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The Final thesis

”Geriatric” Pregnancy

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SUMMARY

Nowadays, more women delay childbearing into their forties or even fifties due to several reasons like the greater availability of contraceptive methods, better fertility treatment options and the greater availability of socioeconomic resources. Together with this demographic shift in childbearing over time, some pregnancy related complications were found to occur more often in pregnant women aged 40 years and above. Women of advanced maternal age are at higher risk for fetal chromosomal abnormalities, spontaneous abortions, placenta previa, preterm delivery and stillbirth (1–5). Moreover, they tend to have more often pre-existing comorbidities like diabetes mellitus and hypertension that might lead to serious complications as for example preeclampsia (6,7). All the complications contribute to a higher perinatal mortality in women of advanced maternal age hence it is important to adjust current pregnancy monitoring algorithms and develop new recommendations. While most studies review disadvantages of pregnancies at advanced maternal age, some advantages can be described. The advantages are based primarily on the improvements over time that affect children born to a later birth cohort as long-term trends are positive for many important outcomes (8). Furthermore, due to sociodemographic changes women of advanced maternal age nowadays have a higher educational level, are more often employed, and have a higher income compared with their younger counterparts. Some studies even suggest that the advantages, to a degree, may counterbalance the biological disadvantages (9).

KEYWORDS

Advanced maternal age; adverse pregnancy outcome; pregnancy complications; advantages; disadvantages; pregnancy

INTRODUCTION

During the last decades, the maternal age of childbearing has undergone demographic changes and delayed childbearing has become more common all over the world, due to assorted reasons. In the United States, the rate of primigravidae aged 40-44 began to increase significantly in the 1980s and has more than doubled from 1990 to 2012 (10). Nowadays the birth rates among women above 40 years are still increasing. In the year of 2018, the birth rate for women aged 40-44 was 11.8 births per 1000 women, which is 2% more than the year before while the birth rate for women in the age group 20-29 declined by almost 5%. The birth rate for women aged 45-49 including also women aged 50 or older was 0.9 births per 1000 women, which has generally increased since 1997 (11).

Similar trends can be observed in other countries. In China, the birth rate in women aged 40 to 44 raised from 1.77‰ in 2004 to 3.96‰ in 2014. In contrast to that, the birth rate in women of 25 to 29 age decreased from 102.44‰ to 93.62‰ (12).

Historically, advanced maternal age used to be defined as the age of 35 or more but in many studies the cut-off value has been changed to the age of 40 (13). Previously woman who gave birth later in their life used to be of high parity and a rather low socioeconomic status, but this trend has inversely changed to low parity and high socioeconomic status (14).

There are many reasons why pregnancies at advanced maternal age are increasing but the most significant one seems to be the improvement of assisted reproductive technologies. Social egg freezing or embryo freezing give women the physiological possibility to postpone childbearing (15).

Huge changes in work and society have led to the desire for higher education and to obtain financial security before becoming a mother (15). Moreover, for women nowadays it is important to live a self-determined life and to be financially independent from their family and partner. Furthermore, higher education levels among females are associated with a better knowledge of different types of contraception, that together with a greater access to birth control methods, contribute to an increased maternal age (16).

The positively changing and greater availability of socioeconomic resources for women of advanced maternal age nowadays influences the maternal well-being in a positive way. Some studies even come to the conclusion that women of advanced maternal age have a more positive happiness trajectory than younger parents (17). While socioeconomic factors affect pregnant women of advanced age mainly in a positive manner, it is believed that advanced maternal age is associated with an increased rate of obstetrical and perinatal complications as well as adverse pregnancy outcomes. An important reason for complications that occur during pregnancy are pre-existing comorbidities like diabetes mellitus and hypertension, that exist more often in women over the age of 40 (6,7). One of the most common medical complications during pregnancy is gestational hypertension, while the incidence increases gradually by increasing maternal age (18). Moreover, when compared to groups of younger pregnant women, women of advanced maternal age have a higher risk of other pregnancy related complications like congenital disorders, spontaneous abortion, placenta previa, preterm birth and stillbirth (15). As more women delay childbearing and the risk for pregnancy related complications changes, newer recommendations on the screening and management of these women emerge.

As women delayed childbearing, not only pregnancy related complications and disadvantages could be reviewed. Over the last decades, some advantages for the mother and child raised. For

example, maternal age over 40 seems to serve as a protective factor for postpartum depressive symptoms (19). Furthermore, some studies even suggest that positive trends in the macroenvironment over time, affecting children born to later birth cohorts, may be so strong that postponing parenthood is beneficial for children even if maternal ageing related effects might be negative (8,20).

LITERATURE SELECTION STRATEGY

The literature search was conducted in NCBI using the pubmed database. Keywords related to the thesis topic were identified and used as search terms. The keywords were “advanced maternal age” combined with either “adverse pregnancy outcome”, “pregnancy”, “pregnancy complications”, “advantages” or “disadvantages. The search was limited by publication year and only literature that has been maximum 5 years old was included. As searches were carried out in September 2021 and updated in January 2022, literature that was published between the year of 2016 and 2022 was included. Taking also primary references into account, some literature is older than 5 years. The literature was further limited by including only English and German language articles. For the combination of “advanced maternal age” and “adverse pregnancy outcome” 288 results were given by pubmed. For the combination of “advanced maternal age” and “pregnancy” 2002 results were identified. The combination of “advanced maternal age” and “pregnancy complications” led to 1058 results. For “advanced maternal age” and “advantages” 39 results were identified while for “advanced maternal age” and “disadvantages” only 27 results were identified. All five searches were conducted with consent to the selection criteria. The search for duplicates using Excel revealed 1376 duplicates for the five combinations, therefore 2038 valid literatures were identified. To identify further relevant studies, reference lists from included original literature were searched as well.

Studies using case control or cohort designs were included into the literature review only if the outcomes of women of the age of 40 or above were included and the women below the age of 40 were used as control group. Therefore, maternal age below 40 years was an exclusion-criteria in case control and cohort design studies. The same exclusion exists for study groups that were 55 years or older. The limited literature was reviewed and selected based on their content. Included was literature about complications concerning the maternal and neonatal health throughout the pregnancy and after pregnancy. Other literature about advantages and disadvantages of pregnancies in women between the age of 40 and 55 was included as well.

To get more statistics concerning demographics in the United States, “National vital statistics reports” was used. To determine recent recommendations for the pregnancy management in elderly women, guidelines from different hospitals and associations were reviewed.

COMPLICATIONS

As the maternal age of pregnancies is increasing, many studies researched the complications that occur due to increasing age. As the definition of advanced maternal age is not very consistent across the studies, some studies decided to choose a study group from 35 years and above while others chose the study group above the age of 40. Nevertheless, most studies divided women into age groups of 5 years.

