Chapter 6

Multiple Pregnancy in Women of Advanced Reproductive Age

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Additional information is available at the end of the chapter

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Abstract

Assisted reproduction techniques (ARTs) allow women of advanced reproductive age to become pregnant. One of the most frequent complications of ART is twin pregnancy. Cases where both factors are present represent a specially vulnerable population for obstetric complications and medical perinatal and post-partum consequences for both the mother and babies. Pre-existing medical conditions are more frequent at advanced age, and the pregnancy physiological changes and the high metabolic demand associated with a twin pregnancy may reveal or worsen any previous disease. A careful counselling process is very important in this population and certain obstetric interventions might be particularly addressed to it. Single embryo transfer should be strongly enforced in advanced age women to minimise risk for the mother and children.

Keywords: twin pregnancy, advanced maternal age, ART, obstetric complications, reproductive counselling, oocyte donation, obstetric care

1. Introduction

Dizygotic twin pregnancies are known to increase with age of the mother. Naturally conceived twins are thought to occur in a 0.3% rate in women under 25 years, 1.4% between 25 and 34, 3% between 34 and 39, and 4.1% in women in their 40s or over [1]. We also know that at least 50% of all twin pregnancies are conceived through ART and that this proportion is probably higher for women in their 40s. International guidelines affirm that maternal mortality associated with multiple births is 2.5 times that for singleton births [2]. Since obstetric and obstetric-related medical complications are amplified in the case of women of advanced reproductive age and also in twin gestations, the combination represents a particularly vulnerable group.

In Spain, for example, according to the 2013th ESHRE registry [3], a total of 56,704 treatments were performed, 18,113 consisting in egg donation, which makes almost 32% of all treatments. The percentage of women older than 40 years undergoing treatment and arriving to egg aspiration was 15.7%, with a pregnancy rate of 29.9%, but a delivery rate of 9.5%. For egg donation programmes, the percentage of women over 40 increased to 66.9%, with a pregnancy rate of 48.4 and a delivery rate of 30.5%. This means that in 2013–2014, 4272 women over 40 carried and delivered a baby in Spain. The proportion of double embryo transfers was 71.5%, with 20.9% of twin deliveries in FIV/ICSI treatments and 24.6% in egg donation: around 982 twin deliveries in women over 40 in Spain in 2013. And this only counts for the pregnancies achieved through ART. This same registry suggests that the overall preterm birth rate for twins was 51%.

But, which age is "too old"? Can we set a threshold? Can we legislate against advanced reproductive age? And, would this legislation only account for women seeking reproductive care? If we already know all these, why is it still happening? Can we, as a society, deny maternity to any woman? Can we afford this? What if maternity age continues to increase in the world? Should not this evolve with society? This chapter will raise many questions that, sorry, we would not probably able to answer.

2. Ethical issues in the reproduction clinic

2.1. Setting a threshold for treatment

In most countries, there is no legislation restricting maternal age. Some countries would not include women of advanced age in their public reproduction schemes, but the same restrictions usually do not apply to the private sector. And more importantly, in many countries, there is no restriction in the number of embryos being transferred to these women. Not only access cannot be denied but two and three embryos can also be transferred freely.

Classically, advanced maternal age has been defined as any woman conceiving after 35 years of age. Given the late reproductive trends, this threshold should now be reconsidered, as in developed countries it might include a high percentage of the pregnant population. Advanced maternal age nowadays might be considered as a woman conceiving after 40–43 years of age, which is the approximate age in which ovary ageing may have almost completely prevented spontaneous conception. However, although rare, spontaneous conception over 40s is possible, so is it fair to deny reproductive treatment to a woman whose same-age neighbour might have conceived spontaneously?

In this environment, most clinics set their own thresholds (or not at all) without much governmental support. Very few clinics would accept to perform reproductive treatment on a woman older than 50, which represents an age in which more or less half of the female population is menopausal. However, peri- and postnatal risk for the mother and the babies start increasing progressively much earlier than that. But when a clear guidance does not exist, decision making becomes somehow subjective, mainly considering our previous experiences. Can we impose our own personal opinion over a woman's family desire?

