SYMPOSIUM ON ASSISTED FERTILIZATION IN ELDERLY WOMEN

Obstetric complications and advanced maternal age

Complicaciones obstétricas y edad materna avanzada

Santiago G. Cabrera Ramos[1]

1. Obstetrician-gynecologist. Senior Professor, Faculty of Medicine, Universidad Nacional Mayor de San Marcos (UNMSM). President Postgraduate Committee of Gynecology and Obstetrics UNMSM. Former President Peruvian Society of Obstetrics and Gynecology (SPOG). Former President Peruvian Society of Ultrasound in Obstetrics and Gynecology (SPUOG). Former General Director Hospital Nacional Docente Madre-Niño San Bartolomé. ORCID 0000-0003-4597-1049

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Correspondence:
Santiago A. Cabrera Ramos
✉ drscabrera@hotmail.com

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ABSTRACT

Advanced maternal age is directly proportional to the risk of obstetric and non-obstetric complications during gestation, both for the pregnant woman and the fetus. This is particularly important because the fertility rates of older women have increased. In the US, 10% of first births and 20% of all births occur to women 35 years of age or older. Historically, advanced maternal age has been defined as an age greater than or equal to 35 years, a cutoff point that is supported by declining fertility and the increased risk of genetic abnormalities in the offspring of women older than this age. However, the effects related to increasing age are continuous and the risk is greater the older the age at conception rather than as an effect of passing the 35 years threshold. Research has shown that older pregnant women are at increased risk of early pregnancy complications such as miscarriage, ectopic pregnancy, chromosomal abnormalities and congenital malformations, as well as, preeclampsia, gestational diabetes, placental pathology, preterm delivery, low birth weight, perinatal mortality, multiple pregnancy, dystocic delivery, cesarean delivery and maternal mortality. This article reviews recent publications on the subject and includes statistics from a major hospital in Lima, Peru, and from the National Demographic and Family Health Survey - ENDES, 2022.

Key words: Maternal age, Diabetes mellitus, Preeclampsia, Maternal mortality, Perinatal mortality, Cesarean delivery

RESUMEN

La edad materna avanzada guarda relación directamente proporcional con el riesgo de complicaciones obstétricas y no obstétricas durante la gestación, tanto para la gestante como para el feto. Esto es particularmente importante debido a que a las tasas de fecundidad de las mujeres de mayor edad han aumentado. En Estados Unidos, el 10% del primer nacimiento y el 20% de todos los nacimientos ocurren en mujeres con 35 años o más. Históricamente la edad materna avanzada se ha definido como una edad mayor o igual a 35 años, punto de corte que sustentado en la disminución de la fecundidad y el mayor riesgo de anomalías genéticas en la descendencia de las mujeres mayores a esta edad. Sin embargo, los efectos relacionados al aumento de edad son continuos y el riesgo es mayor mientras mayor sea la edad al momento de la concepción más que como efecto de pasar el umbral de los 35 años. Diferentes investigaciones han mostrado que las gestantes añosas tienen mayor riesgo de complicaciones tempranas de la gestación como aborto espontáneo, embarazo ectópico, anomalías cromosómicas y malformaciones congénitas, así como, preeclampsia, diabetes gestacional, patología placentaria, parto pretérmino, peso bajo al nacer, mortalidad perinatal, embarazo múltiple, parto distócico, parto por cesárea y mortalidad materna. En este artículo se revisa publicaciones recientes sobre el tema y se incluye estadística de un importante hospital de Lima, Perú, y de la Encuesta Nacional de Demografía y Salud Familiar - ENDES 2022.

Palabras clave. Edad materna, Diabetes mellitus, Preeclampsia, Mortalidad materna, Mortalidad perinatal, Cesárea

Introduction

Advanced maternal age has an inversely proportional relationship with fecundity especially after 30 years of age and is directly proportional to the risk of obstetric and non-obstetric complications during gestation, both for the pregnant woman and the fetus[1,2]. However, the evidence indicates that most pregnant women over 40-50 years of age[3,4] have favorable outcomes and are able to cope with the physical and emotional stress related to pregnancy and raising their offspring[5].

Despite the overall decline in fertility rates in most age groups, rates

in older women have increased[6]. In the United States, approximately 1 in 10 first births and 1 in 5 of all births occur to women aged 35 years or older[7]. Likewise, the average age of the mother at the birth of her first child has increased in most countries in recent years and varies according to latitude: 27.1 years in the United States, 29.6 years in Canada, 28 years in many European countries[8], and 22.2 years in Peru[9].

These figures support the importance of recognizing the risk of pregnancy complications in later stages of reproductive age. The present review aims to provide updated information on obstetric complications in pregnant women of advanced maternal age in order to detect, understand and treat them in time.