The first obstacle that women at advanced age wanting to get pregnant are facing, is the conception. It is well known that fertility starts to decline from the age of 30 (21). Therefore, women at advanced age are often dependent on assisted reproductive technologies. A study from the Netherlands compared methods of conception in women at different age groups between the year of 2000 and 2018. The 3 study groups were 40 to 44 years old, 45 to 49 years old and over 50 years old, while the reference group was 25 to 29 years old. Only 3% of all women in the reference group used assisted reproductive technologies like intrauterine insemination, in-vitro fertilization, or ovulation induction. However, the use of assisted reproductive technologies increased with increased maternal age. Of the women aged 40 to 44, 8% used any kind of assisted reproductive technologies and in the age group 45 to 49 already 25% used another method of conception than spontaneous. Of the women aged 50 and more, even 64% used assisted reproductive technologies (22).

Although women delaying childbearing rely on assisted reproductive technologies, success rates decrease with advanced maternal age. Therefore, studies recommend an offer for detailed counselling regarding success rates but also ethical and legal implications of the fertility treatment options. Other studies suggest that women older than 40 years require immediate evaluation and treatment with a hormonal assessment and ovarian testing as soon as they wish to become pregnant (23).

The success of fertility treatments depends on the quality of oocytes and sperm. As oocyte aneuploidy as well as embryonic aneuploidy increases with increasing maternal age, all types of fertility treatments have reduced success rates (24). Consequently, it is important that women who decide to postpone childbearing understand not only the limits of assisted reproductive technologies in general but also the age-related decline in success rates. In addition, assisted reproductive technologies at advanced age have further limitations as multiple pregnancy must be avoided due to associated comorbidities. Therefore, these women should undergo only single embryo transfer which decreases the success rates further (23).

With increasing maternal age, the risk of chromosomal abnormalities increases dramatically. Studies reveal that the absolute risk of having a chromosomally abnormal fetus were between

1.9% and 3.8% for women over the age of 40 while only 0.2% to 0.5% of the under 35 years population were at risk (1). Trisomy cases occur at a frequency of about 2% in women under the age of 25 after which the frequency increases dramatically to over 40% at maternal ages above 40 (25). Trisomy 21 is more common than Trisomy 18 and 13 across all ages but they have a similar increase in risk with increasing maternal age (1).

Fetal chromosomal aneuploidies are not only increasing in advanced maternal age, they are also the main etiology of spontaneous abortions (2). A study evaluated women of different age groups with a history of one or more spontaneous abortions during the first trimester. They found out, that spontaneous abortions in the age group of women above 40 years had a significantly higher percentage of congenital abnormalities than other age groups. Moreover, the range of fetal abnormalities increased with increasing maternal age (26).

More than half of all pregnancies over the age of 40 end with a pregnancy loss. In women at the age of 40 or over the risk of spontaneous abortion is significantly increased, independent from parity or previous spontaneous abortions (27).

First trimester miscarriages occur with a higher prevalence than second trimester miscarriages and they occur at every age group with the lowest risk for women in their twenties. The risk for a first trimester miscarriage is approximately 8 to 10% followed by a steep rise from the age of 30. Advanced maternal age was found out to be a strong independent risk factor as women aged between 40 and 45 have a risk for first trimester miscarriage of 33 to 51%. Women above the age of 45 are at even higher risk that varies from 57 to 75%. The risk for a second trimester miscarriage is likewise increased for pregnant women at advanced age. While only 0.4% to 0.9% of women below the age of 35 will lose their child during the second trimester, 1.7% to 2.2% of women above 40 years will experience a second trimester loss (1).

Advanced maternal age is not only a strong independent risk factor for spontaneous abortion, but it can be even further potentiated by smoking. The risk of a spontaneous abortion in pregnant women of 40 years or older was increased by three times in comparison to women that did not consume nicotine during their pregnancies. Whereas the risk of spontaneous abortions in smoking women between the age of 20 and 29 was increased only by one and a half times (28).

Obesity is another individual risk factor for spontaneous abortions (27). As women at greater age tend to have a higher BMI when compared to younger women, physicians should pay attention to the maternal weight (29).

In contrast to young pregnant women, women of advanced maternal age tend to have more chronic medical conditions that have a negative impact on the course of a pregnancy. Women above the age of 40 have a higher risk for preexisting hypertension and diabetes mellitus.

During pregnancy, preexisting hypertension might lead to preeclampsia, placenta abruption or intrauterine growth retardation. If diabetes mellitus type 1 is not well controlled during pregnancy it might lead to an increased rate of birth defects or even spontaneous abortion. It is important to monitor pre-existing comorbidities of women at advanced maternal age, as they have a higher prevalence in women above the age of 40 and might cause harm during pregnancy (6,7).

Many complications that occur during pregnancy tend to appear more often in women at advanced maternal age than in young women. One of these complications is gestational diabetes which can be defined as glucose intolerance that develops during pregnancy. The main independent risk factors are preexisting diabetes mellitus, advanced maternal age over 40 years and obesity with a BMI of 35 kg/m^2 or greater (30). Many studies not only discovered higher rates of gestational diabetes in older women, furthermore they identified an increasing occurrence with increasing age (22,31,32). Some studies report about a two to three fold risk for advanced maternal age mothers to be diagnosed with gestational diabetes mellitus (12). In another study from Italy only 2.7% of women below the age of 40 developed gestational diabetes while 5.7% of the age group 40 to 44 years developed this complication. Of the women at very advanced maternal age, over the age of 45, 8.2% were diagnosed with gestational diabetes (31).

Therefore, researchers suggest that all women above the age of 35 undergo diagnostic testing for gestational diabetes. Advanced maternal age is not only an independent risk factor for gestational diabetes, moreover it is an independent risk factor for pregnancy related hypertensive disorders. They belong to the most common medical complications during pregnancy (33). The incidence of hypertensive disorders of pregnancy varies among different countries and regions, therefore percentages range from 4% to 25%. Moreover, studies reported an increase in prevalence as maternal age increases with a peak for women at the age group of 45 to 49 years (18).

A subdivision can be made into chronic hypertension, gestational hypertension, preeclampsia, eclampsia and the HELLP syndrome. The ratio of gestational hypertension across all age groups differs between different studies but it accounts to the most common disease of all hypertension related pregnancy disorders. Women at advanced maternal age are at even higher risk as the risk of developing hypertension during pregnancy increases gradually with increasing maternal age (34). Women with gestational hypertension are at greater risk of cerebrovascular events and organ failure while fetuses are at greater risk for intrauterine growth restriction, premature birth, and intrauterine death. Consequently, it contributes to one of the main causes of perinatal

morbidity and mortality for the newborns and women (35). A narrow monitoring of the blood pressure in pregnant women is therefore advisable especially if the women is at advanced maternal age.

The risk of preeclampsia increases as well, particularly for women above the age of 40. Studies report an increasement of one and a half to two times in risk compared to younger women (36). Preeclampsia is most common among women aged between 45 and 54 years. During a study period of 2 years, 10.4 % in that range of age were diagnosed with preeclampsia compared to 6.1% of women between the age of 40 and 44 (32).