2.2. Counselling advanced reproductive age mothers

Autonomy principle involves that appropriately informed patients can decide whether they want to undergo or refuse a diagnostic test or treatment, accepting the benefits and risks of their decision. Following this principle, any woman seeking reproductive treatment after the age of 35, or more appropriately, after the age of 40, should be carefully informed about obstetrical complications and the health implication for them and the child. They should also be informed about preventive and treatment strategies that may be put in place to avoid them. When counselling women with pre-existing medical conditions, their head specialist should review the case and advise for or against pregnancy. It is very important to remember that certain medical conditions do contraindicate pregnancy, as they might lead to a life-threatening situation.

2.3. Fertility in older mothers' children

Although most causes of infertility are not genetic, it has been observed in a US population study that daughters from mothers older than 40 years are more likely to remain childless in their lifetime [4]. However, it is difficult to discern whether this is a "learnt" pattern or a true "inherited" infertility trait. In the same population, daughters from "old" mothers were at double risk for delivering twins than daughters from "young" mothers (OR = 2.1, 95% CI: 0.8–5.4), although this difference was not statistically significant. This may suggest that delaying childbirth might be perpetuated and worsen with time in our current society.

2.4. Oocyte donation programmes

Oocyte donation restores pregnancy possibility in women of advanced reproductive age and reduces the chances for implantation failure found among them. Most women seeking this treatment are happily married women, well-educated and high-income, and physically and psychologically healthy [5]. However, oocyte donation recipients experienced a higher risk of pregnancy complications largely due to advanced maternal age, particularly hypertensive disorders and diabetes, and the risk increases with age [6]. The Ethics Committee of the American Society for Reproductive Medicine recommends women of advanced reproductive age undergo a comprehensive medical test to ascertain fitness for pregnancy in order to prevent the rise of obstetric complications during pregnancy [7]. Multiple pregnancy is known to increase obstetrical and neonatal risks in women of all ages; therefore, it is particularly important to avoid a twin gestation in older mothers.

3. Reproduction treatment and advanced maternal age

3.1. Low ovarian reserve

The effect of age in the ovarian reserve is unavoidable. Although menopause is considered the end of the reproductive age in women, changes in the ovarian cycle take place many years prior to menopause. These changes may lead to a fertility dysfunction in women that decide to get

pregnant at an advanced age. The primary mechanism behind this process is the decrease of primordial follicle count in the ovary susceptible to developing a good-quality ovule. Classically, follicle count during menstrual cycle has been assessed using ultrasound. In addition, numerous studies have reported changes in the hormone patterns associated with reproductive ageing, such as shortened follicular phase, elevated follicular phase oestrogen, and decreased luteal phase progesterone [8–13]. During the last decade, anti-Müllerian hormone (AMH) has emerged as an early biochemical marker able to predict the decrease in the ovarian reserve. Low AMH serum levels predict an altered folliculogenesis by inhibiting the recruitment of primordial follicles and its sensitivity to FSH [14]. The reduction of AMH serum levels appears to be more strongly and more consistently correlated with age than the decrease number of antral follicles observed in the ovary by ultrasound, inhibin B levels, or FSH levels [15, 16].

3.2. Ageing uterus

In addition to changes observed in the ovarian reserve and quality of the oocytes, the uterus is an essential organ to achieve pregnancy. As in any other human organ, ageing also has an effect on the uterus of fertile women. Even though it is difficult to evaluate these changes in humans, animal studies indicate that older mice show an impaired artificially induced decidual response, probably due to reduced progesterone secretion [17–19]. Microscopic changes have also been confirmed, with more hyperaemia and higher vascular development and growth of the myometrium and stroma of young hamsters in comparison with the older ones [20]. Older mothers are also more likely to experience intrapartum complications and the rate of caesarean delivery is higher, suggesting that myometrial function is impaired by advanced maternal age [21]. The risk of stillbirth in mothers over the age of 40 is twice as high as younger mothers due to foetal chromosomal abnormalities, multiple pregnancy, obesity, pre-eclampsia, insulin-dependent diabetes, and multiple pregnancy [21, 22]. These evidences suggest that changes in the uterus in older women may have a reflection on fertility and the ability of maintaining a pregnancy.

