

# The Effect of Very Advanced Maternal Age on Maternal and Neonatal Outcomes: A Systematic Review

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## Abstract

**Objective:** To summarize information on the maternal and perinatal outcomes among pregnant women with a maternal age greater or equal to 45 years old compared with women with a maternal age of less than 45.

**Methods:** A comprehensive systematic search of online databases from January 1946 through June 2015 was completed. The maternal outcomes were: fetal loss, preterm birth, full-term birth, complications of pregnancy, the type of delivery, and periconception hemorrhage. The fetal outcomes were: intrauterine growth restriction/LGA, fetal anomalies, APGAR score, and neonatal death.

**Results:** Twenty articles were included in the systematic review and 15 included in the meta-analysis. There was a 2.60 greater likelihood of fetal loss ( $I^2 = 99\%$ ). Newborns of women of a very advanced maternal age were 2.49 more likely to have a concerning 5-minute APGAR score. Very advanced maternal age women had a 3.32 greater likelihood of pregnancy complications ( $I^2 = 91\%$ ). There was a 1.96 greater likelihood of preterm birth at very advanced maternal age ( $I^2 = 91\%$ ) and a 4 times greater likelihood of having to deliver through Caesarean section ( $I^2 = 97\%$ ).

**Conclusion:** This systematic review showed an increased risk of adverse maternal and perinatal outcomes. The large amount of heterogeneity among most outcomes that were investigated suggest results must be interpreted with caution.

## Résumé

**Objectif :** Résumer et comparer les issues maternelles et périnatales des femmes de 45 ans et plus à celles des femmes de moins de 45 ans.

**Key Words:** Very advanced maternal age, advanced maternal age, systematic review, adverse birth outcomes

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**Méthodologie :** Nous avons mené des recherches systématiques exhaustives dans des bases de données en ligne pour la période allant de janvier 1946 à juin 2015. Les issues maternelles retenues étaient : la perte fœtale, l'accouchement prématuré, l'accouchement à terme, les complications durant la grossesse, le type d'accouchement et les hémorragies. Les issues fœtales retenues étaient : le retard de croissance intra-utérin, le fait d'être gros pour l'âge gestationnel, les anomalies fœtales, l'indice d'Appgar et le décès néonatal.

**Résultats :** Au total, 20 articles ont été retenus pour la revue systématique, et 15 pour la méta-analyse. Les femmes dont l'âge maternel était très avancé couraient un risque 2,60 fois plus élevé de perte fœtale ( $I^2 = 99\%$ ) que l'autre groupe, et leurs nouveau-nés couraient un risque 2,49 fois plus élevé de présenter un indice d'Appgar inquiétant à cinq minutes de vie. Elles présentaient également un risque 3,32 fois plus élevé de complications durant la grossesse ( $I^2 = 91\%$ ), un risque 1,96 fois plus élevé d'accouchement prématuré ( $I^2 = 91\%$ ) et un risque 4 fois plus élevé de césarienne ( $I^2 = 97\%$ ).

**Conclusion :** Cette revue systématique a montré que les femmes d'âge maternel très avancé courent un risque accru d'issues maternelles et périnatales indésirables. Les résultats doivent toutefois être interprétés avec prudence, en raison de la grande hétérogénéité observée pour la plupart des issues à l'étude.

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## INTRODUCTION

Over the last 30 years, there has been an increase in the number of women conceiving and giving birth at an advanced maternal age defined as 35 years of age or older. One in five births in Canada in 2011 were to women 35 years of age and older.<sup>1</sup> In the United Kingdom, the average age

at time of delivery rose from 28.4 years in 1999 to 29.4 years in 2009.<sup>2</sup> In 1997, 0.09% of all births in the United States were among women over 45 years, and by 2008, that birth rate had doubled to 0.2%.<sup>3</sup> In 2014, the birth rate in this group in Canada had increased to 0.8%.<sup>4</sup> Women who gave birth after the age of 45 are often referred to as being of a very advanced maternal age. Consequently, with a greater number of mothers delivering at a more advanced age, the average age of mothers has dramatically increased.<sup>1,2</sup> Eleven percent of women who gave birth for the first time in Canada in 2012 were of an advanced maternal age.<sup>4</sup> Other higher income countries, such as the United Kingdom and Australia have also shown similar trends in the pregnant population.<sup>5</sup>

