

How does advanced maternal age influence perinatal outcomes?

Valentin Varlas^{1,2},
Vlad Dima²,
Roxana
Georgiana Borș²,
Simona
Vlădăreanu³,
Roxana-Elena
Bohilțea^{1,2}

1. Department of Obstetrics
and Gynecology,
"Carol Davila" University
of Medicine and Pharmacy,
Bucharest, Romania

2. Department of Obstetrics,
Gynecology and Neonatology,
"Filantropia" Clinical Hospital
of Obstetrics and Gynecology,
Bucharest, Romania

3. Department of Obstetrics
and Gynecology,
"Elias" University
Emergency Hospital,
Bucharest, Romania

Corresponding author:

Vlad Dima
E-mail: dima.vlad@yahoo.com

Abstract

Background. The birth at an advanced age of the mother, especially after 35 years old, is more and more frequently observed, not being without risks both for the mother and for the fetus or newborn. This study aims to evaluate the effects of the mother's advanced age on obstetric and perinatal outcomes. **Conclusions.** Pregnancy in the elderly mother is often accompanied by adverse obstetric and perinatal outcomes. In such cases, counseling and monitoring of pregnancies regarding pregnancy risks should be a priority. **Keywords:** advanced maternal age, adverse pregnancy outcomes, perinatal outcomes, maternal outcomes

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Rezumat

Introducere. Nașterea la o vârstă înaintată a mamei, mai ales după 35 de ani, se observă din ce în ce mai frecvent, nefiind lipsită de riscuri, atât pentru mamă, cât și pentru făt sau nou-născut. Acest studiu își propune să evalueze efectele vârstei înaintate a mamei asupra rezultatelor obstetricale și perinatale. **Concluzii.** Sarcina la femeile în vârstă este adesea însoțită de rezultate obstetricale și perinatale adverse. În astfel de cazuri, consilierea și monitorizarea sarcinilor cu privire la riscurile legate de sarcină ar trebui să fie o prioritate. **Cuvinte-cheie:** vârstă maternă înaintată, rezultate adverse ale sarcinii, rezultate perinatale, rezultate materne

Introduction

In the last decade, it has been observed that the advanced maternal age (AMA; ≥ 35 years old) of procreation of women is constantly increasing, being associated with various complications of pregnancy and childbirth.

In the developed countries, the tendency of women to conceive at an advanced age is closely related to the progress of assisted reproduction techniques (ART), the increased number of women with higher education, career advancement, difficulties in starting a family and, last but not least, the line of progress in perinatal management.

A comparative study among 29 countries in Africa, Asia, Latin America and the Middle East revealed that the prevalence of pregnant women with AMA was about 12.3%⁽¹⁾.

In Europe, according to Eurostat, the average age of primiparous has increased from 23.5 years old in 1966 to 28.5 years old in 2011, due to the increase in the number of women giving birth at an advanced maternal age after solving career problems. This phenomenon is also explained by the increasing involvement of ART, which multiply the chances of women above 40 years old to become pregnant⁽²⁾.

In recent years, there has been an increase in the number of women who will give birth at ≥ 40 years old. The advanced maternal age is usually 35 years or older, while very advanced maternal age (VAMA) is defined as being older than 40 or 45 years old. The widespread

use of family planning measures, the postponement of pregnancy due to career goals and the advances in assisted reproduction techniques contribute to this growth. While some researchers have observed an increased rate of adverse pregnancy outcomes in women over the age of 35, others have been unable to find any association between the advanced maternal age and the adverse perinatal outcomes.

AMA is associated with an increased incidence of chromosomal and genetic abnormalities, requiring pre-conceptional counseling of these patients at increased risk of miscarriage. AMA is frequently associated with perinatal and maternal adverse outcomes (e.g., emergency surgical births)⁽³⁾.

There is a relatively high rate of women who conceive at an advanced age which requires a more accurate analysis of the risks in mothers and newborns. Studies have found an increased risk of fetal death, abnormal Apgar score at 5 minutes, complications during pregnancy, risk of premature birth, increased caesarean section, and IUGR.

Wu et al., in a retrospective study, assessed the higher risk of adverse maternal and neonatal outcomes of patients ≥ 43 years old correlated with ART⁽⁴⁾. The profile of patients aged above 45 years old is represented by white patients with high socioeconomic status, primiparous, and who will give birth by caesarean section⁽⁵⁾.

Older women are increasingly using ART, which has been shown to correlate with low and very low birth

weights, premature births, and *placenta praevia*. In addition, unlike spontaneous conception, in patients who used ART, the rate of genetic abnormalities was much lower^(6,7). In recent years, an increase in oocyte donation pregnancies has been observed in women with very advanced maternal age (VAMA), with a decrease in the live birth rate as the recipient's age increases.

The risk of stillbirths compared to AMA is increased to about 4.7%. Other associated risks are fetal growth restriction (FGR), neonatal death, and restriction of admission to the intensive care unit. The risk of stillbirths increases in direct proportion to age, and the association with various associated maternal diseases has not been demonstrated⁽⁸⁾.