Definition

Historically, advanced maternal age has been defined as an age greater than or equal to 35 years at the estimated date of delivery. The selection of this cutoff point was based on declining fertility and concerns about the increased risk of genetic abnormalities identified at the end of the last century in the offspring of women older than this age[10]. Higher level evidence, such as the FASTER (First and Second Trimester Evaluation of Risk) study[11] and the NBDPS (National Birth Defects Prevention Study)[12], has demonstrated a significant association of chromosomal abnormalities and possible congenital malformations in the offspring of women aged 35 years and older.

However, the effects related to increasing age appear to be continuous, so that the risk is greater the older the age at conception, rather than as a threshold effect as the age in question passes[12,13]. There is still no universal definition of advanced maternal reproductive age in women, so the 35-year threshold used in most studies is arbitrary[14].

Likewise, research evaluating the effect of certain chronic medical conditions such as diabetes mellitus, hypertension, and obesity that may exacerbate gestation-related morbidity appears to show an increasing risk with increasing age at the time of pregnancy[15-18]. Therefore, recognizing the possibility of progressive age-related risk, the most recent research tends to stage the age of pregnant women starting at 35 years in quinquennial increments: 35-39 years, 40-44 years, 45-49 years, and 50 years and older[14].

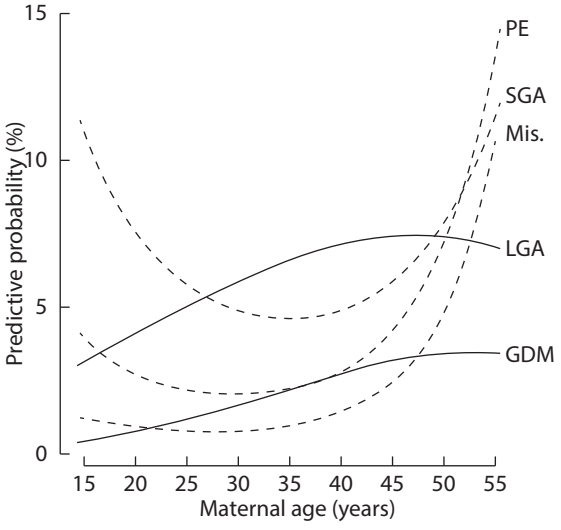
Early pregnancy complications

Complications associated with advanced maternal age are the same as those that can occur in younger women, but the risk increases with age. Early complications include miscarriage, ectopic pregnancy, chromosomal abnormalities and congenital malformations.

Older pregnant women experience a higher rate of miscarriages (Figure 1), with age over 35 years being the most important risk factor due to its strong association with fetal chromosomal abnormalities[19-21]. These losses can be trisomic or euploid and are mainly due to decreased oocyte quality as well as changes in uterine and hormonal function. In a prospective cohort study of more than 421 thousand pregnancies, it was found that the risk of miscarriage was 10% in people aged 25-29 years, furthermore the risk increased considerably after the age of 30 years and reached a maximum of 53% in women aged 45 years or older. In addition, most cases occur between 6-14 weeks of gestation[19].

The risk of eventual miscarriage in older women is significant even after demonstrating fetal cardiac activity by transvaginal ultrasound[22,23]. This was evidenced in a study of more than 148 thousand pregnancies obtained with assisted

Figure 1. Predictive probability of spontaneous abortion (Ab), preeclampsia (PE), small fetus for gestational age (SGA), gestational diabetes mellitus (GDM) and large fetus for gestational age (LGA) as a function of maternal age[21].



reproductive technologies, in which the rate of miscarriage after showing fetal cardiac activity at 7 weeks according to maternal age was 9.9% in those under 33 years, 11.4% at 33-34 years, 13.7% at 35-37 years, 19.8% at 38-40 years, 29.9% at 41-42 years and 36.6% in those older than 42 years[23]. The presence of fetal cardiac activity shows that the increased rate of pregnancy loss was not limited to non-evolving gestations.

On the other hand, ectopic pregnancy is also related to maternal age. Maternal age 35 years or older is associated with 4-8 higher risk of ectopic pregnancy compared with younger women[20,24] (Table 1). This high incidence in older women may reflect cumulative risk factors over time. Additionally, ectopic pregnancy mortality is strongly influenced by both advanced maternal age and racial disparities[25].

Karyotype analysis of miscarriages, pregnancy terminations, amniocentesis, and live and stillbirths shows a steady increase in the risk of aneuploidy as women age[10,14,26] (Table 2).

Age-related errors appear to increase the risk of nondisjunction resulting in unequal chromosome products at the end of division. These age-related errors may be associated with cumulative oxidative stress, depletion of normal oocyte numbers, and shortening of oocyte telomeres[27,28].

Theoretically, preimplantation selection of normal embryos, both chromosomically and morphologically, could increase the chances of successful implantation and continued pregnancy, as well as avoid chromosomally abnormal births. Despite the high number of aneuploid embryos excluded from transfer by this procedure, data from randomized controlled trials have shown that preimplantation screening does not improve the implantation rate or live birth rate but decreases multiple gestation rates[29-31].