3.3. Chromosomal abnormalities

Women who delay childbearing are at an increased risk of foetal chromosomal abnormalities. This occurs as a consequence of an error in chromosomal disjunction during maternal meiosis I or II, which has been reported as more frequent in advanced age women [23–25]. Among them, numeric chromosomal abnormalities seem to be more frequent than structural chromosomal abnormalities. Chromosomal aneuploidies related to maternal age include trisomy 21, trisomy 18, trisomy 13, triple X syndrome, and Klinefelter syndrome [26]. A recent study highlights that trisomy 21 showed an incidence rate of 11.34 out of 1000 cases at the age of 35 years, 15.41 cases at the age of 40, and 37.04 cases at the age of 45. In addition, trisomy 18 showed an incidence rate of 1.89 out of 1000 cases at the age of 35 years, 5.14 cases at the age of 40, and 37.04 cases at the age of 45. Nowadays, prenatal diagnostic techniques such as ultrasound and cell-free foetal DNA test allow professionals to make an early screening for foetal aneuploidy. However, invasive techniques remain the gold standard for definitive diagnosis,

with a risk of miscarriage *per se* of 0.35% (CI 95%: 0.07 to 0.63) following amniocentesis and 0.35% (95% CI: -0.31 to 1.00) following chorionic villus sampling [27].

3.4. Oocyte donation

The use of donor oocytes in assisted reproduction techniques (ARTs) during the last decades has been a great advance for women whose reproductive dysfunction could not be treated otherwise. It was initially addressed for young women with premature ovarian failure. But this technique provides a valuable weapon to avoid age-related changes in the ovary, allowing premenopausal and menopausal women to get pregnant and fulfil their reproductive desire with acceptable success rates [28–30]. Moreover, the use of oocytes from donors has numerous advantages, as it reduces the rate of aneuploidies and stillbirth in women of advanced age. Case reports of successful pregnancy and delivery in a 70-year-old patient with donated oocytes demonstrate that the uterus may be able to maintain pregnancy far beyond the age of menopause [21]. Women are delaying childbearing; it is likely that the percentage of women looking for donor oocytes will increase, as it has been in the last decade.

3.5. Strategies to reduce twin pregnancies in the elderly mother

Twins occur spontaneously, and we still do not understand the causes or the conditions under which an embryo decides to split in two. However, the vast majority of twin pregnancies, particularly in women of advanced reproductive age, happened as a result of ART. Women seeking reproductive treatment usually have been trying to conceive spontaneously for a long period of time, and many have undergone previous unsuccessful treatments. Frustration, impatience, and economic costs are probably the main reasons why transfer of two and even three embryos is still a common practice in many countries [1]. This practice increases the chances of achieving pregnancy per embryo-transfer but also increases the chances of obtaining a multiple pregnancy. Multiple pregnancies have an important impact on the mothers' and babies' health as a consequence of medical and obstetric complications, and this carries an important economic burden for society, mainly due to preterm delivery, long hospital stay of the premature babies, and treatment of subsequent disabilities in the long term [31].

For obvious reasons, the main strategy to reduce the number of twin pregnancies in all women is the widespread use of the single embryo transfer (sET) during a fertility treatment. Our target should be to resemble the spontaneous twinning rate of embryos. Thanks to the development of vitrification, a fast freezing technique that increases post-thawed embryo survival rate, a single embryo can be transferred in a fresh cycle, while the rest will be transferred posteriorly in vitrified-thawed cycles without any loss of implantation potential [32]. The latest studies show the promising potential of sET to markedly reduce the risk of multiple pregnancy without affecting pregnancy outcomes. Even though sET might increase the time to pregnancy, minimising the risk of twin pregnancy becomes a huge advantage for public and individual health, particularly for elderly mothers.

4. Physiological homeostasis changes that may affect elderly mothers' health

During pregnancy, a series of physiological homeostatic changes take place in a woman's body that activate numerous adaptive mechanisms, mainly cardiovascular, respiratory, and hemodynamic. These changes are essential for the evolution and progress of a normal pregnancy. Adaptive mechanisms can be compromised as a consequence of underlying diseases, which appear more frequently in women of advanced age.

