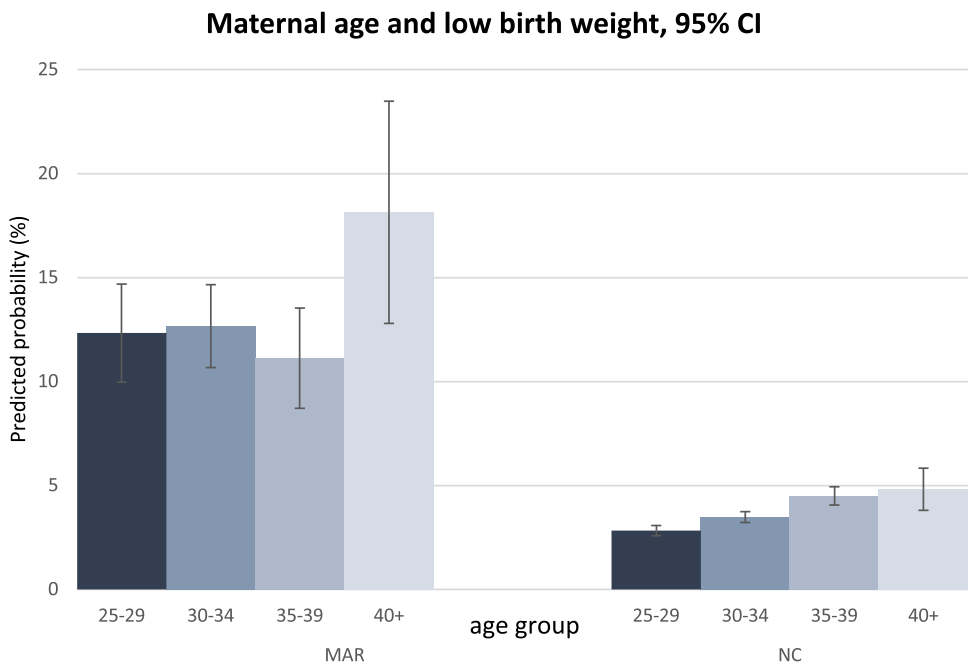
Among the MAR mothers, maternal age was not associated to an increased risk of preterm birth at ages 25–39, while the risk of preterm birth was 2.59 percentage points higher at maternal ages 40+ than at ages 25–39 (Table III). However, a relatively wide range of risk differences, running from a negative association to a substantial positive association, was compatible with our data (95% CI: −3.76 to 8.94). The coefficients of maternal age were only slightly reduced after adjustment for the mothers' pre-pregnancy health conditions and socio-economic indicators. The age gradient for the mothers who conceived naturally was similar to that observed for LBW.

These results suggest that although an age gradient in the probability of poorer birth outcomes at birth was clearly observable among the mothers who conceived naturally, with the probability of a LBW or a preterm birth increasing with maternal age across all age groups, no such age gradient was observable among the MAR mothers. The probability of giving birth to a LBW or a preterm child was higher only for the MAR mothers aged 40 or older, while the risk of an adverse birth outcome was not associated with maternal age for the MAR mothers younger than age 40. We also ran the same linear probability models (Model 1) on the whole sample and included the interactions between MAR and maternal age groups (Supplementary Table SV). The results of joint tests on the interactions showed that the age gradient of the mothers who conceived through MAR and of the mothers who conceived naturally differed significantly for low birth weight ($P = 0.078$), but not for premature birth ($P = 0.359$).

As a robustness check, we estimated the models while excluding multiple births. The results for both low birth weight and preterm births among singletons (Supplementary Table SVI) support the main study arguments.

Discussion

Our results, which are based on a large representative sample of Finnish women, show that an increasing maternal age was not associated with worse birth outcomes for MAR mothers who were aged 25–39 at the time of birth. These results are in line with Wennberg *et al.* (2016), who found that there was no significant increase in the risk of adverse birth outcomes with older maternal age among MAR pregnancies. Differently from their results, which showed no increased



Abbreviation: MAR, medically assisted reproduction. NC, natural conception.

Figure 1 Predicted probability of low birth weight for children conceived through MAR ($n = 2624$) and naturally ($n = 51\,999$) in Finland in 1995–2000 by maternal age categories. Results from adjusted linear probability models. MAR, medically assisted reproduction; NC, natural conception.