Also, the risk of congenital anomalies appears to increase with maternal age. Historically, the increase in congenital anomalies with advancing maternal age has been attributed to the increase in aneuploidies and the association of aneuploid fetuses with structural anomalies[13,32]. However, several studies have suggested that the risk of nonchromosomal abnormalities also increases as women age. In particular, cardiac anomalies appear to increase with maternal age independently of aneuploidy[33].

The NBDPS study is a case-control study that included more than 20,000 infants as cases and 8,000 controls and excluded chromosomal abnormalities. Compared with the group of women aged 25-29 years, the offspring of women aged 40 years or older had a significantly increased risk of several types of heart defects (OR = 2.9), as well as esophageal atresia (OR = 2.9), hypospadias (OR = 2.0), and craniosynostosis (OR = 1.6)[12].

Other observational studies have concluded that the risk of some non-chromosomal congenital anomalies, such as cardiac anomalies, clubfoot, diaphragmatic hernia, among others, increased with increasing maternal age[34]. However, these results have not been consistent[12,35,36], possibly

Table 1. Percentages of complications at conception according to maternal age.

Maternal age	Spontaneous abortion* (%)	Ectopic pregnancy (%)	Neonatal mortality (rate / 1000)
12 - 19	13.3	2.0	5.0
20 - 24	11.1	1.5	4.2
25 - 29	11.9	1.6	4.0
30 - 34	15.0	2.8	4.4
35 - 39	24.6	4.0	5.0
40 - 44	51.0	5.8	6.7
>= 45	93.4	7.0	8.2

**Total miscarriages were estimated using the assumption that only 80% of women with miscarriages in recognized pregnancies were hospitalized (20).*

Table 2. Chromosomal alterations in pregnancies according to maternal age*[14].

Maternal age	Trisomy 21	Trisomy 18	Trisomy 13	Sexual aneuploidy (45X0, XXX, XXY)	All chromosomal alterations
20	1:1,250	1:5,000	1:10,000	1:294	1:122
25	1:1,000	1:5,000	1:10,000	1:294	1:119
30	1:714	1:2,500	1:5,000	1:294	1:110
35	1:294	1:1,111	1:2,500	1:285	1:84
40	1:86	1:333	1:714	1:196	1:40

**Not all chromosomal alterations increase with maternal age.*

due to differences in methodological designs, case definitions and possible confounding factors.

Late complications of pregnancy

Late complications include preeclampsia, gestational diabetes, placental pathology, morbidity (preterm delivery and low birth weight) and perinatal mortality (fetal and neonatal death), multiple pregnancy, dystocic delivery, cesarean delivery and maternal mortality.

Some obstetric complications in older women appear to be related solely to the aging process, while others are largely related to coexisting factors such as multiple gestation, multiparity, and chronic medical comorbidities, factors that are less likely to be observed in younger women. Both of these elements may contribute to increased pregnancy-related maternal morbidity.

In a retrospective cohort study of more than 800,000 singleton births, women aged 40 years or older had 8 times the risk of amniotic fluid embolism and 3 times the risk of obstetric shock compared with women aged 25-29 years[37]. Similarly, another retrospective cohort study of nearly 37 million deliveries found that women aged 45-54 years had nearly 3.5 times the risk of severe maternal morbidity compared with women aged 25-29 years, and had the highest rates of cesarean delivery, preeclampsia, postpartum hemorrhage, gestational diabetes, thrombosis, and hysterectomy after adjusted analysis[38](Figure 2).

The short intergestational interval appears to further increase the risk of adverse maternal events in older women. In a cohort study of more than 148,000 pregnancies, the risk of serious morbidity and maternal mortality was increased in women aged 35 years or older who had 6-month intergestational intervals compared with 18-month intervals, but not in women aged 20-34 years with the same time intervals[39].

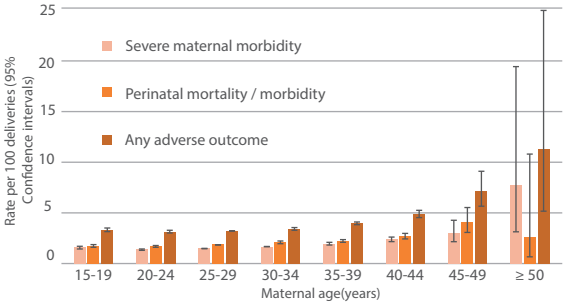
On the other hand, the prevalence of medical and surgical diseases such as neoplasms, cardiovascular, renal, and autoimmune diseases, as well as obesity, increases with age. For this reason, women aged 35 years and older experience 2-3 times higher rates of hospitalization, cesarean delivery and pregnancy-related complications than their younger counterparts[13,40,41]. Also, smoking has been associated with increased perinatal morbidity and fetal death in all age groups; the risk is particularly high in older smokers[42,43].