The increase in cardiac output, extracellular volume, and arterial compliance and the decrease in arterial blood pressure (BP) and peripheral resistance are some of the cardiovascular changes that occur in pregnant mothers [33]. Mean BP decreases during pregnancy presenting its lower values in the middle of the second trimester and then it starts to increase reaching values comparable to non-pregnant women at the end of pregnancy. In addition, redistribution of blood flow to different organs is essential in order to cover for the higher metabolic requirements, and so venous return and cardiac output raise dramatically [34]. There are also hormonal factors that favour these changes to appear. Oestrogens and relaxin are both involved in the production of nitrous oxide (NO), which produces vasodilatation during pregnancy and facilitates the distribution of blood to key organs [35, 36]. Ageing is associated with structural changes in the vascular wall, which leads to loss of arterial elasticity and reduced arterial compliance. Cardiovascular adaptive mechanisms could be impaired in elderly mothers due to pre-existing hypertensive disorders or venous insufficiency; therefore, they are at high risk of suffering from complications such as preeclampsia and placental insufficiency, increasing morbidity and mortality for both the mother and the baby.

Modifications in the respiratory system also take place during pregnancy. Pulmonary function is affected by location and orientation changes of the airway and configuration of the thorax due to the presence of the gravid uterus as well as hormonal effects. The elevation of the diaphragm decreases the lung's vertical diameter and subsequently enlarges the transversal and anteroposterior diameters. The displacement of the diaphragm produces a progressive decline in expiratory reserve volume and residual volume. Progesterone, cortisol, and relaxin produce dilatation of the airway in pregnant women reducing pulmonary resistance [37]. Ageing is associated with structural changes not only in the chest bones and diaphragm but also in the lung tissue. The dilatation of the alveoli decreases the exchange surface increasing the residual volume and functional residual capacity. These physiological changes added to those typical from pregnancy can cause alterations in the ventilation-perfusion ratio in elderly mothers.

Dilatation of the renal pelvis and ureters is characteristic during pregnancy on account of the growth of the uterus and the effect of hormones, such as progesterone, that cause relaxation of the smooth muscle. This predisposes women to suffer from urinary tract infections during pregnancy. Renal function is also modified during this period with an increased blood flow and glomerular filtration up to 60% [38]. Precisely for that reason, we should be aware of any medical pre-existing renal dysfunction that can worsen during pregnancy. For example,

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diabetes mellitus type 2 appears more often after the fourth decade of life and affects directly the renal function. Renal function–affected women need to be closely monitored during pregnancy.

These are only some of the major adaptive mechanisms in a woman's body during pregnancy, but there are many more subtle changes that occur in this period. We should pay attention to any minimal sign of hemodynamic decompensation especially in pregnant women of advanced age who are more likely to suffer from diseases, previously undiagnosed, as a result of ageing of their organs.

5. Obstetric complications in twin pregnancy related to age

There are not many studies specifically evaluating obstetric outcomes in twin pregnancies in advanced maternal age, and most of them are retrospective. These studies usually set the threshold for advanced maternal age at the "classic" 35 years, but in current times, this threshold should probably be reconsidered. A recent study by Zhu et al. [39] showed that, in twin pregnancies, advanced maternal age was associated with a higher risk of post-partum haemorrhage, gestational diabetes, and preterm delivery. However, other studies do not demonstrate any significantly increased risk over controls [40].

Much more attention has been paid to the obstetric complications in twins resulting from ART. Particularly, they are at increased risk of placenta praevia, caesarean section birth, preterm birth, and low birth weight [41]. Again, other studies showed no significant differences [42]. What we can be sure of is that twin pregnancies represent a huge demand for the body and that they do come with a higher obstetrical risk. Advanced age mothers' physical fitness necessarily cannot be the same to compensate for this fact.

5.1. Preterm delivery

We defined preterm delivery as birth prior to 37 weeks of gestation. Preterm birth complicates 5–18% of pregnancies and is the leading cause of neonatal death and the second cause of childhood death below the age of 5 years [43]. We should distinguish between preterm deliveries medically indicated secondary to foetal or maternal complications during pregnancy, such as preeclampsia, intrauterine growth restriction, or gestational diabetes, from those that occur after spontaneous onset of labour. Many studies have described multiple risk factors for preterm birth [44–47], although others propose this entity is a syndrome caused by multiple pathologic processes [43].

