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Should Advanced Maternal Age be a Deterrent for Attempting a Pregnancy?

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Abstract

In the developed world, the trend toward women of advanced age bearing children is very prevalent and seems likely to continue. For a variety of reasons, women are delaying pregnancy until 35 years and older when they suddenly seem keenly aware that their biological clocks are ticking. A review of various studies obtained from the Proquest and EBSCO databases indicates that there are definitely certain risks associated with advanced maternal age (AMA). As females age, the reduced number and quality of their remaining eggs contribute to reduced fertility. Congenital anomalies involving the number of chromosomes in the embryo increases as well. The risk of miscarriage gradually climbs with the mother's age and stillbirth is more likely than in younger women. The health of the older women prior to pregnancy is often compromised and birth-related complications are more common. Studies of mice have shown that maternal age influences the structure and functionality of the uterus. It has been suggested that delayed childbearing has an effect on the gene frequency in the general population since the zygotes best able to adapt to the Advanced Maternal Age (AMA) uterine environment were favored (Gloria-Bottini et al., 2005). Although women who postpone parenthood should take the increased risks into account, findings suggest that maternal age, per se, should not be a deterring factor when considering bearing a child. Individual health circumstances and behavioral choices are more important than age. With proper prenatal counselling and care, AMA women can hope to have normal pregnancies and deliver healthy babies.

Introduction

Advanced maternal age is defined as pregnancy in women equal to or greater than thirty-five years of age. It is becoming a growing trend, especially in high-income countries, to delay childbearing. Pregnancy in AMA mothers constitute 20% of pregnancies in the UK and 16% of pregnancies in the US as of 2014. Many women marry later, spend a decade or more building up their careers, pursue higher education, or enjoy the single life before deciding to have a family. Others may find themselves having their first child in their thirties because of previous fertility complications. Although better socio-economic conditions and developments in assisted reproductive technology are allowing women to have babies later in life, this new trend can possibly present clinical risks both to the mother and baby (Lean et al., 2017a).

Prenatal concerns for AMA mothers include fetal loss, chromosome anomalies such as Down's Syndrome, multiple births, hypertension, and gestational diabetes. Complications in labor and delivery might include placenta previa (when the placenta covers the opening in the cervix), caesarean birth, preterm birth, placental abruption (when the placenta detaches from the womb), low birth weight, trisomies, and other non-disjunction problems. Abnormal functioning of the placenta, due to aging, can result in fetal growth restriction and even stillbirths (Radhakrishnan, 2016).

It is important to point out that women who are pregnant and are older than 35 have some distinct advantages. They are more likely to follow the regimen outlined for them by their obstetrician, such as taking a folic acid supplement before conception and throughout their first trimester which helps decrease the risk of neural tube defects. These mothers are more likely to be diligent about keeping prenatal appointments. They are usually more established in their personal and professional lives and are more mature and knowledgeable, with a higher degree of personal control and coping strategies. Their higher income tends to contribute to more positive results in terms of their health. Lastly, AMA mothers tend to breastfeed more than younger mothers. Breastfeeding is considered the most optimal way to feed the infant. Its benefits include protecting the baby with passive immunity to infections of the respiratory and gastrointestinal tracts. Breastfeeding has maternal benefits as well; it reduces postpartum bleeding, returns the mother to pre-pregnancy weight faster, and decreases the risk of breast and ovarian cancers (Radhakrishnan, 2016).

Notwithstanding all of the above advantages, the ideal time for a woman to give birth remains up until the age of 35, during which time fertility is at its peak. Women who are older have a harder time conceiving. They usually also have longer work hours and stressful work environments and tend to drink more alcohol, putting the fetus at risk of Fetal Alcohol Spectrum Disorder, which can cause birth defects and neuro-developmental disorders. They have also been exposed to environmental toxins for a longer time. Most importantly though, their increased age makes medical conditions such as cancer, diabetes, hypertension, and arthritis more likely. These conditions, as well as their associated treatments and medications, can harm the fetus (Radhakrishnan, 2016).

Many studies have been done in various developed countries, investigating the impact AMA has on perinatal and neonatal outcomes in these women. These studies are important for both the mothers and the healthcare providers. The effects of AMA on maternal and fetal morbidity and mortality is of great concern.

Methods

The research was obtained from the online Touro College Library. Articles were collected from the Proquest and

EBSCO databases. The studies presented a comprehensive analysis of the topic and allowed for a conclusion to be reached regarding the research question.

Discussion

A systematic review and meta-analysis were done to determine the risk of stillbirth and other negative pregnancy outcomes in AMA women. It was the largest and most comprehensive review investigating pregnancy outcomes of AMA mothers and the only one specifically focusing on the increased risk of stillbirth. The studies in the review were significant considering that in 2013 the rate of births in England and Wales to women of 35 years and above was 20% as compared to a rate of 6% in 1980 (Lean et al., 2017a).

In the review, 63 cohort studies and 12 case control studies were included. The studies incorporated control groups of mothers younger than 35 years of age and AMA groups greater than or equal to 35 years. Primary outcomes studied were stillbirth and fetal growth restriction. Secondary outcomes were neonatal death, small for gestational age, neonatal intensive care unit (NICU) admissions, preeclampsia (blood pressure > 140/90 with significant amount of protein in the urine), placental abruption, preterm birth, and gestational diabetes mellitus. Studies that involved pregnancies of multiple fetuses or those that focused on chromosomal abnormalities or substance abuse were eliminated. Correlations between stillbirth rates and maternal obesity, diabetes, hypertension, and assisted reproductive therapies were recorded (Lean et al., 2017a).

