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THE FETUS AS A PATIENT

CURRENT PERSPECTIVES



Frank A Chervenak
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Advanced and Very Advanced Maternal Age: Impact on Perinatal and Obstetric Outcomes

4

INTRODUCTION

Historically, advanced maternal age (AMA) is defined as maternal age 35 years or above at delivery, and is associated with several obstetrical and perinatal adverse outcomes.[1-3]

Assisted reproductive technologies (ART) have made it possible for women to conceive and have children at late peri- and postmenopausal age.[4,5] Hence, two new terms are used in literature, very advanced maternal age (VAMA) and extremely AMA for women delivering at age 45–49 and more than or equal to 50 years, respectively.[6,7] The proportion of births to women of AMA (age ≥ 35 years) and VAMA (age ≥ 45 years) has increased overtime throughout the developed world,[8-10] and in developing countries.[11] The first birth rate for women 35–39 years of age in the United States increased from 2.0 to 11.0 per 1,000 (1970–2012), and for women aged 40–44 years it increased from 0.5 to 2.3 per 1,000 (1985– 2012) (Fig. 4.1).[9] In the USA, from 1970 to 2000 prevalence of live births among women aged 35 years and older has increased from 4.5% to 13.8%.[12] Most recent data from Australia indicate that at this very moment, over 20% of women giving birth are older than 35 years.[13] The increase in prevalence of older maternal age at birth is related to various social factors (e.g. longer schooling, higher professional goals, and late marriage), improved awareness and availability of effective contraception, and improvement in ART. The higher risk of poor maternal and birth outcomes in older mothers coupled with increasing frequency of childbearing among older women pose challenges for healthcare providers.[14]

Higher level of maternal services used for AMA women[1,15,16] lead to the higher number of obstetrical interventions and investigations, which tend to make care more costly.[17] Unfortunately the increased intervention rate is independent of maternal complications of pregnancy, labor, and other potentially influencing factors.[16] Often, the "high risk" label is a major factor lowering the threshold of intervention in older women compared to their younger counterparts.[18] Ezra et al. reported that anxiety of clinicians and patients was found to be the leading factor for increased intervention rates.[19] Similarly, Wagner has reported that counseling by obstetricians may play an important role in maternal anxiety and their decision for cesarean delivery (CD) over vaginal birth or trial of labor.[20]

ANTEPARTUM AND INTRAPARTUM COMPLICATIONS

Advanced maternal age has been linked to an increased frequency of CD, preeclampsia, gestational diabetes mellitus (GDM), preterm deliveries (PTDs), and stillbirth.[6,10-12,14,21-24] Similarly, VAMA has been linked with significantly higher frequency of GDM, pre-GDM, and hypertensive disorder associated with pregnancy and chronic hypertension (HTN).[25-28] However, some reports are contradictory to these findings. Two studies from Turkey reported no association between AMA (>40 years) and several complications including GDM, HTN,

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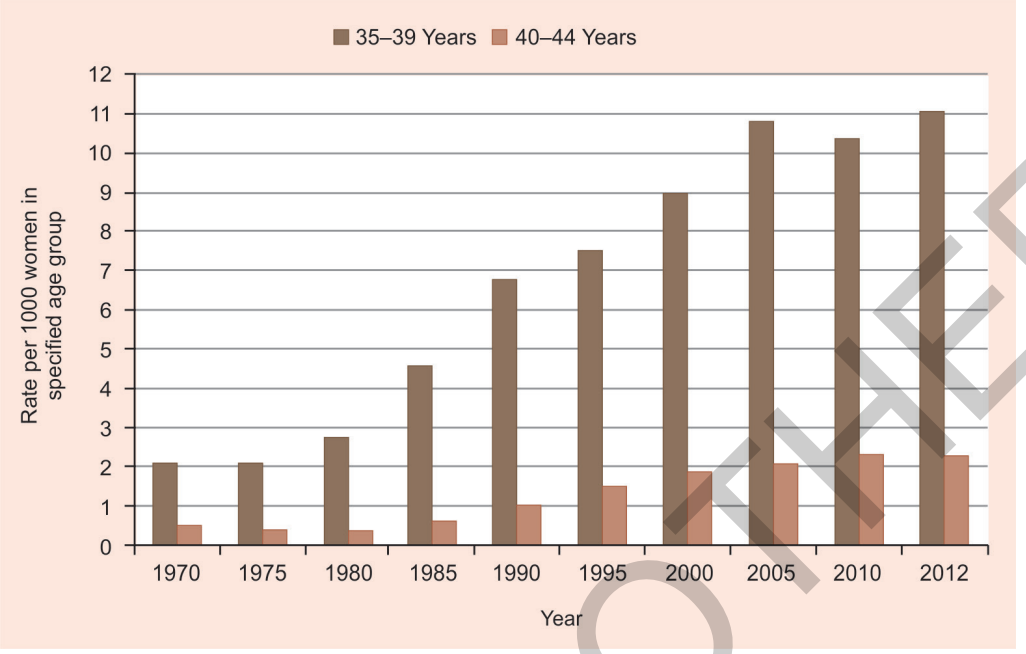