Twin pregnancy has been classically described as one of the risk factors associated with preterm birth. Although multiple gestation accounts for only 2–3% of all births, this type of gestation constitute 17% of births before 37 weeks of gestation and 23% of birth before 32 weeks [48]. The mechanism for preterm birth in multiple gestations may be related to the increased uterine distension; however, some studies suggest that the increased amount of oestrogen,

progesterone, and sex steroids compared with singleton pregnancies could play an important role in the physiopathology of the syndrome [49, 50].

The effect of maternal age also influences the risk of preterm birth. Some studies suggest that even after adjusting for cofounders such as hypertension, diabetes, race, and mode of conception, maternal age over 40 years is an independent risk factor for preterm delivery [47, 51].

The widespread availability of reproductive technology has increased the percentage of multiple gestations and preterm delivery as an aftermath. Therefore, it is our duty to inform women of the risk of this type of pregnancies and enforce the use of the different strategies in order to achieve singleton pregnancy.

5.2. Preeclampsia

As we have seen before, mean BP decreases during the first and second trimesters secondary to the reduction of peripheral resistances and starts to increase reaching values similar to non-pregnant women in the third trimester.

Preeclampsia (PE) is a hypertensive disorder that appears during pregnancy. PE is a major obstetric complication that causes 15–20% of maternal mortality worldwide, especially in developing countries [52]. It is characterised by the presence of high BP (> 140/90 mmHg) and proteinuria (> 300 mg/dL) beyond 20 weeks of pregnancy. The finding of higher values of BP before this stage of pregnancy is considered chronic hypertension, which can also worsen in the second half of pregnancy, with what we call superimposed preeclampsia. The physiopathology of this multisystemic disorder still remains unknown.

In the last decades, several aetiologies have been described. Some authors suggest that it appears secondary to an abnormal vascular response of the uterine blood vessels to trophoblast invasion, causing platelet aggregation and endothelial dysfunction [52–54]. The increase of BP during pregnancy can also have an effect on the foetus, developing complications such as low birth weight, oligoamnios, and intrauterine growth restriction [54, 55]. In addition, preeclampsia is considered severe when it affects multiple organs, finally producing pulmonary oedema, renal failure, seizures, thrombocytopenia, elevation of liver enzymes, and disseminated intravascular coagulation [54].

The rate of preeclampsia ranges between 2 and 7% in healthy nulliparous women [54, 56, 57]. These rates increase to 14% in twin pregnancies [58]. Preeclampsia is regarded as typical of the first pregnancy. In spite of this, the risk of developing preeclampsia in subsequent pregnancies raises till 18% [58].

Numerous studies proposed several risk factors to classify a specific group of women who are at a high risk of developing preeclampsia, including nulliparity, older age, chronic hypertension, and diabetes mellitus [59–61]. Other studies indicate that, after adjusting for other cofounders, women of advanced maternal age are 1.5 times more likely to have preeclampsia compared to those under 35 years of age [62]. Multiple pregnancy is a moderate risk factor for the development of pre-eclampsia during pregnancy. Women with multiple pregnancy, who have any of the other moderate risk factors for pre-eclampsia (first pregnancy, age 40 years

or older, pregnancy interval of more than 10 years, BMI of 35 kg/m^2 or more at first visit, or family history of preeclampsia), should receive a daily aspirin dose [63].

As we have seen before, single-embryo transfer is the main technique to reduce the rate of twin pregnancies. We should focus our effort on identifying those women with pre-existing medical conditions who are predisposed to suffer PE and, if applying ART, enforce the importance of achieving a singleton gestation to avoid adverse perinatal outcomes.