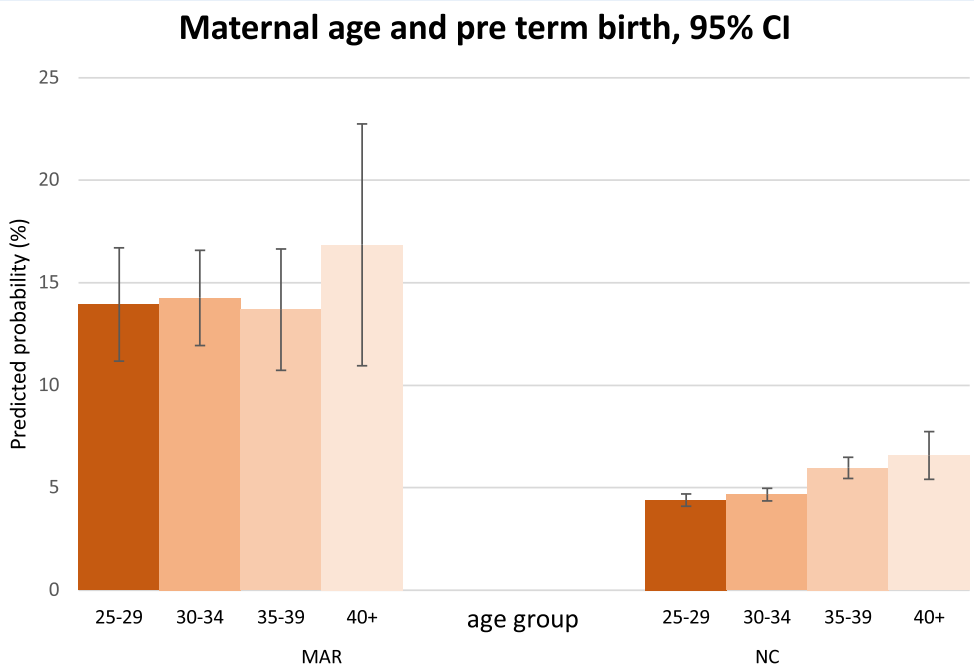


Figure 2 Predicted probability of preterm birth for children conceived through MAR ($n = 2624$) and naturally ($n = 51\,999$) in Finland in 1995–2000 by maternal age categories. Results from adjusted linear probability models.

risk for the whole age range considered (up to 46 years), we also observed an increased risk for mothers aged 40 or older. However, in our sample, only a small proportion (7%, 182 women) of all mothers who used MAR to conceive were aged 40+, which means that we only

observe an age-related increase in the risk of adverse outcomes for a limited proportion of the studied population. Importantly, in this study, we were able to show that these results are robust to adjustment for the mothers' socio-economic characteristics. This is important, in light of the potential selected profile of MAR mothers (Chambers *et al*., 2014; Barbuscia and Mills, 2017) and especially of those who conceive at a more advanced age. Older MAR mothers might thus represent a group that has higher incomes, is better educated and adopt healthier lifestyles during pregnancy than many older SC mothers, which might explain why no adverse birth outcome risk excess was observed in previous studies (Wennberg *et al*. 2016). We were also able to control for maternal health before the pregnancy. Although the available information did not allow us to control for all health characteristics that might be associated with both birth outcomes and the use of MAR treatments, our measure was able to capture the presence of a series of important chronic or acute health conditions (Cleary-Goldman *et al*. 2005) that could confound the results.

The results indicate that there was a clear age gradient in birth outcomes among mothers who conceived naturally, with the probability of poorer birth outcomes increasing with the age of the mother; this finding is also in line with the existing literature (Aldous and Edmonson, 1993; Hemminki and Gissler, 1996; Jolly *et al*., 2000; Carolan and Frankowska, 2011, Klemetti *et al*., 2016; Goisis et al., 2017). For all births, the link between older maternal age and adverse birth outcomes is partly explained by subfertility (Leridon, 2004; Thomson *et al*., 2005; Kondapalli and Perales-Puchalt, 2013; Somigliana *et al*., 2016). A possible interpretation of our finding that there was no age gradient in adverse birth outcomes prior to age 40 among the MAR mothers is that, within this group, subfertility was experienced at all ages, including at younger ages.

It is also possible that the women who seek MAR treatments at younger ages differ substantially from the women who seek MAR treatments at older ages. Moreover, the women's reasons for accessing these treatments might differ by age as well. The women who use MAR treatments at relatively young ages (35 or younger) may have health/subfertility conditions that they were informed of early in life, which could indicate that they suffer from more serious health problems than the women who access MAR treatments at older ages. This selection would bias our results by increasing the incidence of adverse birth outcomes among younger mothers and would therefore mask the more typical age gradient found for naturally conceived births. Unfortunately, we were not able to include any controls for the reproductive conditions linked to the use of MAR as they are not included in the category for special reimbursement, and information on the specific diagnoses behind other prescriptions is not available in the medication registry. However, our descriptive statistics suggest that this was not a serious issue in our analysis, as the women who conceived through MAR at younger ages do not seem to differ substantially from their counterparts who conceived at older ages in terms of their health conditions or experience of miscarriages.