AMA was found to increase the rate of stillbirth in the population to 4.7%. In addition, AMA increased the risk of fetal growth restriction, neonatal death, NICU admission and gestational diabetes mellitus. The relationship between AMA and stillbirth was not found to be associated with maternal morbidities, with the exception of hypertension which was positively correlated with AMA in women between the ages of 35 and 40. The use of assisted reproductive therapy (ART) showed no relationship to stillbirths in women equal to or under 35 years of age and was negatively correlated to stillbirth rates in women over 40. AMA only significantly increased the risk of fetal growth restriction in women over 40. The majority of secondary outcomes were more prevalent in AMA women but only NICU admissions and neonatal deaths had a substantial correlation to the increasing age of the mother (Lean et al., 2017a).

Stillbirths in advanced countries are presently thought to be related to placental dysfunctions. Accelerated aging of the placenta, altered vascular function and altered transport of nutrients compared to a control group have all been detected. Another theory for the cause of stillbirths is the diminished genetic quality of the aging oocyte (Lean et al., 2017a).

Another consideration that may contribute to fetal health with an AMA pregnancy is advanced paternal age. Research in this area is sparse. One study found a 24% increase in stillbirth rate with paternal age between 40-45 years old and a 50% increase with paternal age over 45, independent of maternal age. More studies are needed where paternal age is a co-variate to determine how it contributes to increased risk of stillbirth in AMA mothers (Lean et al., 2017a).

Future studies should be done to understand the mechanisms contributing to the increased risk of stillbirth in AMA, specifically in mothers over the age of 40, so that proper intervention can be applied to improve positive outcomes to those at greatest risk (Lean et al., 2017a).

The increased risks of fetal growth restriction and stillbirths in AMA mothers have been found to be independent of co-morbidities. These risks also do not seem to correlate with factors such as socio-economic status, nutritional supplementation prior to conception, good prenatal care, and the mothers being non-smokers. A hypothesis was offered that maternal aging was associated with utero-placental dysfunction which contributed to negative fetal outcomes (Lean et al., 2017b).

Dysfunction of the placenta is a major cause of fetal growth restriction and placental causes are noted in up to 65% of stillbirths. In both conditions, major changes in placental morphology were found, including lower placental weight, irregular shape to the placenta, and irregular insertion of the umbilical cord. Placentas from fetal growth restriction pregnancies had less vascular branching and fewer capillaries. These structural abnormalities were found even more in stillbirths related to fetal growth restriction (Lean et al., 2017b).

Abnormal function of the placenta was also apparent in fetal growth restriction and stillbirths. Among these were reduced amino acid transport in the placenta and impaired endocrine function (Lean et al., 2017b).

A study was done to test the hypothesis that AMA is associated with dysfunctions of the uterus and placenta. Women of AMA were studied along with young controls (20-30 years) with normal pregnancies. Investigations into these pregnancies identified multiple placental and utero-placental dysfunctions, potentially linking those mechanisms and increased fetal growth restriction and stillbirths in AMA women (Lean et al., 2017b).

The studies revealed increased placental weight but reduced placental efficiency in pregnancies of AMA women

with changes in placental morphology and function similar to the phenotype of placentas in fetal growth restriction and stillborn pregnancies. This phenotype was seen even in normal pregnancy outcomes which indicate both the negative effects of aging on the placenta and potential adaptation to achieve a normal birthweight. The abnormal placental phenotype was more evident in women >40 years of age who have a higher risk of adverse pregnancy outcomes (Lean et al., 2017b).

AMA mice displayed an even more exaggerated abnormality in placental phenotype than humans, with reduced number of offspring, late fetal deaths, and over half of offspring in the category of fetal growth restriction. Many similarities were found in the placental phenotype in the mice and human pregnancy models, including increased placental weight, decreased placental efficiency, and altered vascular function (Lean et al., 2017b).

All of these support the hypothesis that maternal aging is associated with placental dysfunction, which may result in higher rates of fetal growth restriction and stillbirths in AMA pregnancies. Abnormal cell turnover, abnormal nutrient transport, and increased relaxation of placental arteries all helped contribute to the less than ideal functioning of the placenta in AMA mothers (Lean et al., 2017b).

Another study was done to determine whether advanced maternal age in mice has a bearing on their pregnancy outcomes. The purpose of this study was to evaluate whether negative reproductive outcomes in aged female mice are a result of a dysregulation of methylation, and thus expression, of imprinted genes in their reproductive tissues. Tissues from the fetus, placenta, and ovaries were collected from young pregnant mice (4-5 weeks old) and aged mice (15 months old) and compared to matured oocyte and uterine tissue from non-pregnant ones (Paczkowski et al., 2015).

Results showed fetal growth restriction and overgrowth of the placenta in the older pregnant mice. Placental tissue showed aberration in methylation and transcript abundance of imprinted genes. Methylation and gene expression were severely dysregulated in the ovaries and in the uterus, including nutrient transport genes. There was also increased transcript abundance in oocytes obtained from older females, compared to younger ones (Paczkowski et al., 2015).