5.3. Gestational diabetes

Gestational diabetes mellitus (GDM) is a diabetic state diagnosed for the first time in pregnancy. It is one of the most common metabolic disorders in pregnancy. GDM complicates 3–5% of pregnancies and it is considered a risk factor for adverse perinatal outcomes, such as macrosomia, shoulder dystocia, cerebral palsy, and foetal death [64–66]. It is defined as basal glucose ≥126 mg/dl (7.0 mmol/l), HbA1c ≥ 6.5% (47.5 mmol/mol), or glucose levels ≥200 mg/dl (11.1 mmol/l) at any time of the day or screen positive for any of the GDM tests available [67].

Diabetes predisposes pregnant women to suffer urine infections, hypertensive disorders, and prematurity. It is well known that pregestational diabetes can cause foetal malformations, intrauterine growth restriction, stillbirth, and congenital heart disease probably due to vascular alterations in mothers. Both gestational and pregestational diabetes have effects on the foetus secondary to hyperinsulinemia, such as macrosomia, polyhydramnios, and foetal lung immaturity that may cause foetal neonatal distress.

Women of advanced maternal age are at a higher risk of developing GDM [68]. Twin pregnancies have also been related to GDM [69]. The development of GDM usually indicates a reduced pancreatic reserve in the pregnant mother and is a marker of pre-diabetes, putting them at a higher risk of developing diabetes mellitus type 2 in the future. It is essential to highlight the importance of adopting healthy habits during pregnancy in order to avoid consequences for the future health of both the mother and the baby.

Gestational diabetes in twins is also associated with an increased risk of hypertensive disorders, macrosomia, and preterm birth, but it reduces the risk for low birth weight [70]. Furthermore, it has been suggested that gestational diabetes could potentially benefit twin pregnancies, as low 5-min Apgar score and neonatal death are reduced in twins compared to singletons when this maternal complication is present, maybe due to the increased birth weight of the twin pairs [71, 72]. However, growth in the twin pair tends to be asymmetric when GDM or glucose intolerance is present [73].

Early diagnosis and treatment are essential in order to avoid complications during pregnancy. Nowadays, guidelines from different countries recommend the screening for gestational diabetes in women with risk factors such as previous history of gestational diabetes, obesity (body mass index over 30 kg/m^2), and previous delivery of a macrosomic baby [74–76]. Some of them support the use of a universal screening test in the second trimester and also in the first trimester in every woman over the age of 35 [77]. However, the increase in maternal age over the last years implies offering this diagnostic test to a very high percentage of the

pregnant population [70]. Given the importance of early treatment, all twin pregnancies, as well as in the case of advanced maternal age, first trimester screening should be considered, although there is no international agreement [78].

5.4. Growth abnormalities

In mothers older than 40, small and large for gestational age babies and intrauterine growth restriction (IUGR) are increased [79, 80]. Small-for-gestational-age babies (SGA) and IUGR are assumed to be due to placental dysfunction, whose incidence increases with age.

One study found in a very large twin cohort that advanced maternal age was indirectly associated with SGA babies. However, when SGA was present in an older mother, neonatal mortality increased compared to appropriate-for-gestational-age twins in the same age range [81], maybe suggesting an increased severity of the syndrome in this women.

Although it may look as a contradiction, foetal macrosomia also seems to increase with age. It has been suggested that this increased incidence in large-for-gestational-age babies might be due to an overall increase in the body mass index with age [82] and an increased risk of gestational diabetes. However, as we previously mentioned, the increased birth weight in twin pregnancies associated with gestational diabetes could be beneficial for the twin pair, or at least not as detrimental as it could be in singletons.

5.5. Post-partum haemorrhage

Most protocols worldwide recognise maternal age as an independent risk factor for >10,000 mL blood loss during delivery and for post-partum haemorrhage, in both vaginal and caesarean births. Mechanisms behind this increased risk are not well established. Most doctors working in a labour ward are persuaded that uterine atony is somehow more common among older mothers, although there is no evidence for that. Age is associated with certain obstetric complications, such as hypertensive disorders, placental abnormalities, or preterm birth. On the other hand, advanced maternal age increases the risk of induction of labour, large foetuses for gestational age, prolonged labour, oxytocin augmentation, or caesarean delivery. All of the above are well known risk factors of post-partum haemorrhage [83, 84]. So age may not act as a completely independent factor for post-partum haemorrhage. Results from the WOMAN trial showed an adjusted odds ratio of peripartum hysterectomy of 5.98 (95% CI: 3.34–10.70) for women between 30 and 39 years and of 11.73 (95% CI: 6.30–21.85) for women aged ≥40 [85]. This is a trend shown to be repeated worldwide [86]. Advanced maternal age does not only increase the risk of excessive bleeding but also its severity and the risk of needing aggressive treatment strategies, such as hysterectomy.