Fig. 4.1: First birth rate by selected age of mother (35–39 years and 40–44 years), 1970–2012.
Source: Matthews TJ, Hamilton BE. First births to older women continue to rise. NCHS Data Brief. 2014;(152):1-8.

preeclampsia, CD, stillbirth, PTD and macrosomia, and newborn respiratory difficulties.[29,30] Some authors have reported no significant difference in the perinatal and obstetrical outcomes,[31,32] birthweight, Apgar score, and admission to the neonatal intensive care unit for AMA patients compared to younger age women.[33] However, majority of the studies do not assess maternal socioeconomic status, parity, and educational level, which may ameliorate some of the adverse effects of the AMA on perinatal outcome.[34-37]

On the other hand, older women are more likely to have preexisting conditions, such as benign uterine growths and leiomyoma, than younger women. Romero et al. indicated that leiomyomas are independently associated with increased risk of placental abruption, dysfunctional labor, fetal malpresentation, and CD.[38]

Preterm Delivery

Preterm birth is the leading cause of infant morbidity and mortality and it complicates between 5% and 18% of all pregnancies.[38] There are conflicting reports on the relationship between maternal age and risk of prematurity. The contributing factors to increase the risk are smaller for gestational age (SGA),[34] hypertensive disorders, and multiple gestations.[10,39] Dulitzki et al. reported higher risk of preterm delivery (18.3% vs 8.4%) and birthweight less than 2,500 g (11.0% vs 4.2%) in women more than 44 years compared to women who were 20–29 years old, respectively.[5] The impact of AMA on the risk of preterm birth in twin pregnancies in the USA Matched Multiple Birth Data Set from 1995 to 1998 reported that only older women with lesser education were at risk of very preterm delivery occurring before 33 weeks.[40]

Hypertensive Disorders

Typically, with normal physiological change in pregnancy, the mean arterial blood pressure is decreased by 5–10 mm Hg, and there is approximately 35% increase in cardiac output from rise in stroke volume and heart rate.[41] Aging makes these adaptations to pregnancy related hemodynamic changes more difficult due to age-related gradual loss of vascular responsiveness to endothelium-dependent vasodilators and loss of myocardial compliance.[42]

Hypertensive disorder is a prominent contributor to maternal morbidity in older women.[43] Gilbert et al. reported that chronic HTN is increased by five-fold in older nulliparous and nine-fold in older multiparous women compared to their younger counterparts.[44] Most of the studies have shown an increased incidence

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of preeclampsia in both nulliparous and multiparous women older than 35 years of age, complicating up to 17% of these pregnancies.[43-46] Barton et al. reported that the higher risk of preeclampsia rate in women more than 35 years of age could be attributed to preexisting maternal hypertensive conditions.[47] However, Cleary-Goldman et al. indicated that advancing age is not associated with higher pregnancy related hypertensive disorders when confounding factors such as body mass index, preexisting medical condition, history of adverse pregnancy outcome, race, education, marital status, smoking, and use of ART are controlled.[48]