Major alterations in methylation and gene expression in the older ovary suggests that the environment in the follicle may not be optimal. This affects oocyte growth and quality, leading to compromised embryonic and fetal development. Aberrant methylation and expression of imprinted genes in the uterus obtained from aged mice may cause reduced implantation. Even though AMA mothers have an equal chance of becoming pregnant after ART cycles when using donor eggs, this study shows that the environment in the uterus may be compromised. If using their own eggs, the environment of the follicles may be compromised, indirectly effecting the development of the oocyte (Paczkowski et al., 2015).

Overall, AMA in mice changes methylation patterns of imprinted genes in reproductive tissue, which results in dysregulated gene expression associated with poor reproductive outcomes. This study is significant in that it suggests a possibility that the same factors in aged human females might cause negative outcomes in their pregnancies as well (Paczkowski et al., 2015).

A study was done where associations of maternal age at childbearing with gestational age (number of weeks fetus was in the womb) and fetal growth (birthweight adjusted for gestational age) were examined. Those features are important to study because these problems predict mortality and morbidity across the lifespan of the human, including psychological, health, academic, social, and economic difficulties. Preterm birth is associated with decreased cognitive functioning in childhood and the use of psychiatric medications in adults. Poor fetal growth has been found to be linked to psychiatric diagnoses in childhood (autism and ADHD) and adult health problems (cardiovascular disease and diabetes). Given these major health concerns, it is imperative to obtain a better understanding of the possible causes of these adverse perinatal outcomes (Sujan et al., 2016).

The study was designed in such a way as to rule out genetic and environmental factors that might contribute to the results. To assess potential familial confounding, two genetically informed designs were used comparing cousins and siblings. To be able to generalize results, data was taken from two samples with different cultures, races, ethnicities, economic backgrounds, and healthcare coverage. Some covariates were offspring birth order, and parental characteristics such as levels of education, history of severe psychiatric problems, history of substance abuse, household income, maternal race, and maternal age at first childbirth (Sujan et al., 2016).

There was strong evidence that AMA at childbirth was associated with a shorter gestational age. The gestational age of offspring born to 30-34 year old mothers, 35-39 year old mothers, and mothers of 40 years and above, were all less than the gestational age of offspring born to 25-29 year old mothers. Even after accounting for shared familial factors, the data pointed to a strong link between mothers who are older at childbirth with shorter gestational age. This did not hold true for lower fetal growth.

Results from the study supported a causal association between AMA at childbearing and shorter gestational age (Sujan et al., 2016).

Further research is needed to explore specific factors that might account for the findings. Some possibilities might be maternal diseases, such as hypertension, diabetes, and the quantity of oxygen and nutrients received during the prenatal period (Sujan et al., 2016).

Another study tested the hypothesis that reduced fetal weight and lower success of pregnancy outcomes in AMA rats may be attributed to sex-specific changes in the morphological development of the placenta and in its nutrient transport function. It was found that the sex of the fetus did indeed influence the placenta and offspring outcome in response to the adverse environment in the uterus during gestation (Napso et al., 2019).

Young (3-4 months old) and aged (9.5-10 months old) Sprague Dawley female rats were mated with young male Sprague Dawley rats (3-5 months old) and were evaluated on gestational day 20. The study demonstrated that advanced maternal age caused modifications in the phenotype of the placenta and in this way, altered its ability to support the growth of a fetus. In particular, it modified the expression of genes and proteins that are crucially important in placental growth, transfer of nutrients, endocrine control of maternal physiology, and control of exposure of the fetus to glucocorticoids. AMA causes oxidative stress and cell death in the placenta, in a manner that is partially dependent on the sex of the fetus. The study also indicated that gene expression changes in the placenta of female fetuses were mostly beneficial, with an up-regulation of genes that support the function of the placenta. Gene expression changes in the placenta of male fetuses, though, were mostly detrimental for placental growth and functional phenotype in older rats. There was similar growth restriction in both male and female fetuses, although the absolute weight of male fetal heart, brain, and liver were more reduced in fetuses of aged rats than younger ones (Napso et al., 2019). There were previous studies that demonstrated poorer cardiovascular outcomes for adult male rats born from aged mothers (Shah et al., 2018 as cited in Napso et al., 2019).

The sex-dependent changes in glucocorticoid handling in the placenta of AMA mothers affects health outcomes of offspring later in life. Elevated prenatal exposure to glucocorticoids affects development of the fetus and permanently alters the structure and functions of its organs, predisposing the offspring to certain diseases later in life such as hypertension (Napso et al., 2019). Even though the fetal weight for male and female fetuses of aged rats was compromised similarly, studies showed that adult male offspring of aged rats have a greater chance of developing cardiovascular dysfunction as adults, as compared to female offspring (Shah et al., 2018 as cited in Napso et al., 2019).

In summary, AMA affects the phenotype of the rat placenta in a sex-dependent manner. In female fetuses from aged rats, there were larger beneficial changes in structure and/or expression of genes related to placental transport of nutrients from mother to fetus and improved handling of glucocorticoids. In male fetuses of aged rats, there were no beneficial changes in the transport system and there was less protection from glucocorticoids, greater oxidative stress, and elevated levels of apoptosis. These sex-dependent changes in placental response to the environment in the uterus of the aged mother play a role in the future health of female and male offspring. The results of this study have implications for managing human pregnancies, especially in developed countries where women are becoming pregnant at an older age. Targeted interventions can be developed to improve placental development and function which, in turn, will aid fetal growth and development for mothers of AMA (Napso et al., 2019).