The two most frequent medical pathologies that complicate pregnancy are arterial hypertension (preexisting and pregnancy-related) and diabetes mellitus (pregestational and gestational). Both conditions increase in older women, especially in those who are overweight and obese.

Arterial hypertension is the most frequent medical pathology encountered during pregnancy and is particularly common in older women. The probability of being diagnosed with chronic hypertension is 2-4 times higher in women aged 35 years or older compared with women aged 30-34 years[17,41]. The incidence of preeclampsia in the general obstetric population is 3-4%. However, this increases 5-10% in women over 40 years of age and reaches up to 35% in women over 50 years of age[44,45] (Figure 1). Despite this rise with age in incidence, maternal and fetal morbidity and mortality related to hypertensive disorders during pregnancy can be reduced through careful follow-up and timely intervention, at the expense of an increase in preterm deliveries, small-for-gestational-age newborns, and cesarean deliveries[14].

Also, the prevalence of diabetes mellitus increases with maternal age. The rates of preexisting diabetes mellitus and gestational diabetes increase 3-6 times in women aged 40 years or older compared with women aged 20-29 years[13,44-46]. The incidence of gestational diabetes in the general obstetric population is 3%, increasing 7-12% in women older than 40 years and reaching 20% in women older than 50 years[44,45](Figure 1). In addition, pre-existing diabetes is associated

Figure 2. Age-specific rates of severe maternal morbidity and perinatal mortality/severe neonatal morbidity[37].



with increased risks of congenital anomalies and perinatal morbimortality, while the main complication of gestational diabetes is macrosomia and its sequelae[47].

The Hospital Nacional Docente Madre-Niño San Bartolomé in Lima, Peru, is a level III hospital that receives referral patients at the national level. Of a total of 4,872 deliveries, it was observed that 2.5% of women aged 20-24 years had diabetes compared to 17.3% in women over 45 years of age. Likewise, the percentage of hemorrhages due to uterine atony increased from 7.8% in women aged 20-24 years to 26% in women over 45 years (Figure 3).

The Peruvian National Demographic and Family Health Survey (ENDES 2022) shows an increase in hemorrhage by age group (Figure 4).

Placental pathology, such as placental abruption and placenta previa, is higher among older women[48]. Multiparity represents excess risk for both disorders. There is no significant correlation between maternal age and abruption when parity and hypertension are considered. In contrast, age and parity appear to be independent risk factors for placenta previa. Nulliparous women aged 40 years or older have a 10-fold increased risk of placenta previa compared with nulliparous women aged 20-29 years, although the absolute risk is small (0.25 and 0.03%, respectively)[49].

Figure 3. Gestation complications according to age - Hospital Nacional Docente Madre Niño "San Bartolomé", 2022.