Diabetes Mellitus

Advanced maternal age is considered a risk factor for GDM. Abnormal glucose tolerance is three- to fivefold higher in women with AMA.[10,44,49] History of GDM increases risk of GDM in a subsequent pregnancy to as high as 36.5%.[50] Prevalence of pregestational diabetes is also higher in AMA women.[5,7,51] Pancreatic β cell function and insulin sensitivity decline with age.[49] Accelerated nonspecific atherosclerosis might be contributing to higher risk of preeclampsia, placental abruption, and fetal growth restriction in AMA with diabetes. Other diabetes related complications like macrosomia, polyhydramnios, and PTDs are also noted to be higher in AMA women.[52] Cleary-Goldman et al. reported age dependent increase in the risk of GDM, with odd ratio (OR) 1.6 (OR 1.6, 95% CI 1.5–2.1) and OR 2.4 (OR 2.4, 95% CI 1.9–3.1) for GDM in women 35–39 years and more than 40 years, respectively.[48] Gilbert et al. reported a four-fold higher risk of GDM in older women.[44] Bianco et al. reported similar findings, OR 2.7 for GDM in women more than 40 years in nulliparous and 3.8 for multiparas compared to women in 20–29 years.[45]

Metabolic Disorders in Pregnancy

Maternal obesity is a serious health issue in developed and urban areas of developing countries.[53] Obesity is more prevalent in AMA women, and it is commonly associated with pregestational and GDM, HTN, and preeclampsia. Obese patients are reported to have higher risk of congenital malformations, fetal macrosomia, CD, and traumatic delivery.[54,55] Children of obese mothers are at increased risk of developing metabolic syndrome in their later life.[56] Early placentation and fetal programing play an important role in long-term impact on fetal health, as suggested by Barker theory.[57] The effect of poor maternal nutrition, preeclampsia, and poor placentation is linked to adult disease later in life like metabolic syndrome, atherosclerosis, coronary heart disease, type 2 DM, stroke, and obesity.[57-60]

Cesarean Section

Advanced maternal age and VAMA patients have significantly higher risk of delivering via cesarean section.[13,18,30,61,62] Women aged more than or equal to 45 years are sevenfold higher risk of CD when compared to younger women (<30 years), while women older than 50 years almost always deliver via cesarean section.[45]

The higher cesarean section rate in older women is probably due to the following plausible factors:

- Progressive increase in labor dystocia related to maternal age[43,63]
- The uterine arteries develop significant atherosclerosis, which is well correlated with electrocardiogram abnormalities and HTN[64]
- Decreased pelvic compliance, reduced maternal efforts, and decrease in the oxytocin receptors number in the uterus[65]
- Higher maternal request for CD[4]
- Providers not offering a trial of labor.[4]

The frequency of CD for patients more than or equal to 50 years with singleton pregnancies varies from 68% to 100%.[4,66,67] However, none of these studies mentioned attempted trial of labor before CD. If trial of labor was offered to VAMA and extremely AMA women the majority of them (74%) had successful vaginal delivery, without significant adverse maternal or neonatal outcomes.[44] Hence, both trial of labor or CD without trial of labor are reasonably safe options for extremely advanced age women given the knowledge that none are associated with significant maternal or neonatal morbidity.[43] Herstad et al. reported close association between older maternal age more than 40 years and emergency operative deliveries in low-risk primiparous women.[68]

Placenta Previa and Placental Abruption

The premature separation of placenta in placental abruption is attributed to age-related progressive vascular endothelial damage and associated chronic hypertensive

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disorders.[69] Antepartum hemorrhage from placental abruption and placenta previa is reported to be more frequent in older women.[10,39,45,48,49,64,70,71] Salihu et al. documented a *dose dependent* association of maternal age and risk of placental abruption.[39] Ananth et al. reported a 23% increase in placental abruption for AMA women 35–49 years, with twin pregnancies having the highest increase in the risk with age,[72] while Cleary-Goldman et al. did not find any higher rate of abruption and previa until after the age of 40 years.[48] Placental abruption is higher among women with placenta previa, recorded in 28.6% and 24.2% per 1,000 singleton and twin live births, respectively.[72,73]

Placenta previa is an obstetric complication where the placenta is in close proximity to the internal cervical os or obstructs it. It is an important cause of antepartum bleeding especially in second half of pregnancy.[74] This condition is reported to be 2–6% per 1,000 pregnancies.[73] Aging of the uterus and effect of repeated pregnancies have been strongly implicated in the association between maternal age, gravidity, and placenta previa. The incidence of placenta previa is reported to be higher in AMA women.[6,75,76]