Although women of AMA are a growing population in all developed countries with greater obstetric risks, women who live in the Mediterranean have specific characteristics that are different than other areas. A study was done to establish an AMA cut-off age in a selected Mediterranean population in Barcelona. Although most studies define AMA as being above 35 years, this study defined AMA in Spain as being above 40 years. The average age of women delivering their first baby rose from 25.2 years in 1975 to 30.7 years in 2016. Models predict that by 2050, the average age of a first pregnancy will be 33 years. In 2016, 38.7% of deliveries in Spain were to mothers over 35 years, and 8.39% were to mothers over 40 years. The average age of women at childbirth in 2017 was 32.5. The scientific community is interested in gaining information about the impact of AMA on obstetrical outcomes so that they can better assess risks in this increasing population (Nieto et al., 2019).

The cohort in this study were women who gave birth between January 2007 to June 2017. A total of 25,054 pregnancies were included. The average maternal age was 34.7 +/- 4.2 years. In this study, 2,807 patients were between 40-44 years and 280 patients were >45 years. Of the total pregnancies, women above the age of 40 accounted for 12.3% of the deliveries. Confounding factors were considered, which included chronic hypertension, pregestational diabetes types I/II, use of ART, obesity, smoking, previous C-sections, and multiparity (having more than one child). Over 97% of the women were Caucasian and

99.8% were from the Mediterranean area. After adjusting for confounding factors, age proved to be a significant risk factor in developing gestational diabetes, especially in women >40. The risk of placenta previa increased as well in women >40 years. Preeclampsia and prolonged hospitalization were only associated with women >45 years. The risk of these negative outcomes increased as the age of the women increased (Nieto et al., 2019).

It was suggested that the reason for the increased risk of gestational diabetes in women >40 might be endothelial damage. Age is known to be a cardiovascular risk factor that produces structural and functional changes in the vascular system. Dysfunctional endothelium increases the risk of developing insulin resistance, which then increases the risk of hypertension, type II diabetes, and other metabolic syndromes (Nieto et al., 2019).

In summary, in this study, women >40 were the most positively associated with complications of gestational diabetes, placental previa, caesarian delivery, and prolonged hospitalization. They were the ones with the highest clinical risks. These patients were also at greatest risk for iatrogenia (effects from medical interventions) since they have high elective C-section rates. Future investigations should therefore address medical interventions and pregnancy surveillance to improve outcomes in AMA patients (Nieto et al., 2019).

Another cross-sectional study tested the hypothesis that there is an association between AMA and maternal and neonatal morbidity. The study was based on data obtained from 3,315 births. It compared the births of women who were 35 years and older, with a reference group of women between the ages 24-27 (Casteleiro et al., 2019).

Results of the study confirmed the hypothesis. Repeated spontaneous abortions were 2.2 times more frequent in the older age group compared to the younger reference group. There was a greater incidence of gestational diabetes in AMA women, particularly in primiparous women where the risk was eight times more prevalent. The possibility of giving birth with the help of instruments was multiplied by 1.6 and the possibility of a cesarean delivery was multiplied by 1.5 in both primiparous and multiparous AMA women. Lastly, there were correlations between preeclampsia, preterm birth (<37 weeks) and low birthweight in the older age group, although the numbers were not high enough to have statistical significance (Casteleiro et al., 2019).

The cause of repeated abortions in AMA women may be attributed to alterations in the chromosomes, which increase along with increasing maternal age. The cause of gestational diabetes is being continually researched. One theory is that diabetogenic hormones, such as the growth hormone that releases corticotropin, produce an increased insulin resistance which AMA women are not able to overcome (Casteleiro et al., 2019).

A study was done to ascertain the effect of advanced maternal age on singleton pregnancies in nulliparous women. Records of obstetric patients were reviewed from routine fetal ultrasonograms that were taken in the middle trimester of pregnancy. Three groups were included in this study: a control group of ages 18-34 years old, advanced maternal age women of 35-39 years, and very advanced maternal age women over 40 years of age. Altogether, 957 women met the criteria to be included in the study (Kahveci et al., 2018).

The study clearly demonstrated that AMA nulliparous women with no previous chronic diseases (including obesity) had higher rates of adverse perinatal and neonatal outcomes such as gestational diabetes, gestational hypertension, preeclampsia, small for gestational age, spontaneous late preterm delivery (between 34-37 weeks of gestation) and cesarean delivery. Gestational diabetes, gestational hypertension and cesarean delivery rates were more common in the VAMA group compared to the AMA and young age group. No increased risk was found for spontaneous preterm delivery before 34 weeks, prolonged rupture of membranes, placenta previa, large for gestational age, and operative vaginal delivery (Kahveci et al., 2018).

It has been suggested that poor oxygen exchange may be a factor in the association between AMA and small for gestational age. This stands to reason because when an unborn baby doesn't get enough oxygen during pregnancy, its organs don't grow as much as they should (Kahveci et al., 2018).

Concerning neonatal outcomes, admission to a NICU was more likely to occur in the AMA groups, but there was no major difference in APGAR scores, occurrences of low birth weight, and neonatal morbidity between the groups (Kahveci et al., 2018).

During the last few decades, there has been a significant increase in the amount of pregnancies involving multiple fetuses due to the use of ART. Even in singleton pregnancies, AMA poses a risk for more maternal and neonatal complications. Multiple gestation drives this risk up even more (Gluck et al., 2018).