However, the strongly increased risk of adverse birth outcomes found among the women who conceived through MAR at age 40 or older might be partly attributable to their more prolonged exposure to the stress associated with undergoing MAR treatment. Indeed, an older maternal age might be associated with having undergone a series of unsuccessful treatments before the treatment that resulted in a live birth. The link between maternal stress and the risk of a preterm birth or a LBW has been reported in the literature for naturally conceived births (e.g. Smits *et al*. 2006; Torche, 2011). Mothers aged 40 or older might also represent a particularly selected subgroup in terms of their health conditions or other characteristics not captured by our control variables. These characteristics might help to explain why these mothers took a long time to conceive, and why they faced a much higher risk of poorer birth outcomes. In addition, conceiving at an older age might imply that the mother used a more invasive treatment, such as IVF and ICSI, whereas a younger mother may have achieved pregnancy through ovulation induction. Finally, it is possible that the explanation for this association is multifactorial, and that the increased risk of adverse birth outcomes observed among MAR mothers aged 40 or older is the result of the cumulative interactive effects of the use of MAR treatments and advanced maternal age. The medical literature has identified age 40 as a clinically meaningful threshold for a higher probability of adverse birth outcomes (Mills and Lavender, 2007; Klemetti *et al*., 2016).

Strengths and limitations

In the interpretation of the results, some methodological issues need to be considered. First, we could not reliably distinguish between the different kinds of MAR treatments used, which include less invasive treatments that are less strongly associated with adverse birth outcomes, (De Geyter *et al*., 2018), such as ovulation induction, as well as more invasive treatments, such as IVF. Because we did not have access to the National Procedure Register, we could not reliably distinguish IVF treatments from the less invasive treatments, which led us to underestimate the percentage of children conceived by IVF by about 10% (Goisis *et al*. 2019). Despite these data limitations, we conducted robustness checks to test whether our results could be driven by differences in the types of MAR treatments that younger and older mothers undergo. We estimated the models while adjusting for treatment type, and the results were unchanged. We estimated the models separately for the group of children conceived by IVF (40% of all MAR births), and the results supported the main study argument. This evidence suggests that our results are unlikely to be driven by differences in the types of treatment used by younger and older MAR mothers. Second, our measures of maternal health before pregnancy did not cover all of the health conditions that might be relevant for both maternal age at birth and birth outcomes. This could explain why this measure only partially attenuated the increased risk at ages 40+. Third, we did not have information about the duration of the treatments, which might be associated with both maternal age and birth outcomes.

Overall, this study represents an important contribution to the literature on birth outcomes after MAR. We show that maternal age was not associated with adverse birth outcomes below age 40 but was strongly associated with adverse birth outcomes at ages 40+. We also show that this increased risk was only partly explained by the mother's health condition or by other potentially crucial factors, such as the mother's income and whether she smoked during pregnancy. Having a better understanding of the birth outcomes of MAR mothers at advanced ages is crucial in light of the increasing number of women and couples undertaking MAR at older ages. More conclusive evidence about the risks associated with very advanced maternal ages (≥40) will enable the many women and couples with infertility or subfertility problems to make well-informed choices about the use of MAR treatments. When interpreting our results, it is important to bear in mind that our sample

only includes women who succeeded in conceiving through MAR, and who had a pregnancy that ended in a live birth. The live birth rate after MAR decreases dramatically with age (among others, see Ferraretti *et al*., 2017). Therefore, our results do not suggest that maternal age is irrelevant for the outcomes of MAR, or that it should not be considered when making decisions about MAR treatments. Instead, our findings suggest that maternal age is not necessarily associated with a higher incidence of LBW or preterm deliveries in the MAR pregnancies of women under age 40.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

Substantial contribution was made by A.B. and A.G. in terms of devising the idea, designing the study and critically discussing the results. A.B. wrote the first draft of the manuscript. A.G. executed the data analysis. A.G., P.M., H.R., E.S., R.K. and M.M. contributed with statistical advise, critical comments and revising the paper. All authors approved the final version of the paper.

Funding

European Research Council [803959 MARTE to A.G. and 336475 COSTPOST to M.M.].

Conflict of interest

E.S. reports personal fees from Theramex, personal fees from Merck Serono, personal fees from Health Reimbursement Arrangement, non-financial support from Merck Serono, grants from Ferring and grants from Theramex, outside the submitted work. The remaining authors have no competing interests.

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