POSTPARTUM COMPLICATIONS

The rate of postpartum hemorrhage (PPH) is significantly increased in older women, even after adjusting for possible confounding factors like race, medical history, and route of delivery by OR 3.0 (95% CI 1.4–8.9).[45,49] For women with multiple gestation the risk of PPH was higher for AMA women compared to younger women with multiple gestation.[70]

Childbearing *per se* represents a highly vulnerable period to develop mood disorders. Depression, anxiety, and post-traumatic stress disorders (PTSD) are common perinatal mental health issues. Depression is defined as a state of low mood or loss of pleasure or interest in activities.[77] Anxiety is characterized by feeling of stress and worried thoughts.[77] PTSD is a myriad of psychological symptoms which typically develop after exposure to a traumatic life event.[78] More than 10% of women develop major depressive disorder in their first postpartum period, and older women have higher risk of postpartum depression.[79] Anxiety disorders in antenatal and postpartum periods adversely affect maternal and child health like preterm births and low birthweight.[80] Anxiety disorders prevalence varies from 4% to 39% in antenatal versus 8.5–17% in postpartum periods.[81-83] The prevalence of postpartum depression in the USA and UK is between 6.5% and 14%, respectively,[84-86] while the prevalence was noted to be much higher in low- and medium-income countries (between 28% and 32.6%).[87,88] AMA and VAMA patients are associated with increased pregnancy-related risk, and being "at risk" may cause patient anxiety and increase risk of mood disorders.

Late childbearing, low birthweight infants, multiple births, smoking, and living with grandparents are important factors associated with lower OR for breastfeeding.[89] Liu et al. also found some common factors for shorter breastfeeding, like older age at childbirth, smoking, and living with grandparents.[90] Similarly, Kitano et al. reported highest risk of difficulty with breastfeeding in primiparous AMA women compared to multiparous and younger women at childbearing.[91]

Fortunately, most measures of maternal morbidity are not increased in older women. However, prolonged length of hospital stay in postpartum period is noted among AMA and VAMA patients.[92,93] Campbell et al. studied length of stay in 92 low- and middle-income countries, and explored factors associated length of hospital stay after childbirth, and confirmed that older age at childbirth was a single factor associated with longer hospital stay.[94]

While maternal mortality continues to be a huge concern in developing countries; in the USA and Canada, maternal mortality has significantly declined during the course of last century, but no substantial decrease in the maternal mortality rate (MMR) was noted for the period from 1982 to 1997.[46] This coincided with a dramatic increase in the number of women with AMA, in whom the MMR is reported to be three- to four-fold higher,[46,95,96] with considerable racial disparities within the overall number, being the highest for black women over age 40 years at delivery.[46,95] The higher MMR in older women is thought to be due to various contributing factors like cardiovascular diseases, increased number of CD, placenta previa, placental abruption, and multiparity,[97] though older women with no underlying medical morbidities might not be necessarily at increased risk of such complications.[98]

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PERINATAL OR NEONATAL COMPLICATIONS

Aneuploidy and Congenital Malformations

Numerous studies confirmed that fetal chromosome abnormalities, primarily trisomies, increase with maternal age.[98] The explanation is that oocytes reach metaphase I during the fetal period, and chromosomes remain aligned in the metaphase plate until the oocyte divides prior to ovulation. Aging oocytes have increased risk of nondisjunction due to dysfunctional meiotic spindle, which leads to higher rates of aneuploidy embryos, higher rates of spontaneous abortion, and poor pregnancy outcome.[99,100] Epidemiologic studies revealed a possible correlation between gene abnormalities and advanced maternal and paternal age.

After excluding infants with aneuploidies, the incidence of structural malformation remained significantly elevated in older women.[101] Congenital anomalies, which are more prevalent in AMA patients, are spina bifida, cleft palate, syndactyly, limb defects, male genital malformations, cardiac defects, clubfoot, and diaphragmatic hernia. The risk of cardiac defect is twofold, clubfoot is threefold, and diaphragmatic hernia is 10-fold in older women.[102,103] Therefore, AMA patients should be offered screening for fetal aneuploidy and a detailed fetal anatomy ultrasound scan and fetal echocardiography to look for fetal birth anomalies and cardiac defects.[104]