Not only advanced maternal age increases the risk of preeclampsia, being overweight or obese aggravates the risk further. A study found an almost four-fold increase in incidence when compared to patients of normal BMI. As women aged above 40 years tend to have a higher BMI than younger women, it contributes to an even higher risk of preeclampsia to women at advanced maternal age (12). As rates of preeclampsia are increasing with increasing age, it is believed that the occurrence of eclampsia and the HELLP syndrome is as well increased as they either result from preeclampsia or are commonly found together.

Placenta previa is a commonly discussed pregnancy complication as it is significantly associated with perinatal mortality, congenital malformations, and intrauterine growth restriction (37). Many studies report an increased occurrence of placenta previa in women aged above 40 years, while no significant association between maternal age and placental abruption can be found (3,38). Placental insufficiency can be found more frequently in women that smoke during pregnancy as well as in women of advanced maternal age. In addition, women above the age of 40 have the highest risk for intrauterine growth restriction. These findings underline that placental insufficiency is a common cause of intrauterine growth restriction. Another significant cause for IUGR is preeclampsia (39,40).

Not only preeclampsia leads to a decreased placental perfusion. As previously discussed, gestational diabetes occurs more often in women of advanced maternal age and as diabetes may also lead to a decreased placental perfusion, it contributes to another risk factor for intrauterine growth restriction. Other maternal and fetal causes for intrauterine growth restriction are placenta previa and chromosomal abnormalities, which are also found more often in women of advanced maternal age (41).

Preterm delivery can be defined by the birth of a newborn before the 37th gestational week. Thereby, some studies further divide this term into very preterm, if birth occurs between the 21th to 31th week of gestation, and moderately preterm if birth occurs between the 32th and 36th week of gestation (4). The higher risk of preterm delivery among women at advanced age

is widely discussed in many studies (3,4,33,42). There are contributing factors like preexisting comorbidities, complications during pregnancy and delivery that more commonly exist in advanced maternal age and thereby increase the preterm delivery rates among these women. The risk for very preterm delivery and moderately preterm delivery were both higher in women above the age of 40, while the age-related risks compared between these two groups differed. Moderately preterm birth was consistently lower than the risks of very preterm birth. In sum, a stronger association can be found between advanced maternal age and risk of very preterm delivery compared to moderately preterm delivery. In addition, the risk of very preterm delivery is irrespective of parity (4).

Comparing the causes of preterm birth, women over the age of 40 tend to have an iatrogenic origin of prematurity more frequently than a spontaneous origin (42). Furthermore, maternal age can be seen as individual risk factor for preterm delivery (4,33,42). This was proven by studies that adjusted potential confounders like hypertension, diabetes, cardiac and renal diseases, smoking status, placenta previa and so on. After adjustment, advanced maternal age was still associated with preterm birth (42). The reasons for that are still not clear and should be further researched. One reason that could explain the higher risk of preterm birth is the progesterone deficiency as maternal progesterone levels decline with increasing maternal age (4). Another mechanism could be the placental vascular pathology. This can be explained by the fact that spontaneous preterm birth is associated with a four- to seven-fold increase in risk of placental vascular pathology and placental insufficiency is more frequently found in advanced maternal age (33).

It is well known that the risk of stillbirth is increasing in prolonged pregnancies. Therefore, induction of labor is often indicated in women beyond term of pregnancy. This trend of an increased risk of stillbirths that increases with higher gestational age, is more apparent in women aged 40 years and above (5,12,43). Hence, on one side there is the risk related with gestational age and on the other side the risk related with maternal age if talking about stillbirths. The relative risk for stillbirths in mothers over the age of 40 was the highest at 40 weeks of gestation, which leads to the conclusion that it would be reasonable to offer induction of labor if undelivered within 39 weeks of gestation (43).

The underlying mechanisms that contribute to fetal mortality can be found in advanced gestational age and advanced maternal age and thereby explain the higher rates of stillbirths in these groups. For instance, two of the underlying mechanisms are the deterioration of placental functions with increasing gestational age and the increasing risk of comorbidities in women over the age of 40, such as hypertension or diabetes (43).

Consistent findings among different studies were the higher rates of cesarean sections compared to spontaneous delivery among women delivering at advanced maternal age. Some studies report that the cesarean section incidence was 7 or 9 times higher in women aged 40 or above compared to younger age groups (15,22). Therefore, maternal age above 40 years can be considered as an independent risk factor for delivery by cesarean section. Moreover, with increasing maternal age the incidence of spontaneous deliveries decreased continuously while the rate of cesarean sections increased continuously. These findings were still consistent if comparing primiparous with multiparous women (15,44).

While all primiparous women tend to undergo more often cesarean sections compared to multiparous women, the primiparous women above the age of 40 seem to be at highest risk to deliver by cesarean sections (15). In addition, as cesarean section rates were lower in multiparous women of all ages, it is suggested that higher parity rates may function as protective factor despite maternal age (44). Cesarean sections can be further distinguished into elective and emergency cesarean sections. Overall, elective cesarean sections are more common than emergency cesarean sections. Furthermore, elective cesarean sections among women aged 40 and above are performed almost twice as often as among younger patients (15). While elective cesarean section rates increased consistently with increasing maternal age, emergency cesarean section rates were similar among all age groups or even lower in women above the age of 40 (12,15). The study from China that observed highest rates of elective cesarean sections in women above the age of 40 together with lowest rates of emergency cesarean section, suggests that this might reflect maternal and obstetrician preferences to avoid risks, as among older patients there might be an increased occurrence of medical complications during labor. Another important reason for the higher elective cesarean section rates among women at advanced age is the maternal request for cesarean section that was observed in different hospitals (12).

Some other reasons discussed in literature regarding higher rates of cesarean sections in women at advanced age are uterine dysfunctions, decreased uterine activity, reduced myometrial function and a lower number of oxytocin receptors (45). Not only cesarean sections are more common, operative vaginal deliveries like vacuum and forceps deliveries were described by a study to be more often in women over the age of 40 (46). Whereas in another study it could not be confirmed (40). Therefore, more research needs to be performed to evaluate the relation between operative vaginal deliveries and advanced maternal age.

If talking about labor in women at advanced maternal age, it is important to mention that there are some complications that occur more often if compared to younger women. In a large population-based register study from 2017 the risk of labor dystocia in association of maternal

age was evaluated. They confirmed that the risk of labor dystocia increases continuously by increasing maternal age, irrespective of parity. Furthermore, they account maternal age as independent risk factor for labor dystocia (47,48).

Studies explain this interaction by the age related physiological changes of the myometrium and the continuous decline in uterine performance that leads to labor dystocia (48).

This suggests that advancing maternal age has a negative impact on the labor progress.

Other studies identified that women over the age of 40 need pharmacological induction of labor more often than younger pregnant women as uterine contractions are too weak or even missing. The reason for that could be an impaired myometrium that shows decreased blood perfusion and worse innervation if compared to myometrium of younger women (40,49).