A study was done with the goal of comparing obstetrical and neonatal outcomes between women older than 35 years and women younger than 35 with the same type of twin pregnancy. Records were reviewed of all dichorionic-diamniotic pregnancies (in which each fetus has its own placenta and amniotic sac) between 2009-2016 where the babies were delivered after 24 weeks gestation. Pregnancies with abnormalities in the chromosomes

and those with fetal malformations were excluded. The older women were divided into two groups: age 35-39, and those >40. The control group consisted of women younger than 35. Altogether, 716 women were studied. The rate of in-vitro fertilization for conception was higher in the study groups (older women) than in the control group (Gluck et al., 2018).

AMA was found to be independently associated with cesarean section after adjustments were made for nulliparity, in-vitro fertilization, and hypertensive disorders. The rate of hypertensive disorders was significantly higher in women over the age of 35 (Gluck et al., 2018).

Twins born to women over 35 also tended to stay longer in the NICU than those born to the younger women. Other neonatal outcomes in women age 35 or older who were carrying twins were similar to the younger group (Gluck et al., 2018).

A retrospective cohort study was done to evaluate whether AMA was independently associated with an increased risk of childhood cancer in the offspring. There were three maternal age groups studied: 35-39, 40-50, and a control group of 20-34. A comparison was made between the three age groups for incidences of malignant morbidity in the offspring. Pregnancies lacking prenatal care, gestations of multiple fetuses, pregnancies originating with fertility treatments, and pregnancies with fetuses displaying congenital malformations were not included in this study. The offspring were followed up to the age of 18 years. The three most common malignant forms of childhood cancer which were traced included leukemia, brain tumors, and lymphomas (Imterat et al., 2018).

Theoretically, advanced maternal age might correlate with childhood cancers due to DNA damage and decreased repair pathways in oocytes of older mothers. Several previous studies (Ross et al., 2005 as cited in Imterat et al., 2018) showed a connection between AMA and meiosis errors leading to trisomies (particularly trisomy 21 or Down's Syndrome) which are known to predispose for malignancies in childhood. Additionally, ART, which is increasingly used to offset infertility disorders in older women, is suggested as increasing the risk of childhood cancers such as retinoblastoma, by altering gene expression. Finally, changes in maternal hormones during pregnancy that are age-related, such as higher intrauterine exposure to endogenous estrogen and insulin growth factor-1, have been shown to help initiate cancers. Considering all the above hypothetical effects of AMA on childhood cancers, this study was important to conduct (Imterat et al., 2018).

In the study, 201,738 deliveries were included. Results showed that advanced maternal age did not increase the risk of future malignancies in the offspring up to 18 years old. There was some association, though, between maternal age and leukemia of the offspring which warrants further investigation (Imterat et al., 2018). However, overall, childhood cancer of offspring does not seem to be a major concern for AMA women planning to conceive.

A study was done to investigate what effect AMA has separately in nulliparous and multiparous women on obstetric and neonatal outcomes in singleton pregnancies. The study was a hospital-based analysis of 6,619 births between January 2004 and May 2007. AMA was defined as 35 years and older. Nulliparity was defined as women who had not delivered a viable fetus (greater than 24 weeks of gestation in the past) and multiparity was defined as women who had at least one pregnancy in the past that progressed beyond 24 weeks of gestation. The actual parity number wasn't considered. Of the study participants, 42.7% were nulliparous and 57.3% were multiparous. Of the nulliparous, 21.8% were of advanced maternal age and of the multiparous, 42.1% were of advanced maternal age (Wang et al., 2011).

Among nulliparous women, AMA was associated with higher rates of cesarean sections both before and during labor, as well as vaginal deliveries assisted by instruments. Among multiparous women, however, AMA was only associated with a higher rate of cesarean sections before labor. This might be due to a greater percentage of multiparous women requesting cesareans (Wang et al., 2011).

A study was done in order to assess how pre-pregnancy weight (or body mass index) and gestational weight gain affect pregnancy outcomes in AMA women. This retrospective analysis was conducted on postpartum and hospital delivery data in China. A total of 1,015 women were included in the study who gave birth from January-June 2017. In China, 60% of all pregnancies are in women greater than 35 years of age and half of these women are above 40 years of age. AMA women are often overweight before pregnancy and are more likely to have internal diseases. They are also more likely to be multiparas having had at least one previous child. Age is also an independent risk factor for adverse pregnancy outcomes (Lin et al., 2019).

The women were divided into an advanced age group (35-40 years) and a super advanced age group (>40 years). Body mass indices prior to pregnancy were divided into underweight, normal weight, overweight and obese groups. Gestational weight gain was subdivided into three groups (Lin et al., 2019).

Results showed that being overweight prior to pregnancy increases gestational diabetes mellitus, hypertensive disorders complicating pregnancy, and fetal macrosomia where a newborn is significantly larger than average.

Poor weight gain during pregnancy increased the risk of preterm births, but excessive weight gain during pregnancy increased macrosomia in the babies of AMA women (Lin et al., 2019).

The women in the super advanced maternal age group had higher incidences of both being overweight and obese than those in the AMA group. The super advanced maternal age group had more incidences as well of gestational diabetes mellitus, hypertensive disorders, and macrosomia than in the advanced age group (Lin et al., 2019).

Overall, controlling weight gain both prior to and during pregnancy reduced adverse pregnancy outcomes in AMA women (Lin et al., 2019). It is good advice for older women who are planning to conceive to get their weight under control beforehand.