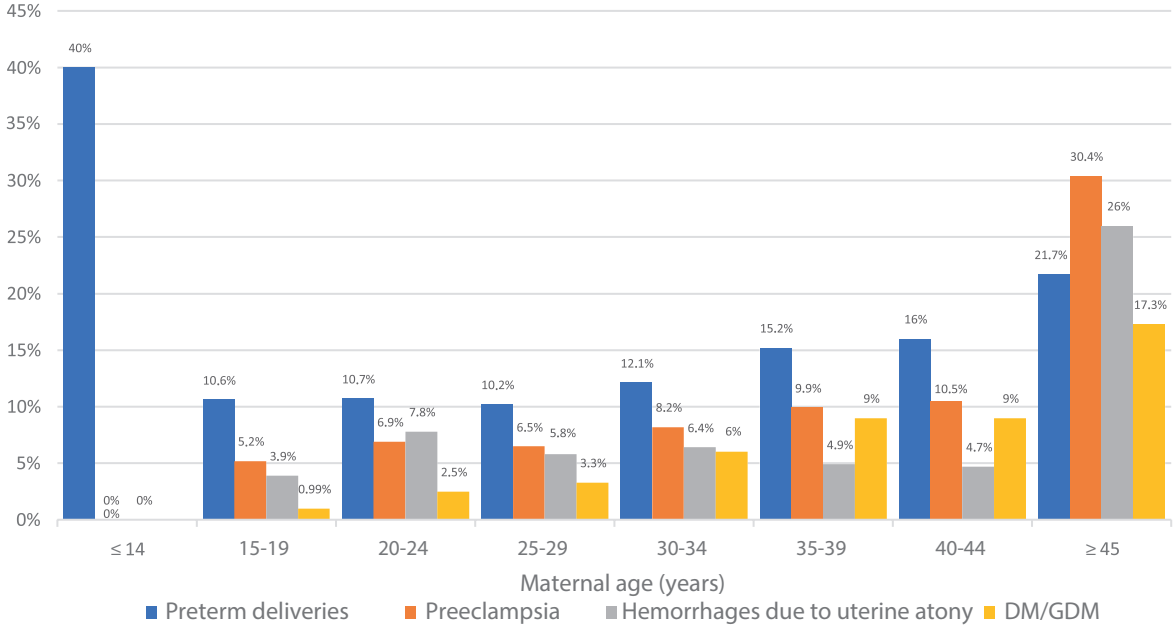
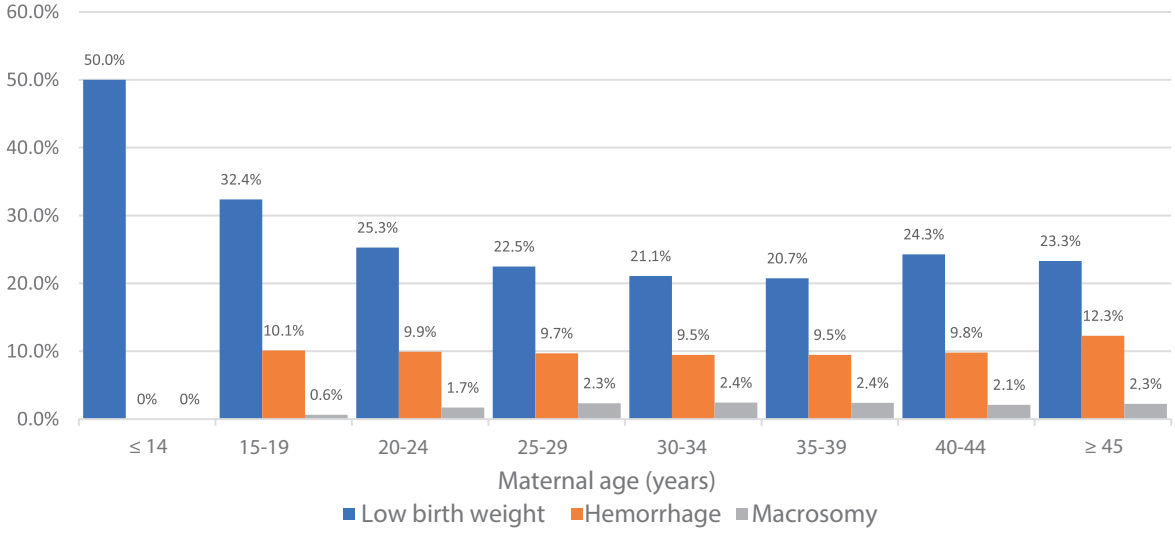


Figure 4. Gestational complications according to age - Demographic and Family Health Survey (DHS), 2017 - 2022.



Advanced maternal age is associated with increased rates of low birth weight and preterm delivery in recent years[4,13,50-52](Figure 1). In a prospective cohort study of more than 170,000 healthy nulliparous women, age 35-40 years was significantly associated with low birth weight (OR = 1.9), preterm delivery (OR = 1.7), and small for gestational age (OR = 1.7), compared with age 20-24 years[53]. Another prospective study in more than 32,000 women aged 40 years or older confirmed the higher risk of preterm delivery in older women, after evidencing preterm delivery less than 32 weeks in 1.01, 1.80, and 2.24% in women aged 20-29, 40-44, and 45 years or older, respectively[54].

The Peruvian National Demographic and Family Health Survey (ENDES, for its acronym in Spanish) 2022 does not show a significant increase in low birth weight by age group (Figure 4).

In the San Bartolomé Hospital in Lima, Peru, out of a total of 4,872 deliveries during 2022, pregnant women aged 20-24 years had 10.7% preterm births compared to 21.7% in women over 45 years (Figure 3).

Although older mothers are at higher risk of preterm delivery, their preterm infants are not at higher risk of morbidity compared with preterm infants born to younger women. This was illustrated in a cohort study of more than 12,000 newborns under 33 weeks gestation admitted to the neonatal intensive care unit, where a trend of higher rates of morbidity-free neonatal survival was observed with increasing maternal age (OR = 1.047, 95% CI: 1.001-1.095)[55].

Regarding fetal deaths worldwide, women aged 35 years or older have a significantly higher risk of fetal death compared with younger women. A systematic review of nearly 100 studies estimated that maternal age older than 35 years was associated with a 65% increased risk of fetal death compared with younger women. Furthermore, it estimated that the risk continues to increase with increasing maternal age, being twice as high in those older than 40 years[56].