19% of women over the age of 40 were induced pharmacologically, while only 16 and 10% were induced pharmacologically at the age of 24 and 34 (40).

Regarding postpartum complications, postpartum hemorrhage is a profoundly serious condition affecting women above the age of 40 more often, if compared to younger women. In a study from 2021, 2.7% of all women over the age of 40 developed postpartum hemorrhage after giving birth. While only 1.4 and 1.5% of the women under 40 years developed this condition (50). These findings are similar to another study from the Netherlands. They found the most notable results in women over the age of 50 as there was a four times increased risk of postpartum hemorrhage for them if compared to younger women (22).

It accounts to the number one cause of maternal death worldwide but it is a preventable and most often a treatable condition (51). Therefore, physicians should pay more attention to the postpartum care in women at advanced age. This can be confirmed by a study that researched the risk for postpartum readmissions. They state that women at advanced maternal age are at higher risk for postpartum readmission and severe morbidity at readmission while the risk is increasing with increasing maternal age. As result, it is advisable to optimize postpartum care in women above the age of 40 if other risk factors are present (52).

To assess the severity of outcomes of pregnant women of advanced age, it is useful to look at maternal and perinatal mortality. A study from the Netherlands researched those outcomes in women of different ages and of different amounts of pregnancies. Overall, maternal mortality was rare but increased for women over the age of 50. Perinatal mortality was observed more often in women over the age of 40. The risk for perinatal mortality during their first or second pregnancy was found to be two times higher if compared to younger age groups. For the women over 45 the risk was even higher as it almost tripled (22).

As discussed previously, the risk for chromosomal abnormalities increases dramatically in women of advanced maternal age. Furthermore, congenital birth defects of the newborn are as well more common in pregnant women over the age of 40 (53). Especially, heart defects and cranial defects can be found more often in those newborns. Congenital defects were found to have a significant correlation with preterm delivery and intrauterine growth restriction. In comparison, birth defects involving the extremities like syndactyly and polydactyly were not found to be more common in women above 40 years as they were increasingly found in the study group of 24 years old women (40).

ADVANTAGES

After reviewing all complications that tend to occur more often in pregnant women of advanced age, the positive aspects of delaying childbirth must be reviewed as well.

There are advantages affecting the mothers health positively like lower vaginal infections rates, lower rates of vaginal birth injuries and fewer postpartum depression symptoms. Moreover, there might be advantages associated with a socioeconomically and behaviorally beneficial profile that may also affect the child's development in a positive manner.

One maternal pregnancy related complication that is less frequently found in women of advanced maternal age are infections of the vagina. Comparing pregnancies of women above the age of 40 with pregnancies of young women, the incidence of infections like chlamydia and streptococcal infections were the lowest in women above the age of 40 (40). A reason why infections are mostly found in young pregnant women could be the worse genital hygiene if compared to women of advanced maternal age. But this is not proven yet. Another reason could be the instability of the relationship and often changing sexual partners in young women that lead to higher rates of infections (40).

Not only physical postpartum complications develop, psychological complications like postpartum depression is a common complication with a global prevalence of 10 to 15% (54). Literatures are reporting, that offspring of women that experienced depression during the perinatal period are more likely to develop psychiatric disorders like depression and psychotic disorders, if compared to children of women without perinatal psychiatric disorder (55). It is already known that a personal history of psychiatric disorders is a strong risk factor for postpartum depression. Furthermore, it is well known that a positive family history as well as the environment plays a role in developing postpartum depression. Known environmental risk factors are low socioeconomic status, immigrant status and low educational status (54).

Reviewing the literature on other maternal and perinatal factors like maternal age reveals conflicting results. Earlier studies had results that showed no correlation with age (56). While

newer studies report a protective effect of advancing maternal age. Psychological distress tends to be more common in women of advanced maternal age only if they have suffered from depression before pregnancy (57). A study with a large and international study population reports highest depressive symptom rates among women aged 18-24 followed by a stepwise decline. Among mothers aged 40 and older a subsequent leveling off was noticed. Only among mothers of twins that were 40 years or older, a highly statistically significant increase was observed (19).

The reason for less postpartum depressive symptoms among women of advanced age could be individual or societal. Women become more stable in finances, careers, and relationships as well as mental health (9). As women of advanced maternal age pregnant with twins are at elevated risk for developing postpartum depressive symptoms, it is recommended that special considerations should be taken into account. During the routine prenatal visit, assessments could be performed that include the psychiatric history and adverse life events (19).

It is well known that nicotine consumption during pregnancy can have a significant impact on the newborn's health. There are short term and long-term outcomes caused by maternal smoking during pregnancy. Some short term outcomes are low birth weight, birth defects, digestive or respiratory symptoms and even infant death (58).

While long term outcomes are neurodevelopmental and behavioral problems, obesity, and asthma. Statistics from the United states report the highest smoking rates during pregnancy among young women until the age of 30. The percentage ranges from 7.5 to 9.2%. While in 2018, only 3.5% of women aged 40-54 were smoking during their pregnancy. Therefore, a decrease in nicotine consumption during pregnancy can be observed by increasing maternal age (11).

An important aspect must be considered if talking about smoking during pregnancy. Even though smoking rates are lower among women of advanced maternal age, the risk of stillbirth is three times higher in smoking women at the age of 40 or above if compared to younger women. The risk of having a stillbirth within the group of 20 to 29 years old was increased only by one and a half times (28). Conclusively it can be said that smoking during pregnancy causes even more harm to the fetus if the women is 40 years or older.

Smoking while pregnant has undergone a change during the last decades. While in the 60s the number of women smoking during pregnancy was high across all maternal ages, nowadays lower rates of smoking while pregnant can be observed in women at 40 years and older compared to younger women. This indicates a strong change in behavioral characteristics of

older mothers during the last decades, that can nowadays be seen as advantage of late pregnancies (59).

Another phenomenon that counterbalances the risks associated with advanced maternal age are the improvements over time on several measures that are closely related to the quality of life of an individual. A women born in 1950 who had a child at age 20 would have given birth in 1970 but if the same women had chosen to have a child at age 40 the children would have been born in 1990. As long term trends are positive for many important outcomes, the improvements over time make a significant difference to children if they were born 20 years later as the women decided to postpone childbearing (8).

Some of the improvements, from which children born to a later birth cohort benefit, is the life expectancy that increased during the last decades while mortality rates of children decreased. Moreover, education became more accessible to all people (20).

Other secular improvements include improving medical and public health conditions that are indicated by an increase in average height of populations across developed countries, a useful indicator of improvements in early life conditions (8). As sociodemographic improvements over time are beneficiary for children born at a later date and to a different birth cohort, it is suggested that parents who have postponed childbearing in the 20th century have increased the socioeconomic opportunities and health of their children. Some even suggest that the positive trends in the macroenvironment affecting children born to a later birth cohort may be so strong that they often overweigh individual ageing patterns (20).

