# Maternal age gradient in children's outcomes among mothers conceiving with Medically Assisted Reproduction

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## Abstract

A consistent evidence shows that children conceived through medically assisted reproduction (MAR) are at higher risk of poorer birth outcomes and especially of being low birth weight and born pre-term. As many women undertake MAR treatments at a relatively advanced age, which is itself a well-known risk factor for adverse birth outcomes, it is suggested that the older age of MAR mothers might play an important role in the observed association between the use of treatments and birth outcomes. However, the evidence is scarce and inconclusive. In this study we use large-scale Finnish register data to examine the association between maternal age and low birth weight among MAR mothers, and whether the maternal age gradient in birth outcomes differ from mothers who conceive naturally. Our first results from the linear probability models show a stronger maternal age gradient among mothers who conceived naturally compared to MAR mothers.

## Introduction

The use of medically assisted reproduction (MAR) – i.e., reproduction brought about through treatments such as ovulation induction, artificial insemination, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and artificial insemination, has increased quickly over the last 4 decades. Since 1978, when the first baby was born *in vitro*, it is estimated that more than 5 million babies have been conceived with the aid of MAR treatments. The proportion of babies born through MAR reached the 6% of all births in some European countries such as Denmark and Belgium (Calhaz-Jorge et al., 2016) and is higher among women conceiving at relatively advanced ages, as fertility treatments are often used to deal with age-related infertility or sub-fertility problems (Luke and Brown 2007).

A consistent evidence has shown that MAR is associated with increased risks of adverse birth outcomes and especially with a higher incidence of low birth weight (LBW) and pre-term delivery, partly due to the high incidence of multiple births occurring among MAR pregnancies (Kalra et al., 2011). However, the mechanisms underlying the association between the use of MAR treatments and birth outcomes have not been fully identified yet (Kalra et al., 2011, Pinborg et al., 2012; Goisis et al., 2018). Multiple births seem to only partly explain the association, as prior studies have shown that singletons conceived through MAR also are at higher risk of being LBW, born pre-term, or small for gestational age (for a review, see Pinborg et al., 2012). Other factors might affect the birth outcomes of MAR-conceived children. The MAR treatment techniques themselves, including IVF and ovarian stimulation, might have a negative impact on the offspring. Moreover, the association might be related to parental characteristics that predispose the parents to seek MAR and that are known risk factors for adverse birth outcomes, such as subfertility and advanced age (Basso and Baird, 2003; Kalra et al., 2011). In particular, given that many women seek MAR treatments at relatively advanced age, and that there exist a well-established association between maternal age and risk of LBW and preterm delivery (Hemminki and Gisler, 2009; Aldous et al. 1993), it has been suggested that the relatively older age of MAR mothers might play an important role for the observed higher risks of adverse birth outcomes (Tough et al., 2000). However, existing evidence indirectly challenges this perspective by showing that, even on adjustment for maternal age at birth, MAR-conceived singletons have higher risks of adverse perinatal outcomes than NC

singletons (Pinborg et al., 2012). This perspective is supported by the only existing study (Tough et al., 2000) which has directly tested the role of maternal age on the birth outcomes of MAR-conceived children and which shows that an advanced maternal age is not associated with worse birth outcome amongst MAR-conceived children. However, the study relied on a small and non-representative sample of mothers in Canada. Therefore, more conclusive evidence on the role of maternal age in explaining the higher risk of poorer birth outcomes amongst MAR-conceived children is needed.

In this study, we address this gap in knowledge and we examine the association between maternal age and the risk of poorer birth outcomes among mothers who conceived thorough MAR compared to those who conceived naturally using, for the first time, large-scale and representative Finnish register data. We included important potential confounders such as whether the child is part of a multiple birth, parity and health conditions of the mother before and during the pregnancy. The question whether and to what extent a more advantaged maternal age is associated with increased risks of LBW and preterm delivery among women conceiving through MAR is of high importance in light of the widespread and increasing use of MAR treatments, especially among older women. Pre-term birth and LBW are associated with lower cognitive ability in childhood as well as other negative outcomes later in life (Black, et al 2007; Saigal & Doyle, 2008). It is therefore important to improve our understanding of the reasons behind the observed increased rates of poorer birth outcomes among MAR children.

## Data

### Study population

The study utilized data from the Finnish population register and other administrative registers. The base dataset was 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 (n=415,000). The linkages between different registers were carried out by Statistics Finland using unique personal identification numbers. In this study, we restricted the data to children who were born in 1995–2000, primarily because the information (described below) on whether the child was conceived through MAR or naturally was available from 1995 onwards. Our final sample consists of 56,026 children, of whom 2,676 were conceived through medically assisted reproduction treatments.

### Birth outcomes

Information on birth outcomes was extracted from the Finnish Medical Birth Register (MBR). We used two dependent variables: whether the child had low birth weight (LBW, less than 2500 g at birth) and whether the child was delivered preterm (less than 37 weeks of gestation). Here, we only show analyses and results for LBW.

### Medically Assisted Reproduction (MAR)

The key explanatory variable is a binary indicator of whether the child was conceived through MAR or naturally. 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. By combining each woman's purchases of fertility drugs with her child's date of birth, we were able to identify children conceived through MAR. We followed the method developed by Hemminki et al., which has been found to be reliable. Detailed information on the data linkage can be found in the appendix of Hemminki's paper.[19]

### Control variables

We control for the basic characteristics of the child (sex and whether she/he was part of a multiple birth) and a number of control variables that might confound the association between MAR treatments and birth outcomes: complication during pregnancy or delivery (whether the child was born through c-section, whether the mother suffered of high blood pressure during

the pregnancy); health before pregnancy (whether the mother experienced one or more miscarriages before the pregnancy).