A study was conducted with the objective of determining whether there was an association between AMA and race on pathology of the placenta in very low birthweight infants. A retrospective cohort analysis was done on placental pathology on very low birthweight singleton infants born between July 2002 and June 2009. There were 739 cases included in this study (de Jongh et al., 2015).

The placenta is the area where maternal-fetal oxygen and nutrients get exchanged and so it has an important influence on birthweight and is necessary for a successful outcome to a pregnancy. Placental growth, which can be measured in terms of placental weight, is a good indicator of how well the placenta is functioning. The placenta weight/birthweight ratio is used to indicate neonatal outcomes (de Jongh et al., 2015). Both high and low ratios have been associated with an increased risk for stillborn and other negative neonatal outcomes (McNamara et al., 1998 as cited in de Jongh et al., 2015).

The subjects of the study were divided into two groups: maternal age <35 and maternal age >35. Mean placental weights, mean birthweights, and placental weight/birthweight ratios were calculated for each age group (de Jongh et al., 2015).

In the final analysis, AMA was seen to be associated with a decrease in placental weight and placental weight/birthweight ratio. AMA, and not race or ethnicity, remained independently associated with placental weight/birthweight ratio. It could not be determined, however, if older maternal age directly causes reduced placental weight/birthweight or whether it represents confounding variables not tested for. Further research is necessary to discover possible causal mechanisms that can explain the relationship between AMA and lower placental weights in very low birthweight babies (de Jongh et al., 2015).

In Denmark, the rate of cesarean sections increased by 49% between the years 1998-2015 and occurred in 21% of all births. This is a cause for concern since cesarean sections can have short and long term consequences for the mother and child and can present risks in future pregnancy. A possible cause of the increase may be the delaying of pregnancy until advanced maternal age. AMA at childbirth has been found to be linked to pre-pregnancy morbidity that might account for the increased risk of cesarean section. The goal of this study that included one million Danish women was to examine the relationship between AMA and cesarean section, taking demographics, health and obstetric factors into the equation. There were three age groups (30-34, 35-39, >40 years) with a reference group of maternal age less than 30 (Rydahl et al., 2019).

A positive association was found between AMA and cesarean section. When adjusting for confounders, there were only minor changes in the risk factor. When compared to the reference group, nulliparous women aged 35-39 had twice the risk of cesarean section, while women of 40 and above had three times the risk. For multiparous women, the risk was more moderate (Rydahl et al., 2019).

Cesarean sections are one of the most intrusive obstetric interventions and is becoming much more common in industrialized countries. The increase in cesarean sections is mainly a result of AMA, especially in nulliparous women. Morbidity tends to increase as age increases, so AMA women will include more individuals with prenatal risk factors such as hypertension, diabetes mellitus, and higher body mass index than younger pregnant women. More women of advanced age will also develop pregnancy related complications, including gestational diabetes, preeclampsia and placenta previa. There is also evidence that there is a decline in the physical ability to maintain uterine contractions which can cause labor dystocia. Future studies on the possibility of advanced age affecting the ability to maintain progression of labor is recommended. Placenta previa in AMA women, as well as non-vertex fetal presentations might also necessitate a cesarean delivery (Rydahl et al., 2019).

The higher cesarean section rate may be a result of these comorbidities related to AMA. It is possible, though, that the lower threshold for cesareans may be influenced by the attitudes of the healthcare professionals treating AMA women who may view them as high-risk patients or by the mothers themselves who choose a cesarean birth because they are more anxious about the health of the fetus (Rydahl et al., 2019).

A study was done regarding the association between maternal age and offspring adult health. There is increasing documentation associating AMA with negative health outcomes in their offspring. This association is considered to be a reflection of aging physiological processes of the

mother, such as the decreasing quality of her placenta or eggs (Myrskyla & Fenelon, 2012).

In this study, the role of socioeconomic selection and lifespan overlap between the generations is examined, as they are related to the association between maternal age and offspring adult health. It was found that offspring born to mothers younger than 25 or older than 35 have the worst outcomes regarding health, height, obesity, and even mortality. The reason for the young maternal age-offspring health link may be due to the physiological immaturity and socioeconomic disadvantage of young parenthood. Regarding the older age group, the results of the study showed that negative outcomes are not due to the mother leaving a physiological imprint in the offspring that causes a predisposition to diseases in adulthood. Rather, maternal education (which is strongly connected to socioeconomic status) and the age at which the child loses the parent are two important factors that affect the correlation between AMA and offspring adult health (Myrskyla & Fenelon, 2012).

Mothers of advanced age have generally had the opportunity to obtain a higher level of education which translates into greater affluence. Childhood socioeconomic status has been found to be strongly connected to adult health and mortality (Myrskyla & Fenelon, 2012).

The age at which a child loses a parent is directly related to maternal age. If all other factors are held constant, a child born to a younger mother will have many more years of lifespan overlap with the mother than a child born to an older mother. The psychological shock of losing a parent at a younger age is one factor that may affect the adult child's health. Another factor might be the loss of parental involvement with the offspring. Thirdly, a shorter lifespan overlap might indicate a genetic frailty that runs in the family (Myrskyla & Fenelon, 2012).

Maternal age, therefore, is related to the mother's education, socioeconomic status, and lifespan overlap with the offspring, all of which were found to be confounders in the maternal age-offspring health association. These factors all help explain the mechanism behind the association of AMA and negative health outcomes in the offspring and challenge the standard interpretation for that association. The reason this study is important is because today's parents, even if they reproduce at an older age, will likely live longer due to medical advances and therefore have a longer lifespan overlap with their offspring. If biological aging is indeed not the factor to influence the adult health of offspring but rather lifespan overlap is, AMA women can be reassured going forward that their late childbearing will not adversely affect their offspring (Myrskyla & Fenelon, 2012).