A study from Sweden shows that "individuals born to older mothers are taller, remain longer in the educational system, are more likely to attend university and perform better on standardized tests than their sibling who were born when their mothers were younger" (8). These results show that in countries where social conditions and health is improving as well as education is expanding, postponing parenthood is beneficial for children even if maternal ageing related effects might be negative (8).

Another example that shows how postponement of motherhood can affect children positively by changing sociodemographic over time, was discovered by a study from the United Kingdom. While in birth cohorts from 1958 and 1970 children born to a mother aged 35 and above scored lower in cognitive development tests at age 11 than children born to a mother aged 25 to 29, this disadvantage to children of mothers at advanced maternal age had reversed to an advantage in the 2000 to 2002 birth cohorts. Children who were born when their mothers were 35 years or older, scored higher than children born to younger mothers. For maternal ages of 40 and above, the pattern was qualitatively similar (60).

The reversed change of a better cognitive ability of children born to older mothers nowadays can mostly be explained by changing sociodemographic. Previously in the early 20th century, women who gave birth at a later age had a lower socioeconomic status. They had low levels of education and higher parity which might have led to dilution of family resources across many children. These factors contributed to the decreased cognitive ability of children born to older women. Whereas in the cohort between 2000 and 2002 the women of advanced maternal age had a socioeconomically advantaged family background as their education was better if compared to younger mothers. "Consequently, the children that are born to older parents are not disadvantaged the same way as the children with older parents used to be" (60).

Another aspect of delaying childbirth is the maternal well-being. Studies looked at several aspects of maternal well-being and had mixed findings that ranged between advantages and disadvantages for women at advanced maternal age. Viewing demographic data, it was found out that women above 35 years have a higher educational level, are more often employed, and have a higher income compared with their younger counterparts (9). Research suggests that the availability of better socioeconomic resources might influence the mother towards being less stressed as it gives them a greater financial flexibility and better options for childcare (17). Moreover, women of advanced maternal age frequently express a "readiness for parenting" that was not present when there have been younger. That "readiness" is often associated with stability as there is financial security and a stable relationship to their partners. Furthermore, women of advanced maternal age were ready to settle down and had no feeling about the child as causing them to have missed something (61).

Another study analyses the subjective well-being and happiness of parents over time. Among those who had experienced their first birth at ages 35 and above, happiness is elevated during the year of birth and then after a small drop, happiness remains at or above baseline. This happiness trajectory is much more positive if compared to younger parents. For the younger counterparts, happiness is increasing only temporarily and declines to prebirth levels within a few years (17).

These studies show that advanced maternal age is often associated with better socioeconomic resources if compared to younger pregnant women, that may help to alleviate stress and lead to a greater overall happiness (20). Women of advanced maternal age also tend to be more grateful and express more appreciation towards the opportunity to be mother (61). The reason for that could be the lower chances of getting pregnant at advanced maternal age as fertility starts to decline from the age of 30 (21).

A study from China researches the physical and mental health-related quality of life over the course of all three trimesters to assess maternal well-being. They include women of the age 35 to 39 to their advanced maternal age group and further research should be made to evaluate if the results are still the same if the definition of advanced maternal age is changed to women aged 40 or above. This study comes, like other studies, to the conclusion that women of advanced maternal age are more likely to be employed and have a higher income if compared with younger women. Furthermore, the study revealed that these women have a more satisfied relationship with their husband and mother in law if compared to their younger counterparts (9). This finding is consistent to previous studies that older women have a stronger family functioning and higher social support (62). While previous studies already suggested that postponing childbearing may be beneficial from a psychological point of view, the study from China had consistent findings (19). According to that study, maternal age can be seen as a predictor of mental health-related quality of life as the women of advanced maternal age scored higher than women below the age of 35. Concludingly, a better relationship to family members and a better socioeconomic status, that are more often in women of advanced maternal age, lead to a better mental health-related quality of life (9).

DISADVANTAGES

After discussing the complications concerning the maternal and children health of women at advanced age and the advantages of delaying childbirth, more disadvantages can be named. While women of advanced maternal age had a better mental health-related quality of life, the physical health-related quality of life during the first two trimester was worse if compared with their younger counterparts. During the third trimester no significant difference was found between the women of advanced maternal age and the younger pregnant women. Therefore, the third trimester by itself was a predictor of physical health-related quality of life. But moreover, maternal age over 35 was a predictor as well. That finding reflects a decline in physical capacity in advancing age. The study suggests like previous studies, that the biological disadvantage of women at higher age is to a degree balanced by the social advantage in pregnant women of advanced maternal age (9).

Fatigue and sleeping problems can be accounted to disadvantages that are more common in women of advanced maternal age (63). Looking at social aspects of a delayed pregnancy, women that decide to postpone childbearing often experience social stigma and judgement. They often get questions about their age and how they conceived, some might even be mistaken for grandparents which leads to feelings of loneliness and isolation. Women of advanced

maternal age are often marginalized by younger mothers and same aged peers who are past the stage of active parenting of their child (61).

While some studies conclude that women of advanced maternal age have a more satisfied relationship with their partners, a study of first-time mothers over 40 report that almost half of the participants experience lower levels of intimacy and neglect of the partner after childbirth. As mothers from the unintended pregnancy group were no more likely to report negative relationship changes, the study speculates that greater life experiences could serve as buffer against a decline in relationship satisfaction (9,61). While some studies report a higher social support, others noted a lack of social support that older mothers receive, particularly from their ageing parents, who may be physical unable to help and in fact may require support themselves from the new mother. They usually get less help and support from surroundings due to the perception that older mothers are more capable of parenting. Often the lack of social support is compounded by an unwillingness of older mothers to ask for support due to pride and their perception that managing their life before pregnancy should translate into motherhood automatically. Furthermore, they often report "sandwich generation" issues, as they must care for both a young child and an ageing parent. Worries about the own health decline, mortality and the future care of their children are no rarity among women of advanced maternal age. Older mothers often have mature management strategies and an organized life that might lead to disappointment and unpreparedness for the unpredictability and need for flexibility that comes with having a child (61).

RECOMMENDATIONS

As pregnancies of women at advanced age come along with more complications, are more frequent than in the past and will be increasing further, the pregnancy management should be adjusted.

During preconception counseling women of advanced maternal age should be encouraged to optimize their health by achieving a normal body weight, being physical active and taking folic acid supplements. As women of advanced maternal age tend to have more preexisting medical conditions it is important to evaluate them and optimize their control (64).