## Methods

We implemented linear probability models where the birth outcomes (as binary variables) are the dependent variable, and maternal age group is the main explanatory variable. Our reference category is maternal age between 30-35. First, we examine the unadjusted association of maternal age-group with the birth outcome (controlling for sex of the child and whether she/he was part of a multiple pregnancy). In subsequent models, we adjust for the birth order of the child, and for complications experienced by the mothers during and before the pregnancy.

## Preliminary Results

Descriptive statistics (Table 1) show that mothers who conceive through MAR are on average older then mothers who conceive naturally, and that MAR children show a higher prevalence of multiple births, LBW and pre-term births. However, the results from the linear probability models for low-birth-weight show a stronger maternal age gradient among mothers who conceived naturally compared to MAR mothers. Mothers aged 35 and over who conceived naturally experienced significantly higher risk of giving birth to a LBW child compared to their counterparts who gave birth at ages 30-34. In contrast, amongst mothers who used MAR to conceive, the risk increased only for mothers aged 40 and above – who represent only 7% of mothers who conceive through MAR. These preliminary results question the role of advanced maternal age in explaining the increased risk of poorer birth outcomes amongst children conceived through MAR. We will build and expand on these results and test the same associations using preterm delivery as an outcome and using different maternal age categories to check the robustness of these findings.

**Table 1: Descriptive characteristics of the sample, by maternal age-group and whether the child was conceived through MAR (%)**

| | ***Natural conception*** | | | | | ***MAR*** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **25-29** | **30-34** | **35-39** | **40-44** | **Tot** | **25-29** | **30-34** | **35-39** | **40-44** | **tot** |
| LBW | 3.02 | 3.42 | 4.32 | 4.79 | 3.46 | 10.66 | 13.75 | 11.16 | 18.28 | 12.59 |
| Pre-term | 4.51 | 4.68 | 5.87 | 6.46 | 4.88 | 12.43 | 15.45 | 13.80 | 16.67 | 14.31 |
| 1st parity | 44.36 | 27.61 | 18.88 | 15.35 | 32.48 | 73.77 | 61.99 | 46.98 | 44.09 | 60.35 |
| 2nd parity | 37.34 | 38.39 | 30.61 | 21.70 | 36.04 | 20.77 | 29.74 | 32.40 | 30.65 | 27.99 |
| 3rd parity | 18.30 | 33.99 | 50.51 | 62.95 | 31.48 | 5.46 | 8.27 | 20.62 | 25.27 | 11.66 |
| Girl | 48.75 | 48.97 | 48.74 | 51.21 | 48.79 | 46.45 | 48.88 | 50.39 | 47.31 | 48.47 |
| Multiple birth | 1.60 | 2.61 | 2.93 | 2.05 | 2.23 | 14.48 | 24.08 | 20.47 | 19.35 | 20.25 |
| c-section | 13.81 | 16.67 | 20.38 | 25.26 | 16.45 | 25.82 | 29.29 | 35.50 | 45.70 | 30.98 |
| High pressure | 3.48 | 3.45 | 4.40 | 6.03 | 3.72 | 6.69 | 7.01 | 6.98 | 8.06 | 6.99 |
| N | 40.63 | 38.59 | 17.30 | 3.48 | 100.0 | 27.35 | 41.59 | 24.10 | 6.95 | 100.0 |

**Table 2: Linear probability models on low birth weight (% change in the predicted probability), by mode of conception**

| | *Natural births* | | | *MAR births* | | |
|---|---|---|---|---|---|---|
| | **Model 1: unadjusted** | **Model 2: birth order** | **Model 3 health before/during pregnancy** | **Model 1: unadjusted** | **Model 2 birth order** | **Model 3 health before/during pregnancy** |
| | B | β | β | β | β | B |
| Maternal age 25-29 (*reference: maternal age 30-34)* | -0.09 | -0.55*** | -0.21 | 0.51 | -0.06 | 0.14 |
| Maternal age 35-39 | 0.81*** | 1.06*** | 0.61** | -1.21 | -1.01 | -1.62 |
| Maternal age 40+ | 1.53*** | 1.89*** | 0.81 | 6.30** | 6.41** | 5.01* |
| Multiple birth | 29.76*** | 29.7*** | 27.74*** | 37.73*** | 37.41*** | 35.73*** |
| Girl | 0.52*** | 0.51*** | 0.60*** | -0.89 | -1.1 | -0.87 |
| Pregnancy order second (*reference: first*) | | -2.57*** | -1.83*** | | -5.82*** | -5.12*** |
| Pregnancy order third | | -2.71*** | -1.78*** | | -0.44 | -0.16 |
| C-section delivery | | | 5.59*** | | | 5.21*** |
| High blood pressure during pregnancy | | | 9.86*** | | | 11.01*** |
| Miscarriage before pregnancy: 2 (*reference one*) | | | 0.40* | | | 0.28 |
| Miscarriage before pregnancy: 3 or more | | | 1.18*** | | | 2.69 |
| Constant | 2.39*** | 4.30*** | 2.31*** | 5.10*** | 7.04*** | 4.53*** |
| Number of observations | 53,350 | 53,350 | 53,350 | 2,676 | 2,676 | 2,676 |

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