The authors performed a literature search on the following MESH terms: (1) "advanced maternal age", (2) "adverse pregnancy outcomes", (3) "perinatal outcomes", and (4) "maternal outcomes", during 10 years. We completed the electronic search on PubMed®/MEDLINE, with filters: clinical trial (CT), randomized controlled trial (RCT), meta-analysis (MA) and systematic review (SR). The records retrieved by search were 2381 articles with 64 CT/RCT, and only four articles on the topic, with 111 SR/MA and only 10 articles on the topic.

This study aims to highlight and personalize maternal care in terms of pregnancy in older women. In addition, in this study, we aimed to review the impact of advanced maternal age on pregnancy complications and fetal outcomes.

Perinatal outcomes

The mother's advanced age was associated with low birth weight, premature birth, low Apgar score, a higher number of newborns hospitalized in the neonatal intensive care unit (NICU), and perinatal death⁽⁹⁾.

An increased incidence of obstetric complications was observed either in the chronologically obsolete pregnancy or in the situation of iatrogenic prematurity. Another common situation is that caused by the association of comorbidities in women over 40 years old. Berger et al. showed that there is a higher incidence of preterm birth (PTB) in older women without comorbidities regardless of birth weight, low birth weight (LBW) regardless of the term, LBW term births, and LBW PTB. Compared to young hypertensive women, those with the same pathology were more likely to have PTB, regardless of birth weight. Thus, AMA is associated with adverse birth outcomes among women with and without health conditions compared to younger women with similar health conditions⁽¹⁰⁾.

Regardless of parity, monitoring pregnancy in AMA requires an optimized screening related to the maternal-fetal health conditions during pregnancy.

Schimmel et al., in a retrospective study, observed that elderly primiparous benefited from an increased number of emergency caesarean sections compared to the control group of young pregnant women. There was also a significant increase in the incidence of small for gestational age (SGA) infants⁽¹¹⁾.

Leader et al. performed a meta-analysis of studies revealed in the systematic search and found that women over the age of 45 have a higher risk of premature birth, FGR, low Apgar score at 5 minutes, and caesarean delivery⁽¹²⁾.

In VAMA, the absolute rate of perinatal deaths remains low, at less than 10 per 1000 births. The chances increase if these pregnant women do not have comorbidities, if they are hospitalized in tertiary centers or if they are monitored by maternal-fetal medicine specialists⁽²⁾.

Older pregnant women are twice as likely to give birth prematurely. Newborns from these pregnant women were 2.5 times more likely to have low Apgar scores and 3.3 times more likely to develop complications in pregnancy. These problems that may occur require good counseling for these patients before they decide to become pregnant. Both maternal and neonatal complications due to premature birth can be followed by neurological sequelae, in addition to the associated costs to manage the possible complications caused by premature birth.

Frederiksen et al. revealed that women older than 40 years of age have an increased risk of birth before 34 weeks of gestation compared to those aged 20-34 (2.01% versus 1.21%). Possible factors associated with the adverse effects of pregnancy due to advanced maternal age are maternal ethnicity, parity, history of pregnancy with a previous chromosomal abnormality, smoking, maternal BMI and use of ART⁽¹³⁾.

Maternal outcomes

The maternal age threshold of above 35 years old is accepted as advanced age, but the research conducted by Kyozyuka et al. found an increased risk of PTB, SGA and LBW in the first pregnancy in 30-year-old patients⁽¹⁴⁾.

How the aging process causes obstetric complications is not completely deciphered. This may be due either to atherosclerotic changes in the myometrial arteries or to a process of degeneration in the myometrial fibers. Vascular changes associated with advanced maternal age result in a low tissue oxygen supply, which will be associated with a phenomenon of either fetal hypotrophy or intrauterine growth restriction. In elderly pregnant women, a switch is observed in terms of the balance between proangiogenic growth mediators (PIGF) and antiangiogenic factors (sFlt-1). Thus, there is an insufficiency of the process of placental angiogenesis by decreasing the PIGF concentration and increasing the levels of sFlt-1^(9,15). The possible mechanisms are arterial deficient remodeling and placental hypoperfusion⁽¹⁶⁾.

Studies show an association in elderly pregnant women with placental changes (placental abruptio, placental necrosis) correlated with preeclampsia, diabetes or with other maternal comorbidities. The advanced age of the mother is associated with oxidative stress (OS) secondary to changes in the production and elimination of free radical species, which lead to their excessive accumulation, with proinflammatory effects. OS generation

interferes with placental angiogenesis through the imbalance of angiogenic growth mediators, ultimately leading to various degrees of placental insufficiency and implicitly on the fetoplacental unit⁽¹⁷⁾.