Especially preexisting diabetes mellitus and hypertension should be evaluated and monitored, as they have a higher prevalence in women above the age of 40 and might cause harm during pregnancy (6,7). During the first trimester an effective screening for chromosomal abnormalities should be offered and women should be encouraged to perform the aneuploidy screening test, preferably the cell free fetal DNA testing together with a detailed ultrasound (65). Furthermore, women with a high risk based on ultrasound findings should be offered

diagnostic invasive testing like amniocentesis or chorionic villus sampling together with being reassured that the risks of invasive procedure to diagnose chromosomal abnormalities are low (1). According to the American College of Obstetricians and Gynecologists advanced maternal age is a moderate risk factor for preeclampsia and these women should be offered effective screening. If another moderate risk factor or high-risk factor exists, low dose aspirin prophylaxis is recommended (65). A newer approach, that is superior to the risk scoring system, is to estimate the individual patient specific risk of preeclampsia by multi marker models that incorporate maternal age while they combine maternal factors with biomarkers (66). High risk women can then be offered aspirin prophylaxis of 150 mg nightly. According to the ASPRE trial, rates of preterm preeclampsia can be reduced by up to 80% following such a protocol (67). Screening recommendation for gestational diabetes varies according to healthcare settings but some recommend an early Glucose Tolerance test during the first or beginning of the second trimester in addition to the standard screening at 26-28 weeks of gestation, as maternal age is an independent risk factor for gestational diabetes (68).

An increased surveillance for women of the age of 40 or above is widely recommended from 38 weeks of gestation. The King Edward hospital in Australia recommends a twice weekly CTG from gestation week 38 until labor, together with an ultrasound scan at week 38 and 40 (70). To reduce the risk of stillbirth, induction of labor should be offered from week 39 of gestation (1,65). Reviewing postpartum complications of women at advanced maternal age, postpartum hemorrhage was found to affect women above the age of 40 more often than younger women. Therefore, researchers suggest to pay more attention to the postpartum care of women at advanced maternal age (22,50,52).

CONCLUSION

Nowadays more women have the wish to delay childbearing up till their forties due to varies reasons. Thanks to improvements of assisted reproductive technologies, women are able to realize their wish. But with this demographic change, some pregnancy complications and adverse pregnancy outcomes came up more frequently. Henceforth, the relationship of maternal age of 40 or above to pregnancy complications was widely researched across many studies. First of all, becoming pregnant at advanced maternal age gets more difficult as fertility declines (21). Moreover, the success rate of fertility treatments decreases with advanced maternal age (22). Therefore, researchers suggest beginning with evaluations and fertility treatments as soon as the women wish to become pregnant (23). The risk of chromosomal abnormalities like Trisomy 21 starts to increase dramatically from the age of 40 (25). Consistently, the risk of spontaneous abortions during the first two trimester increases

(1,26). Attention should be payed to preexisting comorbidities like diabetes mellitus and hypertension as the prevalence in women above the age of 40 is higher and might lead to pregnancy complications (6,7). A consistent finding among many studies is the increased risk for pregnancy complications in women of advanced maternal age. The risk to develop gestational diabetes increases as maternal age increases (22,24,31). The risk of pregnancy related hypertensive disorders increases, as well, by increasing maternal age (34). As gestational hypertension increases the risk of cerebrovascular events, organ failure, intrauterine growth restriction and premature birth, advanced maternal age increases the risk of perinatal morbidity and mortality for the newborn and the women (22,35). Moreover, maternal age can be seen as individual risk factor for preterm delivery but the reasons are still not clear and further research should be performed (4,33,42).

Reviewing the mode of delivery among women aged 40 or above, rates of cesarean sections were higher if compared to their younger counterparts (15,22). The rate of elective cesarean sections increases consistently with increasing maternal age, while rates of emergency cesarean sections remain similar among all age groups (12,15). The occurrence of labor dystocia increases continuously by increasing maternal age, irrespective of parity (47,48). This finding is consisting with the greater need of pharmacological labor induction in women over the age of 40 (40,49).

Another suggestion that was made by researchers addresses the postpartum care. The risk of postpartum hemorrhage increases in women of advanced maternal age and if more risk factors than maternal age are present, postpartum care should be optimized (51,52).

While gestations received at advanced maternal age are at increased risk for complications, it must be considered that still the vast majority results in an overall favorable outcome for the mother and newborn. Literatures even report of a protective effect of advancing maternal age regarding some pregnancy related complications. One of these pregnancy related complications is postpartum depression. A subsequent leveling off of depressive symptom rates can be noticed among mothers aged 40 and older (19). Maternal age of 40 years and older is furthermore a protective effect concerning nicotine consumption as a lower percentage of women of advanced maternal age smokes during pregnancy if compared to their younger counterparts (11). But if women at the age of 40 or above smoke during pregnancy the risk of stillbirth is three times higher if compared to younger women (28).

Another advantage of delaying childbearing are the improvements over time, like increased life expectancy and decreased mortality rates of children born to a later birth cohort, from which they benefit (8,20). Therefore, parents who have postponed childbearing in the 20th

century, have increased the socioeconomic opportunities and health of their children (20). If compared to women aged less than 40 years, women of advanced maternal age have a higher educational level, are more often employed, and have a higher income (9). Moreover, these women express a “readiness for parenting” that is associated with financial security and stable relationships (61). These studies suggest that advanced maternal age leads to a greater overall happiness due to better socioeconomic resources if compared to women that give birth earlier in life (20). Conversely, women of advanced maternal age have a worse physical health-related quality of life during the first two trimester if compared with their younger counterparts. But it is suggested that the biological disadvantage is to a degree balanced by the social advantage in pregnant women of advanced maternal age (9). Another issue that women of advanced maternal age experience are social stigma and judgement (61).

As pregnancies of women at advanced age are more frequent than in the past and will be increasing further, changes in the pregnancy management have been made. It is important to evaluate and optimize the control of preexisting medical conditions like diabetes mellitus and hypertension (6,7,64). An effective screening for chromosomal abnormalities should be offered and the women should be encouraged to perform the aneuploidy screening test, additionally to the detailed ultrasound (65). The individual patient specific risk of preeclampsia should be evaluated by multi marker models that incorporate maternal age while they combine maternal factors with biomarkers (66). High risk women can then be offered aspirin prophylaxis (67). Some healthcare settings recommend an additional early Glucose Tolerance test (68). A consistent opinion is the need of increased surveillance for women aged 40 or above from 38 weeks of gestation. Further, to reduce the risk of stillbirth, induction of labor should be offered from week 39 of gestation (1,65).

REFERENCES

1. Frick AP. Advanced maternal age and adverse pregnancy outcomes. Best Pract Res Clin Obstet Gynaecol. 2021 Jan 1;70:92–100.
2. Petracchi F, Colaci DS, Igarzabal L, Gadow E. Cytogenetic analysis of first trimester pregnancy loss. Int J Gynecol Obstet. 2009;104(3):243–4.
3. Ludford I, Scheil W, Tucker G, Grivell R. Pregnancy outcomes for nulliparous women of advanced maternal age in South Australia, 1998-2008. Aust N Z J Obstet Gynaecol. 2012 Jun;52(3):235–41.
4. Waldenström U, Cnattingius S, Vixner L, Norman M. Advanced maternal age increases the risk of very preterm birth, irrespective of parity: a population-based register study. BJOG Int J Obstet Gynaecol. 2017;124(8):1235–44.
5. Wie JH, Pak SE, Kim RY, Chung YH, Park IY, Park YG, et al. Gestational age-specific risk of stillbirth during term pregnancy according to maternal age. Arch Gynecol Obstet. 2019 Mar;299(3):681–8.
6. Nabukera S, Wingate MS, Alexander GR, Salihu HM. First-time births among women 30 years and older in the United States: patterns and risk of adverse outcomes. J Reprod Med.