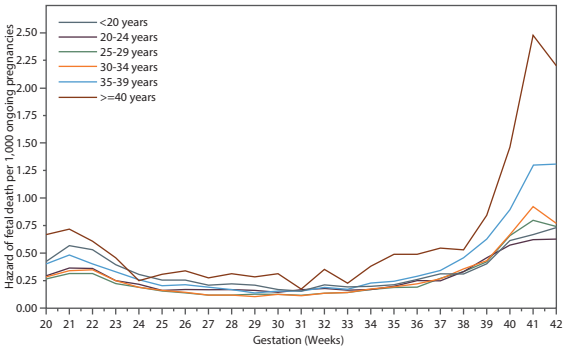
The excess perinatal mortality experienced by older women is largely due to nonabnormal fetal deaths, which are often unexplained even after controlling for risk factors such as hypertension, diabetes, antepartum hemorrhage, smoking, and multiple gestation[54,57-59]. A study of more than 5 million singleton nonabnormal gestations found that the risk of fetal death between 37-41 weeks for primiparous women increased significantly with maternal age. The risk of fetal death for women younger than 35 years, 35-39 years, and older than 40 years was 3.73, 6.41, and 8.65 per 1,000 ongoing pregnancies, respectively. The increased risk of fetal death with age persisted after accounting for medical comorbidities. This risk was most evident after 37 weeks' gestation and increased dramatically at 40 weeks' gestation, suggesting that older women reach 'term' of pregnancy earlier than younger women[60] (Figure 5).

The risk of fetal death in each week of gestation was estimated by dividing the number of fetal deaths occurring during that week by the number of pregnancies in progress at the beginning of that week minus half of the live births in that week.

In contrast to the increased risk of fetal death with increasing maternal age, the risk of neonatal death among preterm infants is lower than in preterm infants born to younger women. In the population-based cohort study of infants less than 33 weeks' gestation admitted to the neonatal intensive care unit (NICU), neonatal mortality decreased progressively with increasing maternal age (OR = 0.922, 95% CI 0.855-0.955)[55]. This may be due to differences in underlying factors, such as greater use of prenatal steroids and cesarean delivery in older women.

Older age is associated with a higher prevalence of twin pregnancies, which is related to a higher risk of naturally conceived twins and greater use of assisted reproductive technologies. Paradoxically, unlike singleton pregnancies, the outcome of multiple pregnancies in older women is

Figure 5. Risk of fetal death in singleton births without congenital anomalies by maternal age and gestational age[60].



as good or better than the outcome in younger women[61].

The optimal gestational age for delivery in older women is unclear. The risk of fetal death increases with increasing maternal age, such that pregnant women 40 years of age or older have the same risk of fetal death at 39 weeks of gestation as patients in their early 20s at 41 weeks of gestation[62,63]. Although some data support delivery at 39 weeks gestation, this has not been associated with increased risk of cesarean delivery and appears to have a neutral impact on prognosis[64-66].

Studies consistently report that women aged 35 years or older are more likely than younger women to experience dystocia at delivery[67] and cesarean delivery[46,68,69]. In a cohort study of more than 78,000 singleton births, the proportion of women undergoing primary cesarean delivery increased with age for both primiparas and multiparous women. By years of age, the rate of primary cesarean delivery was 20% for women aged 25-34 years, 26% for women aged 35-39 years, 31% for women aged 40-44 years, 36% for women aged 45-49 years, and 61% for women aged 50 years and older[69]. For comparison, the overall primary cesarean delivery rate for singleton births in the United States was approximately 22% during a similar period[70] (Figure 6).

In Peru, according to the ENDES 2022 Survey, out of a sample of 18,898 deliveries, cesarean delivery accounted for 34%, while the percentage of vaginal deliveries was 66% (Figure 7).

And if we classify by age group, the cesarean section rate increased from 26.9% in women aged 20-24 years to 41.0% in women aged 40-44 years (Figure 8).

At the San Bartolomé Hospital in Lima, Peru, of a total of 4,872 deliveries in 2022, 55.5% were vaginal deliveries and 44.5% were cesarean sections (Figure 9). And if we consider the rate of cesarean sections by age group, we observe that in this hospital, women between 20-24 years of age had 35% of cesarean sections, contrasting with 82% in women over 45 years of age (Figure 7).

The reason for the high rate of operative deliveries in older women is controversial. It includes a higher prevalence of medical complications, labor induction and fetal malposition or a lower threshold among patients and physicians for cesarean delivery. Also, maternal request for cesarean delivery is becoming more common, particularly among older pregnant women[71].

When specific indications for cesarean delivery are evaluated, older women appear to be at increased risk for failure of labor to progress normally. The nearly linear increase in the relationship between maternal age and uterine dysfunction is a continuous effect throughout the childbearing years[72,73].

Contemporary studies on the effect of age on the duration of the first stage of labor have not found consistent findings, whereas the duration of the second stage appears to increase with

Figure 6. Cesarean deliveries according to parity and maternal age[69].