In elderly pregnant women, the increase of lipid peroxidation does not induce an increased antioxidant response, associated with placental hypoxia, apoptosis, necrosis, endotheliosis, finally altering the OS balance. Therefore, especially during the second and third trimesters, antioxidant supplements are extremely important in maintaining a balance in redox processes.

Intrauterine growth restriction (IUGR), placental abruption and preeclampsia together define the ischemic placental disease (IPD), having as a pathophysiological mechanism the deficient placenta in the first trimester and, subsequently, placental insufficiency^(18,19).

Stratification by age groups showed an increased risk of *placenta praevia* in patients ≥ 40 years old and an increased risk of preeclampsia, long hospital stay and PPRM in women ≥ 45 years old⁽²⁰⁾. A research by Anto et al. identified an increased incidence in the 35-45 age group of elective and emergency caesarean section, premature birth, postpartum hemorrhage, IUGR, placental abruption and dead fetuses compared with the age group 20-29 years old⁽¹⁷⁾.

Nieto et al., in a study of 25,054 women, of which 11.2% were aged between 40 and 44 years old, identified a higher incidence of previous comorbidities among older women: chronic hypertension, diabetes, history of caesarean section and obesity. The age factor is often associated with an increased incidence of women using ART. In the group of women aged ≥ 45 years old, there was an increase in the number of emergency caesarean operations due to elective indications, as well as iatrogenic prematurity above 37 weeks, without any association between AMA and maternal or neonatal outcomes. In women ≥ 45 years old, the risk of emergency caesarean section is significantly higher compared to other age groups, where the rate of caesarean sections for elective indications is increased. This is associated with an increased rate of iatrogenic prematurity above 37 weeks⁽²⁰⁾. This result is in concordance with the results of several other studies^(21,22).

Marozio et al. highlighted that maternal age was an independent risk factor for preeclampsia and diabetes, as well as for *placenta praevia* and preterm birth. Regarding the neonatal results, they were similar in the study groups, except for an increased birth weight rate of less than 2500 g, among women aged 40-44 years old⁽²³⁾.

Gestational and pregestational diabetes mellitus

The advanced age of patients increases the incidence of diabetes secondary to increased insulin resistance and decreased pancreatic B cell function⁽²⁴⁾. Other mechanisms are represented by higher levels of adipokines and oxidative stress⁽²⁵⁾. Preexisting diabetes is more common in older women and is associated with an increased risk of fetal malformations, perinatal complications and stillbirths. The risk of gestational diabetes (GDM) in women

with high preconception BMI was 2.7 times higher in the control group and 3.6 times higher in the elderly age group of the mothers, respectively⁽²⁴⁾.

In a meta-analysis performed on 120 million patients, Li et al. showed a significant correlation between GDM risk and maternal age, which increases in direct proportion to the pregnant woman's age⁽²⁵⁾. Other studies have shown the same results regarding the increased risk of GDM compared to the increase in maternal age^(26,27).

Preeclampsia in pregnancy

Older pregnant women have increased risk factors for high blood pressure, as well as an increased incidence rate for gestational hypertension and preeclampsia. These patients require complete screening, careful monitoring and, whether the situation requires, early intervention to reduce the risk of complications⁽²⁸⁾.

Women with an advanced maternal age above 35 years old have a 4.5 times higher risk of preeclampsia compared to young women⁽²⁹⁾.

According to World Health Organization (WHO) studies, the incidence of preeclampsia is seven times higher in developing countries than in developed countries, being the leading cause of maternal morbidity and mortality by hypertensive disorders in pregnancy^(30,31).

According to the study by Lamminpää et al., women with AMA had a risk of premature birth before 34 weeks of 8.7%; low Apgar scores at 5 minutes of 7.1%; SGA of 26.5%; asphyxia – 12.1%; caesarean section – 25%, and a risk for hospitalizations in NICU of 31.6%⁽³¹⁾. Another study revealed a higher rate of caesarean section, of about 53.5%⁽³²⁾.

Women sometimes perceive the conception of a child at an advanced age as the unique chance of having a child, and thus the concern and anxiety may be different in relation to the way the pregnancy is experienced. Although pregnancy can be uncomplicated, these pregnant women will continue to be concerned throughout pregnancy⁽³³⁾.

In a cross-sectional study conducted with semistructured interviews during 28-36 weeks of pregnancy, Nottingham-Jones et al. sought to highlight interactions of these patients with healthcare providers⁽³⁴⁾.

Kortekaas et al. showed that, in the case of post-term pregnancies which exceeded 41 weeks, pregnant women aged ≥ 40 have an increased risk of maternal and perinatal adverse outcomes⁽³⁵⁾.

Conclusions

Due to the higher rate of comorbidities, these AMA patients should preconceptionally solve their health problems as much as possible or reduce their risk factors: establishing an optimal weight, stopping smoking and alcohol consumption. The high rate of stillbirths among these women recommends inducing labor if the situation is favorable or elective caesarean section at 38-39 weeks of gestation. ■

Conflicts of interests: The authors declare no conflict of interests.

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