2006 Sep;51(9):676–82.
7. Castorino K, Jovanovič L. Pregnancy and diabetes management: advances and controversies. Clin Chem. 2011 Feb;57(2):221–30.
8. Barclay K, Myrskylä M. Advanced Maternal Age and Offspring Outcomes: Reproductive Aging and Counterbalancing Period Trends. Popul Dev Rev. 2016;42(1):69–94.
9. Gao L-L, Yang J-P, Wang D, Sun K. Health related quality of life in Chinese pregnant women at advanced maternal age: a cross-sectional study. J Reprod Infant Psychol. 2020 Jul 9;0(0):1–12.
10. Matthews TJ, Hamilton BE. First births to older women continue to rise. NCHS Data Brief. 2014 May;(152):1–8.
11. National Vital Statistics Reports Volume 68, Number 13, November 30, 2019, Births: Final Data for 2018. :47.
12. Shan D, Qiu P-Y, Wu Y-X, Chen Q, Li A-L, Ramadoss S, et al. Pregnancy Outcomes in Women of Advanced Maternal Age: a Retrospective Cohort Study from China. Sci Rep. 2018 Aug 16;8:12239.
13. Johnson J-A, Tough S, Wilson RD, Audibert F, Blight C, BrockS J-A, et al. Delayed Child-Bearing. J Obstet Gynaecol Can. 2012 Jan 1;34(1):80–93.
14. Hammarberg K, Clarke VE. Reasons for delaying childbearing--a survey of women aged over 35 years seeking assisted reproductive technology. Aust Fam Physician. 2005 Mar;34(3):187–8, 206.
15. Radoń-Pokracka M, Adrianowicz B, Płonka M, Danił P, Nowak M, Huras H. Evaluation of Pregnancy Outcomes at Advanced Maternal Age. Open Access Maced J Med Sci. 2019 Jun 30;7(12):1951–6.
16. Kalayci H, Ozdemir H, Alkas D, Cok T, Tarim E. Is primiparity a risk factor for advanced maternal age pregnancies? J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2017 Jun;30(11):1283–7.
17. Myrskylä M, Margolis R. Happiness: before and after the kids. Demography. 2014 Oct;51(5):1843–66.
18. Wang W, Xie X, Yuan T, Wang Y, Zhao F, Zhou Z, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. BMC Pregnancy Childbirth. 2021 May 8;21(1):364.
19. Bradshaw H, Riddle J, Salimgaraev R, Zhaunova L, Payne JL. Risk Factors Associated with Postpartum Depressive Symptoms: A Multinational Study. J Affect Disord. 2021 Dec 31;S0165-0327(21)01434-8.
20. Myrskylä M, Barclay K, Goisis A. Advantages of later motherhood. Gynakologe. 2017;50(10):767–72.
21. Roustaei Z, Räisänen S, Gissler M, Heinonen S. Fertility rates and the postponement of first births: a descriptive study with Finnish population data. BMJ Open. 2019 Jan 15;9(1):e026336.
22. Rademaker D, Hukkelhoven CWPM, van Pampus MG. Adverse maternal and perinatal pregnancy outcomes related to very advanced maternal age in primigravida and multigravida in the Netherlands: A population-based cohort. Acta Obstet Gynecol Scand. 2021;100(5):941–8.
23. Seshadri S, Morris G, Serhal P, Saab W. Assisted conception in women of advanced maternal age. Best Pract Res Clin Obstet Gynaecol. 2021 Jan 1;70:10–20.
24. Harton GL, Munné S, Surrey M, Grifo J, Kaplan B, McCulloh DH, et al. Diminished effect of maternal age on implantation after preimplantation genetic diagnosis with array comparative genomic hybridization. Fertil Steril. 2013 Dec;100(6):1695–703.
25. Mikwar M, MacFarlane AJ, Marchetti F. Mechanisms of oocyte aneuploidy associated with advanced maternal age. Mutat Res Mutat Res. 2020 Jul 1;785:108320.
26. Dai R, Li L, Zhu H, Geng D, Deng S, Liu R. Effect of maternal age on spontaneous

abortion during the first trimester in Northeast China. J Matern Fetal Neonatal Med. 2018 Jul 18;31(14):1824–9.
27. Benammar A, Sermondade N, Faure C, Dupont C, Cedrin-Durnerin I, Sifer C, et al. Nutrition et fausses couches spontanées : une revue de la littérature. Gynécologie Obstétrique Fertil. 2012 Mar 1;40(3):162–9.
28. Salihu HM, Shumpert MN, Aliyu MH, Alexander MR, Kirby RS, Alexander GR. Stillbirths and infant deaths associated with maternal smoking among mothers aged > or =40 years: a population study. Am J Perinatol. 2004 Apr;21(3):121–9.
29. Fitzpatrick K, Tuffnell D, Kurinczuk J, Knight M. Pregnancy at very advanced maternal age: a UK population-based cohort study. Bjog. 2017 Jun;124(7):1097–106.
30. Teh WT, Teede HJ, Paul E, Harrison CL, Wallace EM, Allan C. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. Aust N Z J Obstet Gynaecol. 2011 Feb;51(1):26–30.
31. Marozio L, Picardo E, Filippini C, Mainolfi E, Berchialla P, Cavallo F, et al. Maternal age over 40 years and pregnancy outcome: a hospital-based survey. J Matern Fetal Neonatal Med. 2019 May 19;32(10):1602–8.
32. Sheen J-J, Wright JD, Goffman D, Kern-Goldberger AR, Booker W, Siddiq Z, et al. Maternal age and risk for adverse outcomes. Am J Obstet Gynecol. 2018 Oct 1;219(4):390.e1-390.e15.
33. Londero AP, Rossetti E, Pittini C, Cagnacci A, Driul L. Maternal age and the risk of adverse pregnancy outcomes: a retrospective cohort study. BMC Pregnancy Childbirth. 2019 Jul 23;19:261.
34. Liu X, Ruan Y, Liu Y, Zhang W. [Relationship between maternal age and hypertensive disorders in pregnancy]. Zhonghua Yi Xue Za Zhi. 2015 Jan 6;95(1):19–22.
35. Kintiraki E, Papakatsika S, Kotronis G, Goulis DG, Kotsis V. Pregnancy-Induced hypertension. Horm Athens Greece. 2015 Jun;14(2):211–23.
36. Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016 Apr 19;353:i1753.
37. Rosenberg T, Pariente G, Sergienko R, Wiznitzer A, Sheiner E. Critical analysis of risk factors and outcome of placenta previa. Arch Gynecol Obstet. 2011 Jul;284(1):47–51.
38. Martinelli KG, Garcia ÉM, Santos Neto ETD, Gama SGN da. Advanced maternal age and its association with placenta praevia and placental abruption: a meta-analysis. Cad Saude Publica. 2018 Feb 19;34(2):e00206116.
39. Ventolini G. Conditions associated with placental dysfunction. Minerva Ginecol. 2011 Oct;63(5):459–64.
40. Kellermann G. Spätgebärende>= 40 Jahre und deren Schwangerschafts-, Geburts-, und Neonatalrisiken im Vergleich zu 24-jährigen und 34-jährigen Schwangeren. :98.
41. Pelikan S, Hodel M. Mütterliche und kindliche Risiken. :5.
42. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: A large cohort study. PLoS ONE. 2018 Jan 31;13(1):e0191002.
43. Avagliano L, Loghi M, D'Errico A, Simeoni S, Massa V, Bulfamante GP. Risk of stillbirth in older mothers: a specific delivery plan might be considered for prevention. J Matern Fetal Neonatal Med. 2020 Nov 23;0(0):1–5.
44. Schildberger B, Linzner D, Hehenberger L, Leitner H, Pfeifer C. Influence of Maternal Age on Selected Obstetric Parameters. Geburtshilfe Frauenheilkd. 2019 Nov;79(11):1208–15.
45. Nassar AH, Usta IM. Advanced maternal age. Part II: long-term consequences. Am J Perinatol. 2009 Feb;26(2):107–12.
46. Gilbert WM, Nesbitt TS, Danielsen B. Childbearing beyond age 40: pregnancy outcome in 24,032 cases. Obstet Gynecol. 1999 Jan;93(1):9–14.
47. Waldenström U, Ekéus C. Risk of labor dystocia increases with maternal age