Again, twin pergnancy is also associated with a higher risk of post-partum haemorrhage. At the same time, twin pregnancy is often associated with other post-partum haemorrhage risk factors, such as preeclampsia, caesarean delivery, and the use of a caesarean delivery for a preterm delivery [87]. Delivery in this group of patients should be undertaken in tertiary hospitals by trained staff.

5.6. Venous thrombosis

The incidence of deep venous thrombosis is increased three times during pregnancy. Pulmonary embolism may occur in 1 in every 1000 pregnancies and represents the leading non-obstetrical cause of maternal death [88]. Both age older than 35 years and multiple pregnancy are listed as risk factors for venous thromboembolism. If we consider that the presence of thrombophilia is more common in women undergoing IVF and that deep venous thrombosis is also more common in these women [89, 90], we could conclude that women of advanced maternal age and carrying a multiple pregnancy definitely represent a high-risk group for venous thromboembolism. Under any other risk factor, thromboprophylaxis should be considered carefully.

5.7. Stillbirth

Advanced maternal age has been associated with an increased incidence of stillbirth [91]. A mechanism under this increase is placental dysfunction, which accounts for around 65% of stillbirths, and it has been observed more frequently in mice models and humans with age. Placentas from older mothers (35–39 and ≥ 40 years old) are less efficient in the sense that foetal/placenta weight ratio was lower than placentas from controls under 30 years old. They seem to be bigger in size and display mechanisms to ameliorate function, like increased relaxation of myometrium arteries and increased amino acid transport, but this does not correlate with a higher birth weight in the offspring. The hypothesis is that an increased size could be an adaptive mechanism trying to make up for placental dysfunction [92]. It has also been suggested that the greater contribution to stillbirth in older mothers could arise from their increased risk of chromosomal abnormalities [80].

Twin pregnancies are also high risk for stillbirth and neonatal death, increasing thirteenfold in monochorionic and fivefold in dichorionic pregnancies compared to singletons [93, 94].

Although this is not under the scope of this chapter, advanced paternal age has also been associated with stillbirth and death of the child before 5 years of age [95, 96]. The risk might be linked to a higher rate of sperm chromatin or chromosomal aberrations. Interestingly, this association dissolves when adjusting for paternal education level, when the association between advanced maternal age and the risk of stillbirth is independent of socioeconomic and educational levels.

6. Delivery and post-partum care in twin pregnancies in advanced maternal age

6.1. Delivery mode and time of delivery

Advanced maternal age is associated with a high frequency of caesarean delivery. Many factors participate in this. For instances, a more frequent prolonged labour due to worse myometrial function and decreased flexibility of pelvic joints [97], increased frequency of large babies

[98, 99], and the presence of coexisting obstetrical or medical complications associated with poorer obstetric outcomes. However, most women over 40 have a successful vaginal delivery even after induction of labour without an increased risk for operative vaginal delivery or perineal trauma [100].

In dichorionic twin pregnancies, the perinatal risks are balanced with the risks associated with iatrogenic prematurity until 37 + 0–6 weeks' gestation and until 36 + 0–6 in monochorionic pregnancies, with higher risks of stillbirths than neonatal deaths beyond this gestation [94].

Pre-labour caesarean delivery may be beneficial in pregnancies with the first twin in non-cephalic presentation or when any or both the twins have a low weight, but evidence for both statements is not strong [100].