In the latter half of the last century, the delay of childbearing in Western cultures has affected the biology of the mother-fetus relationship. Data obtained from experiments, as well as clinical observations, have ascertained this change. As an example, there has been an increase in type 1 diabetes in developed countries during this time. This trend parallels the tendency to give birth at a later age which might suggest a causal relationship between the two events. Delayed childbearing might therefore have a detrimental effect not only on the development of the fetus in the uterus but may possibly be causing a predisposition to certain severe disorders. The change to the reproductive organs due to age, along with changes in hormone activity, may be the causes of this negative relationship (Gloria-Bottini et al., 2005).

A study done in Italy might also suggest that delayed childbearing is causing a change in the genetic composition of the population. Gene frequency refers to the proportion of a population that carries one type of allele, or gene variation, at a particular point on a chromosome. Certain phenotypes either increase or decrease with maternal age. These changes in the genetic composition of AMA women were found to be similar in the mothers and newborns studied (Gloria-Bottini et al., 2005).

The hypothesis of the study, which included over 600 women giving birth, was that advanced maternal age may influence intrauterine selection by favoring genotypes that are best able to adapt to the intrauterine environment of the older mothers. Zygotes that are more resistant to the changes in the maternal environment of older women will be the ones to survive. Maternal and neonatal genotypes were found to be similar in the AMA women studied. Maternal age was, therefore, having an effect on the gene frequency in the offspring (Gloria-Bottini et al., 2005).

Very Advanced Maternal Age (VAMA)

In Australia, as in most other high-income countries, childbearing age has been rising to 35 years and above. A new trend is emerging of pregnancies in women even 45 years and older which comprise 0.1% of all births in the country and is continually rising. This is driven partly by assisted reproductive technologies such as oocyte donation. There were few studies examining perinatal outcomes in this age group. A state-wide population-based study was done in Victoria, Australia covering the years 2005-2006 to determine maternal health and the outcomes of pregnancies of women in this age group compared to women aged 30-34 years (Carolan et al., 2013).

The study revealed prenatal complications of at least one of the following: gestational diabetes, antepartum hemorrhage (bleeding from or in the genital tract),

placenta previa, and multiple births. There was weak evidence for increased risk for preeclampsia. Women >45 were also more likely to have caesarian sections. They were not found to be more likely of having a postpartum hemorrhage (Carolan et al., 2013).

Pre-existing medical conditions of the mothers, as well as parity and use of ART, were taken into account. Women aged 45 and older were most likely to have pre-existing hypertension, but there was weak evidence of pre-existing diabetes. Women in the group were 12 times more likely to have used ART (Carolan et al., 2013).

Babies born to these VAMA (very advanced maternal age) mothers were at a higher risk for preterm birth (between 32-36 weeks gestation) regardless of parity, low birth weight (less than 2,500 grams) for primiparous women and had higher odds of being small for gestational age. Rates of preterm birth were very high for multiple births and for those who used ART (Carolan et al., 2013).

The findings in this study have ramifications for the women as well as for their healthcare providers. Although results displayed higher rates of pregnancy and perinatal negative outcomes for the women aged 45 and older in Victoria, Australia, nevertheless, the findings were reassuring as the vast majority of these women of very advanced age gave birth to healthy babies. The rate of perinatal death was low (less than 10 per 1,000 births). This suggests that with good prenatal care, most women in this group can achieve a live birth. Future studies should include investigations into the future health of these children who were preterm birth or were of low birth weight or small for gestational age (Carolan et al., 2013).

A study was done to investigate the interplay between very advanced maternal age (>43 years) and assisted reproductive technology on adverse perinatal outcomes. Data was taken from a cohort of women who delivered babies in Ontario, Canada between 2012-2015. In Canada, the number of births in women over 40 years of age tripled from 2005-2014. Even though fertility declines as a women ages, ART has allowed many more women of VAMA the chance to become pregnant. ART, though, has been considered a risk factor for adverse pregnancy outcomes as compared to spontaneous conceptions. This particular study aimed to assess the pregnancy outcomes of women who were both of very advanced age and who used ART to conceive. Singleton pregnancies of women >20 years who delivered at 20 weeks of gestation and above and whose offspring's birthweight exceeded 500 grams were included. The women were put into three categories of age: 20-34 years, 35-42 years, and >43 years of age. VAMA was defined as >43. All the subjects used were noted as either having used ART or having spontaneously conceived (Wu et al., 2019).

The mothers age was the independent variable. The type of conception (ART or spontaneous conception) was the main covariate. ART conceptions included intrauterine insemination, intrauterine insemination with ovulation induction but without in-vitro fertilization, in-vitro fertilization, and vaginal insemination. Many potential confounders for adverse maternal and neonatal outcomes were included, such as parity, income, education, body-mass index, drug/alcohol use, and maternal preexisting health issues (Wu et al., 2019).

Women at VAMA had a higher risk of a composite outcome which included preeclampsia, intrauterine growth retardation, stillbirth, and placental abruption than the mothers in a younger age bracket. The fact that ART was used did not add to the adverse effect of VAMA, even though ART may play an independent role for adverse perinatal outcomes. These outcomes were found in 10.41% of women under 35 and in 13.35% in women of VAMA. Regardless of the conception method, women of VAMA had a higher incidence of adverse outcomes (Wu et al., 2019).