irrespective of parity: a population-based register study. Acta Obstet Gynecol Scand. 2017 Sep;96(9):1063–9.
48. Treacy A, Robson M, O'Herlihy C. Dystocia increases with advancing maternal age. Am J Obstet Gynecol. 2006 Sep;195(3):760–3.
49. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. Obstet Gynecol. 2004 Oct;104(4):727–33.
50. Guarga Montori M, Álvarez Martínez A, Luna Álvarez C, Abadía Cuchí N, Mateo Alcalá P, Ruiz-Martínez S. Advanced maternal age and adverse pregnancy outcomes: A cohort study. Taiwan J Obstet Gynecol. 2021 Jan 1;60(1):119–24.
51. Goffman D, Nathan L, Chazotte C. Obstetric hemorrhage: A global review. Semin Perinatol. 2016 Mar;40(2):96–8.
52. Wen T, Overton EE, Sheen J-J, Attenello FJ, Mack WJ, D'Alton ME, et al. Risk for postpartum readmissions and associated complications based on maternal age. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2021 May;34(9):1375–81.
53. Khoshnood B, Bouvier-Colle M-H, Leridon H, Blondel B. [Impact of advanced maternal age on fecundity and women's and children's health]. J Gynecol Obstet Biol Reprod (Paris). 2008 Dec;37(8):733–47.
54. Guintivano J, Manuck T, Meltzer-Brody S. Predictors of Postpartum Depression: A Comprehensive Review of the Last Decade of Evidence. Clin Obstet Gynecol. 2018 Sep;61(3):591–603.
55. Srinivasan R, Pearson RM, Johnson S, Lewis G, Lewis G. Maternal perinatal depressive symptoms and offspring psychotic experiences at 18 years of age: a longitudinal study. Lancet Psychiatry. 2020 May;7(5):431–40.
56. Ghosh A, Goswami S. Evaluation of Post Partum Depression in a Tertiary Hospital. J Obstet Gynaecol India. 2011 Oct;61(5):528–30.
57. Aasheim V, Waldenström U, Hjelmstedt A, Rasmussen S, Pettersson H, Schytt E. Associations between advanced maternal age and psychological distress in primiparous women, from early pregnancy to 18 months postpartum. BJOG Int J Obstet Gynaecol. 2012;119(9):1108–16.
58. Olives J-P, Elias-Billon I, Barnier-Ripet D, Hospital V. Negative influence of maternal smoking during pregnancy on infant outcomes. Arch Pediatr Organe Off Soc Francaise Pediatr. 2020 May;27(4):189–95.
59. Goisis A, Schneider DC, Myrskylä M. Secular changes in the association between advanced maternal age and the risk of low birth weight: A cross-cohort comparison in the UK. Popul Stud. 2018 Nov;72(3):381–97.
60. Goisis A, Schneider DC, Myrskylä M. The reversing association between advanced maternal age and child cognitive ability: evidence from three UK birth cohorts. Int J Epidemiol. 2017 Jun 1;46(3):850–9.
61. Meyer DF. Psychosocial needs of first-time mothers over 40. J Women Aging. 2020 Nov 1;32(6):636–57.
62. García-Blanco A, Monferrer A, Grimaldos J, Hervás D, Balanzá-Martínez V, Diago V, et al. A preliminary study to assess the impact of maternal age on stress-related variables in healthy nulliparous women. Psychoneuroendocrinology. 2017 Apr 1;78:97–104.
63. Nilsen ABV, Waldenström U, Hjelmstedt A, Hjelmsted A, Rasmussen S, Schytt E. Characteristics of women who are pregnant with their first baby at an advanced age. Acta Obstet Gynecol Scand. 2012 Mar;91(3):353–362x.
64. patient-information-leaflet-raised-maternal-age-in-pregnancy-rde-19-089-001.pdf [Internet]. [cited 2022 Mar 8]. Available from: https://www.rdehospital.nhs.uk/media/hrxj1nho/patient-information-leaflet-raised-maternal-age-in-pregnancy-rde-19-089-001.pdf

65. Glick I, Kadish E, Rottenstreich M. Management of Pregnancy in Women of Advanced Maternal Age: Improving Outcomes for Mother and Baby . Int J Womens Health. 2021 Aug 10;13:751–9.
66. Wright D, Tan MY, O'Gorman N, Poon LC, Syngelaki A, Wright A, et al. Predictive performance of the competing risk model in screening for preeclampsia. Am J Obstet Gynecol. 2019 Feb 1;220(2):199.e1-199.e13.
67. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2017 Oct;50(4):492–5.
68. Howell A, Blott M. Very advanced maternal age. Obstet Gynaecol. 2021;23(1):38–47.
69. advancedmatage.pdf [Internet]. [cited 2022 Mar 8]. Available from: https://www.seslhd.health.nsw.gov.au/sites/default/files/documents/advancedmatage.pdf
70. Antenatal care schedule. :20.