6.2. Post-partum care

When obstetric complications such as preeclampsia or diabetes mellitus presented during pergnancy, persistence of medical conditions such as chronic hypertension and type 2 diabetes (T2DM) should be monitored after delivery. Chronic hypertension in women affected by gestational hypertension or preeclampsia is a common event, usually developing years after delivery [101]. Age at pregnancy might reduce this time interval, but this has not been studied before. Likewise, age does not increase the odds of post-partum eclampsia [102]. Age at pregnancy is a risk factor for the development of T2DM when GDM is present [103]. Anyhow, advanced maternal age is a risk factor for developing cardiovascular complications during pregnancy and for developing severe morbidity due to cardiovascular disease [104], so strict and long-term follow-up strategies should be put in place.

Secondary post-partum haemorrhage is increased in women affected by primary post-partum haemorrhage and in women ≥35 years old, both risk factors being independently associated with the event [105].

Maternal age at delivery >35 years has been indicated as a risk factor for venous thromboembolism in the post-partum period and later in life [106]. However, its contribution is probably small when compared to other factors, such as caesarean delivery [107].

Twin pregnancies are also associated with all the complications mentioned above. Again, this specific population is particularly vulnerable for developing post-partum complications.

Various studies suggest that advanced maternal age at the time of delivery is associated with a higher risk of developing stress urinary incompetence (SUI) in the post-partum period [108, 109]. Suspected aetiological mechanisms are many and they are thought to start developing during pregnancy. Some studies suggest that vaginal delivery may worsen SUI, particularly in elderly women, and advise a caesarean delivery in this population when SUI is already present during pregnancy [108]. However, this protective effect is not consistent in literature, so currently, such a recommendation is controversial [110]. Of course, pelvic floor changes are greater in twin pregnancies, as abdominal pressure on it is irredeemably higher [111]. Anyhow, elderly mothers carrying a twin pregnancy are at higher risk of developing pelvic floor disorders, so preventive strategies should be enforced during pregnancy and early investigation and proper treatment in the post-partum period.

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Advanced maternal age is considered to be a risk factor for post-partum depression [112]. This is a poorly studied condition, which can be devastating for the mothers, children, and family. On the other hand, parents of twins frequently experience higher levels of anxiety and depression and are at higher risk for post-partum depression and for marital decline [113, 114]. Post-partum depression has also been linked to preterm birth, so common among twins, due to a lesser mother-infant interaction and parents' concern for both medical and economic subsequent issues [115]. Sleeping disorders 3 months post-partum are more frequent in mothers older than 35 years old [116]. Psychosocial and physical support should be provided.

7. Long-term disabilities due to advanced maternal age

Several neurological disorders have been shown to be more frequent in children born from elderly mothers, particularly cerebral palsy [117, 118] and autism spectrum disorders [119]. In terms of learning disabilities, one study found that developmental vulnerability decreases with the mother's age from 15 to 30 years, but starts to increase when the mother is older than 35, this increase being independent from the socioeconomic status [120]. Interestingly, children born from old parents show a poorer neurocognitive performance in childhood [121]. However, environment might make up for the "biological disadvantage", as older parents are usually in a better financial state, are more highly educated, and usually have reached a more stable couple/marriage situation. All this may give them certain emotional maturity and life experience that improves child-rearing abilities. Compared to singletons, twins exhibited higher rates of cerebral palsy and mental retardation and showed more pronounced speech delays, motor development, and behavioural problems. However, the main explaining factor is the higher frequency for preterm delivery that results in low and very low birth weight children [122]. Maternal age contributes by increasing the risk for preterm delivery, but the same way in singletons and twins.

Trisomy 21 is very well known to increase with maternal age due to meiotic non-disjunction errors. More recently, mitochondrial dysfunction and epigenetic changes associated with oocyte ageing can be inherited by the descendant and may predispose also to chromosome segregation errors in grandchildren [123].

8. Conclusions

Twin pregnancy in advanced reproductive age represents a very vulnerable population for obstetric and medical complication during and after pregnancy. Most of these pregnancies are a result of assisted reproduction. Counselling prior to treatment is essential, particularly to discern whether the woman is fit for pregnancy and to enforce specific preventive strategies, such as single embryo transfer. Both conditions, advanced maternal age and twin pregnancy, are risk factors for many obstetric and medical complications. During pregnancy, early diagnosis and treatment of the issues discussed in this chapter can reduce risks and sequelae to the minimum.

Conflict of interest

The authors declare no conflict of interest.

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