The increase in average age can be largely attributed to the increase in women aged 35 and over becoming pregnant.<sup>3</sup> There are several contributing elements that influence a woman's decision to delay child-bearing, including social, educational, and economic factors.<sup>3</sup> Women with a higher level of education are more likely to postpone pregnancy in order to advance their education or position in their field of work.<sup>5</sup> Furthermore, women in higher income countries are more likely to have greater access to contraceptives, as well as access to assisted reproductive technologies, which may contribute to delayed childbirth.<sup>5</sup> The financial cost of raising a child or the potential costs of associated risks of pregnancy at an advanced maternal age have also influenced decisions to postpone child-bearing.<sup>4</sup>

There are several serious risks for both the mother and child associated with child-bearing at an advanced age, including maternal morbidity (i.e., pre-eclampsia, placenta previa, and diabetes during pregnancy), preterm birth, and stillbirth.<sup>1</sup> As a woman's age increases, fecundity decreases, and this encourages women of an advanced age to seek out other options, including IVF with donor eggs, which has inherent risks such as multiple birth, preterm birth, and increased maternal morbidity.<sup>5</sup> The outcomes of pregnancy at an advanced age have been thoroughly studied, and it has been suggested that as women age, the risk of adverse outcomes increases.<sup>5-7</sup>

The aim of this systematic review was to summarize information on the maternal and perinatal outcomes among pregnant women with a maternal age greater or equal to 45

years old compared with women with a maternal age of less than 45.

## **METHODS**

### **Search Strategy**

A comprehensive systematic search of the online databases Embase and Medline through the Ovid interface from January 1946 through June 2015 was completed. Together, with the aid of a library sciences expert, a search strategy with terms describing advanced maternal age, maternal outcomes, and perinatal outcomes was developed. The maternal outcomes of interest were: fetal loss (miscarriage and still birth), preterm birth, full term birth, complications of pregnancy (hyperemesis, hypertension disorder in pregnancy, diabetes, placental previa, placental accrete/increta), the type of delivery, and periconception hemorrhage (transfusion, hysterectomy, and rate of ICU admission). The fetal outcomes of interest were: intrauterine growth restriction/LGA, fetal anomalies, APGAR (appearance, pulse, grimace, activity, and respiration) score, and neonatal death. Articles in any language were included in the search strategy.

### **Data Abstraction and Assessment of Quality**

A total of 1871 published article titles and abstracts were screened by two independent reviewers throughout all stages of screening. A primary screen of articles was performed in Covidence (<https://www.covidence.org/>), a systematic review software. Articles with the appropriate exposure group (pregnant women 45 years of age and older) or that had a title which suggested the appropriate exposure group and relevance to the study were selected. Publications that only reported on multiples birth were excluded. All conflicts were resolved through discussion between the two abstractors. At the end of the first screen, 272 articles contained the inclusion criteria selected for the study. These articles were fully reviewed through a second screen to ensure relevance to this study. This second screen consisted of obtaining the full text for each article and ensuring to see if the study pertained to our study and met our inclusion and exclusion criteria. After the second screen, the abstractors ensured that there was agreement regarding which articles would be included in the full-text review. Twenty papers were included in the full-text review and 15 papers were included in the meta-analysis. Each reviewer used the Newcastle-Ottawa Scale to independently assess data quality. Using this scale, a study can be given a minimum of zero stars and a maximum of nine stars. Each study was evaluated on three categories: selection, comparability, and outcome (Table 1).

## **ABBREVIATIONS**

ART	assisted reproductive technologies
IUGR	intrauterine growth restriction
VAMA	very advanced maternal age

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