Stillbirth

According to the World Health Organization (WHO), any baby born without signs of life at more than equal to 28 completed weeks' gestation is classified as stillbirth.[10] For practical reasons, legal definition of stillbirth typically requires reportable fetal deaths to attain an SGA (from 20 weeks to 28 weeks) or a birthweight (between 350 g and 1,000 g).[10,105] Yudkin et al. proposed defining stillbirth risk as the number of stillbirths occurring in a defined period after each SGA per 1,000 fetuses undelivered at that SGA.[105] It is well documented that the risk of stillbirth increases with AMA.[71,106-108] Simpson reported that about 10% of all fetal deaths are related to maternal medical illnesses such as HTN, diabetes, obesity, systemic lupus erythematous, chronic renal disease, thyroid disorders, and cholestasis of pregnancy.[109] Other factors that have been attributed to higher risk of stillbirth are placental abruption, SGA, and primiparity.[110]

Fretts et al. documented a 2-fold and 2.4-fold increase in risk of stillbirth rate in women 35–39 years and more than or equal to 40 years compared to women less than 30 years.[106] Reddy et al. reported the relative risk of stillbirth at 37–41 weeks as 1.32 and 1.88 for women 35–39 years and more than 40 years old, respectively.[111] The other group replicated similar findings, with the OR of 1.25, 1.6, and 2.22 for women 35–39, 40–45, and ages more than 45 years, respectively.[112] Stillbirth risk may differ based on demographic factors like multiparity and prenatal care. Khalil et al. did not found any difference in the stillbirth rate in older versus younger women.[113] Raymond et al. noted that higher risk of stillbirth persisted in older women after excluding the confounders such as HTN, diabetes, placental complications, and intrauterine growth restriction (IUGR).[114] Appropriate management of these medical conditions (e.g. preconception counseling, frequent prenatal visits to monitor the control, and increased antenatal fetal surveillance) has reduced the risk of stillbirth to a level that is slightly higher than in general pregnant patient population.[109] Several contributing factors for stillbirth are modifiable like obesity, preexisting diabetes, HTN, and smoking.[110]

Bahtiyar et al. analyzed more than 6 million singleton pregnancies in the USA to determine the influence of maternal age on stillbirth risk.[93] After pregnancies with congenital anomalies and medical complications were excluded, older women were compared with a group of 25–29-year-old women with the lowest stillbirth risk. The odds of stillbirth at term increased significantly with advancing maternal age—30–34 years, OR 1.24, (95% CI 1.13–1.36); 35–39 years, OR 1.45, (95% CI 1.21–1.74), and 40–44 years, OR 3.04 (95% CI 1.58–5.86).[93] The risk of stillbirth for women 40–44 years of age at 39 weeks was comparable to the risk for women 25–29 years old at 42 weeks. The authors recommended that women more than or equal to 40 years of age should be delivered by 39 weeks' gestation, since the cumulative risk of stillbirth in women 40–44 years of age at 39 weeks is the same as the risk in a 25–29-year old at 42 weeks' gestation.[93]

Intrauterine Growth Restriction

Increased risk of IUGR and prematurity is well documented for AMA women.[4,49] These complications are likely related to uteroplacental dysfunction occurring more often in

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older women. Uterine underperfusion has been reported as a potential factor for these adverse perinatal events in older women.[115] Placental volume assessed by 3D ultrasound was correlated with estimated fetal weight,[116] and high uterine artery vascular resistance was detected in patients with smaller placental volume.[117] Spiral artery volume assessed by 3D power Doppler ultrasound was lower in women older than 35 years of age.[118] Salem et al. reported a significant positive correlation between AMA and IUGR, low birthweight, congenital malformations, and perinatal mortality.[119]

Neurologic and Behavioral Disorders

Recently, positive correlation was documented between advanced maternal and paternal age, and autism spectrum (ASD) disorders in their offspring.[120] Maternal obesity and metabolic disorders were reported to increase the risk of attention deficit hyperactivity disorders (ADHD), ASD, anxiety, depression, schizophrenia, eating disorders, and impairment in cognition.[121]