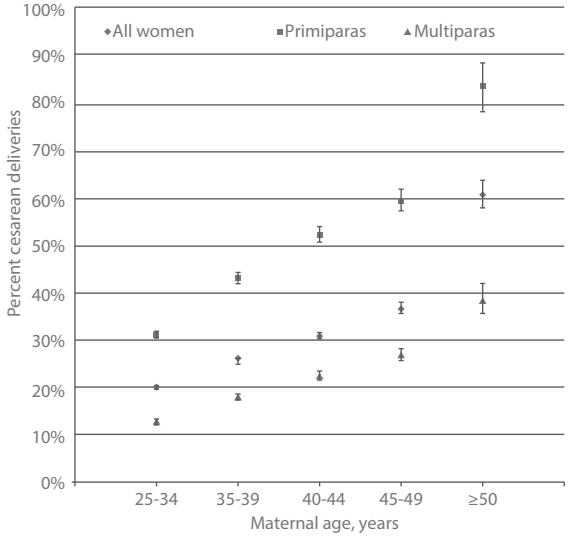


Figure 7. Percentage of cesarean sections according to maternal age. Total births 18,898 and cesarean sections 6,447. Demographic and Family Health Survey (ENDES), 2017 - 2022.

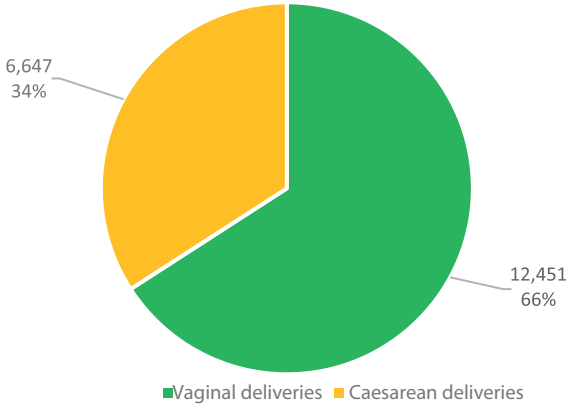


Figure 8. Percentage of cesarean sections according to maternal age. Total births 18,898 and cesarean sections 6,447. Demographic and Family Health Survey (ENDES), 2017 - 2022.

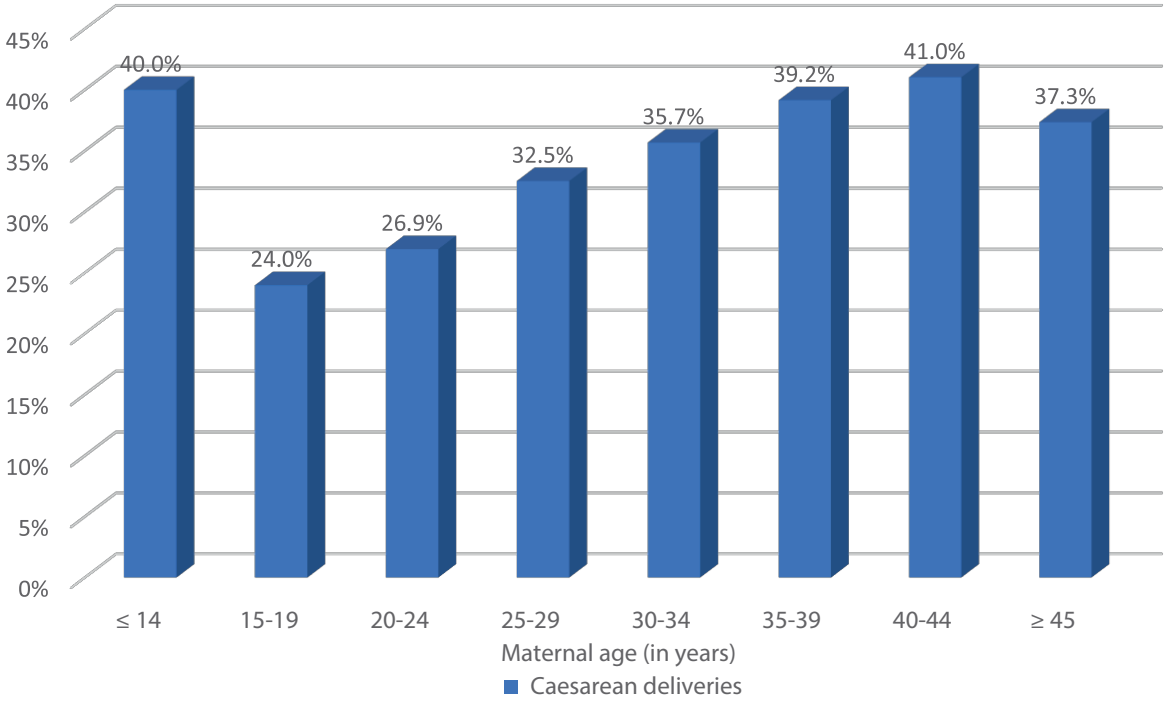
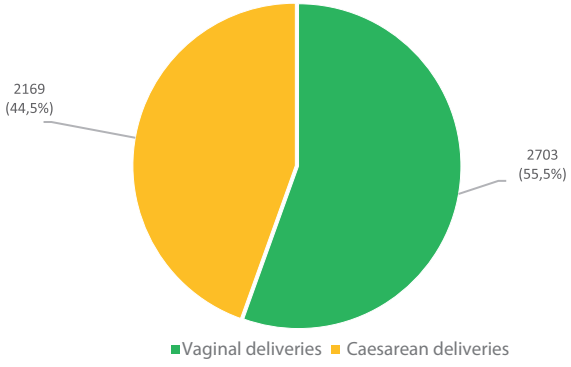


Figure 9. Type of delivery out of a total of 4,872 deliveries. Hospital Nacional Docente Madre Niño "San Bartolomé" 2022.