Another study was done to evaluate if the adverse pregnancy outcomes in women of very advanced age differed by parity and by conception method. According to a national perinatal database in Japan, women of VAMA giving birth rose to 28.1% of all births. A total of 365,417 women over the age of 30 were included. The women were divided into four age groups: 30-34, 35-39,40-44, and >45. Pregnancies involving multiples, as well as fetuses with congenital abnormalities, were excluded (Ogawa et al., 2017).

Compared with the 30-34 year reference group, women aged 45 or older showed a higher risk for cesarean sections, preeclampsia, placenta previa and preterm birth. Placental abruption, very preterm birth, low APGAR score and perinatal death were not seen as being of increased risk in VAMA. The effects of older age on the negative outcomes were significantly higher among those women who conceived naturally, compared to those who used ART to conceive. However, the possibility that abnormal embryos were removed during ART could have skewed the results. The effect of advanced age on cesarean deliveries was stronger among primiparous women, but the risk for preeclampsia was significantly stronger among multiparous women (Ogawa et al., 2017).

The effects of advanced age on preterm birth were significantly greater among women who conceived without ART than among those who used ART to conceive. To clarify, while the risk of preterm birth generally increased with age in women who conceived without ART, it decreased in women who conceived with ART. Therefore,

younger women who conceived through ART, may have a greater risk of preterm birth than women who are older and conceive through ART (Ogawa et al., 2017).

The greater risk of cesareans in primiparous women of advanced age may be due to higher rates of elective cesarean sections requested by primiparous older women. It might also be due to prolonged labor or compromised fetal status requiring emergency cesarean section with increasing age, but these hypotheses were not tested (Ogawa et al., 2017).

While the greater risk of preeclampsia in multiparous older women in this study contrasted to a previous study (Bianco et al., 1996 as cited in Ogawa et., 2017) which found no change in risk of preeclampsia in both primiparous and multiparous women of age, this might be explained by the recent use of low dose aspirin in women with a higher risk of preeclampsia. Since both primiparity and advanced age are both strong risk factors for preeclampsia, these women may be more likely to receive the medication than multiparous women (Ogawa et al., 2017).

Regardless of the way VAMA women conceive, the need for preconception counselling, and greater prenatal care in these women should be a priority. Regular prenatal visits and testing can help address potential concerns early on and reduce the risk of pregnancy and birth complications which can be even more devastating, both emotionally and financially.

Conclusion

Many studies have been done in various developed countries investigating what impact AMA has on perinatal and neonatal outcomes. The consensus is that advanced maternal age increases the mother's risk for developing medical conditions such as cancer, diabetes, hypertension, and arthritis. The probability of pregnancy complications increases as well. Among these complications are chromosome anomalies, placenta previa, placental abruption, caesarean birth, preterm labor and low birthweight. Abnormal functioning of the placenta and impairment in oocyte development potential, both due to aging, can result in fetal growth restriction and even stillbirth. Women who are of very advanced maternal age (over 40 and especially over 45 years of age) seem to be at even greater risk of pregnancy and perinatal difficulties, although risks differ by parity and conception method.

Results of studies have been conflicting at times. The reason for this might be differences in homogeneity in study groups or failure to adjust for potential confounders such as maternal diseases, obesity, assisted conception, pregnancies of multiples, and parity. Differences in definitions of pregnancy outcomes might also be a reason for incompatible conclusions. It is vital to determine if age effects are direct and have a causal relationship with adverse outcomes or if they are indirect since other factors are at play. In order to accomplish this, future studies need to have control groups for age-dependent confounders. Inconclusive results concerning the ramifications of delayed childbirth must be resolved so that women of advanced age can make informed choices when deciding whether to bear children.

Information regarding chromosome anomalies and the availability of prenatal screening tests are vital for any women over the age of 35 who are planning to become pregnant. Those who receive positive results for a screening test can be sent for genetic counselling. Other emotionally supportive forms of help might come in the form of bereavement counselors, adoption services, or information on support groups for parents of multiples or for those who suffered a perinatal loss.

Preconception care is especially important for women of advanced age planning a pregnancy. Fertility concerns, pre-existing health conditions and risks for chromosome anomalies can be discussed. The importance of folic acid during pregnancy to decrease the risk of neural tube defects, reducing workplace risk and avoiding alcohol use and medications are all important topics to address. Older first-time mothers may need counselling regarding their transition into parenthood which may be more difficult for them as opposed to younger, first-time mothers. Most importantly, pregnancy surveillance in this older age group must be stressed in order to improve outcomes for both mother and baby.

The trend of increased advanced maternal age is expected to continue and thus the effects of AMA on maternal and fetal morbidity and mortality is, and will be, of great concern. The unique needs of this population must be addressed not only to benefit the mothers and babies themselves but for the implications that it has for the healthcare system and for service providers. Promoting the health of these women and their offspring and preventing negative outcomes reduces healthcare costs overall and will have an impact, going forward, on employment policies which will, hopefully, become more pregnancy-friendly.

Overall, older women who are in generally good health can hope to have favorable outcomes to their pregnancies with good prenatal care. Advanced technologies in perinatology have improved their chances of giving birth to a healthy child. If the needs for preconception counselling, targeted surveillance and early medical intervention are met, then there is no definite medical reason for excluding AMA women from attempting a pregnancy on the basis of age alone.

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