ASSISTED REPRODUCTIVE TECHNOLOGIES

Fecundity and fertility start declining significantly after age of 32 years in females. Similarly, semen quality and male fertility deteriorate with advancing age, and the risk of genetic disorders in offspring increases.[122] Delayed childbearing is not only associated with infertility but pregnancy outcomes are noted to be adverse in AMA women,[122] and often these pregnancies are conceived by in vitro fertilization (IVF) with oocyte donation.[123] In developed countries, ART contributes to 1.7–4% of all pregnancies.[124] To date, approximately 5 million babies are born worldwide with the help of ART.[125] With advances in ART and oocyte donation, more and more AMA women even in their peri- and postmenopausal period are able to conceive.[126] In contrast to IVF with nondonor oocytes, the success of IVF with oocyte donation does not vary significantly according to the recipient's age up to age 50.[124,125] Older recipient age is associated with statistically reduced rates of implantation, clinical pregnancy, and delivery.[125] Age-related uterine factors are proposed to play a role in these outcomes, with reduced uterine blood flow affecting both the uterine receptivity and pregnancy maintenance.

Due to the use of ART, older women are more likely to have higher order multiple pregnancies.[127] Majority of ART-related obstetrical and fetal complications are due to multiple pregnancies. With increasing the use of ART, multiple order pregnancies are increasing from transfer of two or three embryo to enhance pregnancy rates.[128] Multiple pregnancies are at greater risk of pregnancy loss, preterm birth, and maternal complications, especially in AMA patients. Older women have double risk of extreme prematurity with multiple gestations with donor eggs compared to autologous oocytes.[4] Increased neonatal mortality and developmental disabilities are well documented in these children.[128-130]

Perinatal and Maternal Outcomes with ART versus Spontaneous Pregnancies

Infertility itself is an independent predictor of adverse obstetrical and perinatal outcome.[129,130] A two-fold increased risk of preeclampsia, placental abruption, CD, and five-fold increased risk of placenta previa is reported in patients who had infertility but conceived naturally.[131] Singleton pregnancies achieved through ART compared to spontaneous singleton pregnancies have poorer perinatal outcome.[132] Higher risk of perinatal complications has been reported in women who conceived through controlled ovarian stimulation (COS) using gonadotropins and intrauterine insemination (IUI).

There are conflicting reports on pregnancy related complications in multiple order pregnancies with ART versus spontaneous conceptions. Several studies reported higher risk of low birthweight, preterm birth, perinatal mortality, and congenital malformations.[133-139] Other studies refuted these findings, reporting no differences of outcomes in both groups.[140-143] The conflicting results from these studies could originate from different patient population studied, higher socioeconomic standard of patients undergoing ART, study methodology variations, and possible higher reporting in ART pregnancies, which are more closely monitored compared to spontaneous conceptions.[133,138]

In a recent meta-analysis of 39 cohort studies involving 146,008 multiple births, higher risk of preterm premature rupture of membranes (PPROM), pregnancy-associated hypertensive disorders, GDM, preterm and very PTDs, low birthweight, and increased rate of congenital malformations were reported for ART versus spontaneous conceptions.[144]

While SGA and fetal weight at the time of delivery were lower, preterm delivery, placental abruption, and GDM

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rates were noted to be higher in ART group compared to spontaneous conceptions. However, all these differences in outcome were not statistically significant after adjusting for age, parity, and systematic illness, though higher risk of placental abruption and patent ductus arteriosus persisted.[145]

ETHICAL CONCERNS

With AMA and VAMA patients, several ethical challenges arise. The concerns include a natural change of women biology, risks and efficiency, and maternal life expectancy.[146] Based on a review article on ethical concerns by Harrison et al. 10 out of 12 papers reviewed were in favor of IVF using donor eggs for postmenopausal women. The use of donor oocytes is helpful to reduce genetic risks associated with aged ovaries. However, there is a higher risk of maternal and fetal complications in AMA pregnancies that can be mitigated by appropriate screening for medical conditions and providing individualized healthcare to optimize recipients' health before conception.[146]

There should be attempts to reduce the notion in general population that IVF is successful in facilitating conception at VAMA.[147] Advanced age women should be informed about natural decline in fertility with age, lower success rate of IVF, and risks associated with delayed childbearing. Keeping physical, psychological, and sociocultural circumstances in mind, physicians should assess the fetal and maternal risk with pregnancies in (V) AMA, while ethicist should provide guidance on ethical concerns in this context.[146]