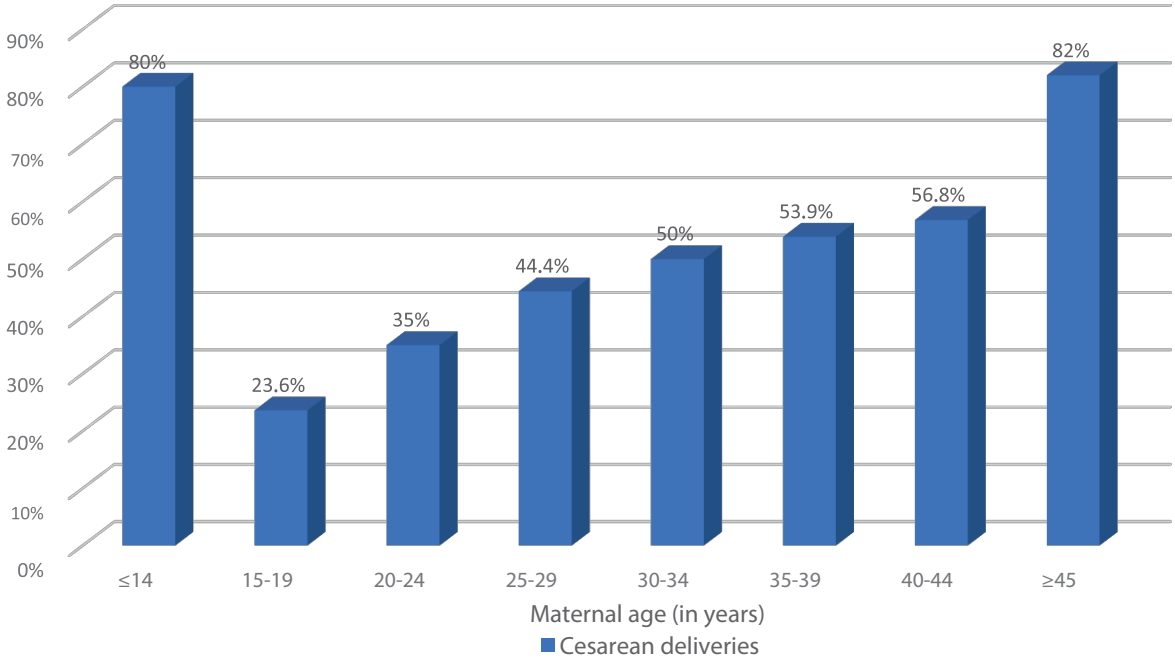
age[74,75]. However, despite the impact of age on uterine function, a meta-analysis of five trials involving more than 2,600 women reported that induction of labor at term in women aged 35 years or older did not increase the rate of cesarean delivery compared with women undergoing expectant management[76]. Older women who undergo trial of labor after a previous cesarean delivery appear to be at increased risk of trial failure and uterine rupture[77].

In terms of maternal mortality, women aged 40 years or older have 6 times the risk of maternal death compared with women younger than 20 years[78]. Additionally, in the United States, there is a further discrepancy when evaluating these figures by race, such that women of African descent are 3 times more likely to die during pregnancy than Caucasian women. Caucasian women aged 40 years or older have a pregnancy-related mortality rate of 51.5 per 100,000 live births, whereas women of African descent of the same age have a rate of 189.7 per 100,000[78].

Conclusions

Women with advanced maternal age are at increased risk of maternal and perinatal complications. However, the definition of advanced maternal age with the historical threshold of 35 years or older has led to research that, in many cases, dichotomizes the age of pregnant women between younger than 35 years and 35 years or older. As demonstrated by numerous observational studies, age-related risks increase with age. Future research should clearly delineate risk by age category for evidence-based recommendations. There are no robust data assessing whether prenatal fetal surveillance reduces the risk of fetal death in this population, and there are limited data on the timing and frequency of testing. There are also limited data on disparities and whether the risks associated with older age of a pregnant woman are increased in different populations, including different ethnicities such as those in our country.

Figure 10. Percentages of cesarean sections (total 2,169) in relation to deliveries (total 4,872) according to age. Hospital Nacional Docente Madre Niño "San Bartolomé" 2022.



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