Figure 4.2 illustrates the relationship between the maternal age and rate of spontaneous abortion, stillbirth and ectopic pregnancy. Data from the literature indicate that there are five main concerning factors with delayed childbearing: (1) increasing chromosomal abnormalities, (2) higher miscarriage and stillbirth rates, (3) declining fertility, and (4) increased risk of hypertensive and (5) diabetes-related complications in pregnancies.[148,149]

It is the responsibility of the physician to inform patients about their reproductive choices. Older patients should be involved in the decision making to meet the

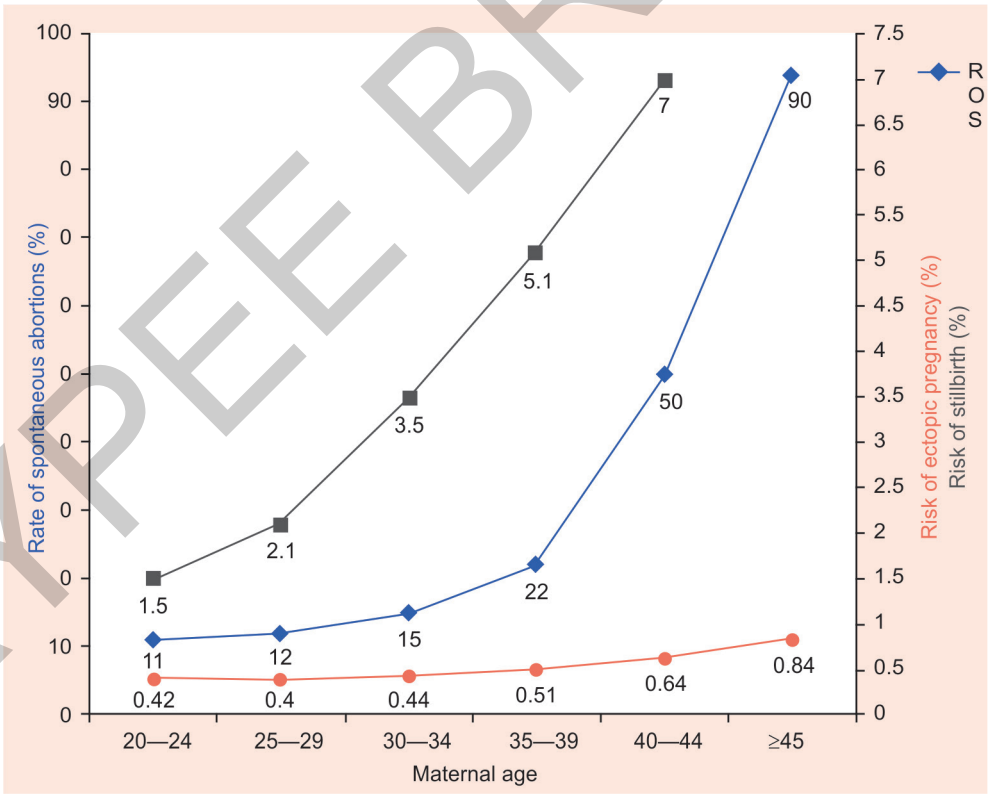


Fig. 4.2: Rate of spontaneous abortions, and risk of stillbirth and ectopic pregnancy as a function of maternal age.
Source: Schimmel MS, Bromiker R, Hammerman C, et al. The effects of maternal age and parity on maternal and neonatal outcome. Arch Gynecol Obstet. 2015;291(4):793-8.
Heffner LJ. Advanced maternal age--How old is too old? N Engl J Med. 2004; 351(19):1927-9.

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individual needs of childbearing desire while respecting their autonomy, and protecting their wellbeing as well as unborn child's future.

HIGHLIGHTS

- Obstetrical and perinatal risks increase with maternal age.
- Significant decline in fecundity and fertility is noted in women after age 32 years.
- Many women are not aware of increasing infertility and poor obstetrical and perinatal outcomes with AMA.
- Patients should be educated and counseled appropriately about their reproductive choices and complications.
- Fetal aneuploidy and congenital malformations are higher with advanced maternal and paternal age; hence, women more than 35 years should be offered fetal aneuploidy screening and detailed second trimester ultrasound.

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CURRENT PERSPECTIVES

This book provides state-of-the-art information about the spectrum of diagnostic and therapeutic advances that can help fetal patients and their healthcare providers throughout the world.

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