Advanced maternal age

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Abstract

The average age of women at childbirth in industrialised nations has been increasing steadily for approximately 30 years. Women aged 35 years or over have an increased risk of gestational hypertensive disease, gestational diabetes, placenta praevia, placental abruption, perinatal death, preterm labour, fetal macrosomia and fetal growth restriction. Unsurprisingly, rates of obstetric intervention are higher among older women. Of particular concern is the increased risk of antepartum stillbirth at term in women of advanced maternal age. In all maternal age groups, the risk of stillbirth is higher among nulliparous women than among multiparous women. Women of advanced maternal age (>40 years) should be given low dose aspirin (in the presence of an additional risk factor for pre-eclampsia) and offered serial ultrasounds for fetal growth and wellbeing; given the increased risk of antepartum stillbirth, induction of labour from 39 weeks' gestation should be discussed with the woman.

Keywords advanced maternal age; antepartum stillbirth; pregnancy complications

Epidemiology

The average age at childbirth in the UK is increasing, and more women are giving birth over the age of 35 years. In 1996, 12% of live births were to women over the age of 35 years, by 2006 that figure had risen to 20% and it has remained static since (20% in 2013). The Office of National Statistics estimated that in 2006, 4.6% of live births were to nulliparous women aged between 35 and 39 years of age and 0.9% were to women over the age of 40. In Scotland the figure was 9%.

The reasons for delaying childbirth are complex and multifactorial and it is important to remember that while some women may make a conscious choice to delay childbearing, it may be the unwelcome sequelae of subfertility for others.

Antenatal effects

Maternal

Women over 35 years are at higher risk of many pregnancy complications. Is this simply because women over 35 years are also more likely to have pre-existing medical conditions than their younger counterparts, pre-disposing them to developing pregnancy complications? In a large prospective cohort study of over 1.5 million deliveries during a 15 year period in Sweden, Jacobsson et al examined the relationship between advanced maternal age (AMA) and adverse perinatal and obstetric outcomes, and what contribution pre-existing maternal medical conditions had on the occurrence of adverse outcomes in women over 40 years of age. The study observed that women over 40 years of age were at increased risk of pregnancy complications and this risk persisted when the data were adjusted for pre-existing maternal disease.

A retrospective observational study of over 150,000 deliveries in Canada considered the relationship between maternal age and adverse outcomes and adjusted for potential confounders, including pre-existing maternal medical disease. A smaller retrospective study of 630 women in Italy examined the relationship between maternal age and pregnancy complications but did not adjust for pre-existing maternal disease. Both of these studies found that pre-existing maternal disease was more common with advancing maternal age.

Women over 40 years have a higher risk of developing gestational diabetes than women aged 20–30 years of age (OR 3.4).

There is some controversy over whether women of AMA are at increased risk of hypertensive disorders in pregnancy. In the previously mentioned Swedish cohort study, women over 40 years of age were found to have a higher risk of developing pregnancy-induced hypertension and severe pre-eclampsia, although they were at a slightly lower risk of developing mild pre-eclampsia. The increased risk of severe pre-eclampsia and pre-eclampsia as a whole were increased when the data were adjusted for pre-existing maternal disease and smoking. There was an increased risk of hypertensive disorders (including pregnancy-induced hypertension and pre-eclampsia) in the Canadian study, after adjusting for pre-existing maternal disease in women over 35 years of age (adjusted rate ratio 2.32) and in women over 40 years of age (adjusted rate ratio 3.55). No relationship between maternal age and hypertensive disorders was found in the Italian study, perhaps owing to the smaller sample size.

Women over 40 years of age are at higher risk of placenta praevia (OR 4.6–5.8) and placental abruption (adjusted rate ratio 1.8).

Fetal

The pregnancies of women over 35 years are at higher risk of perinatal death; this encompasses antepartum and intrapartum stillbirth and early neonatal death.

The Centre for Maternal and Child Enquiries (CMACE) report that perinatal deaths from 24 to 41 completed weeks' gestation affect 0.8% of all pregnancies to women over the age of 35 years, and 1% of all pregnancies to women over the age of 40 years. The distribution of maternal age among the mothers having perinatal deaths is significantly higher than the general maternity population. Mothers having stillbirths and neonatal deaths are more likely to be older (40+ years).

Women of advanced maternal age are at increased risk of preterm labour, both at less than 32 weeks' gestation (ARR 1.36 for women over 35 and ARR 2.41 for women over 40) and at less than 37 weeks' gestation (ARR 1.61 for women over 35 and ARR

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1.8 for women over 40). Women of AMA are at increased risk of bearing a low birth weight infant (<2500 g). Conversely women of AMA are also at increased risk of bearing a macrosomic (>3999 g) infant and the potential complications associated with macrosomia.

Interestingly, it has been reported that women over 35 years of age typically believe that their age puts their infant at increased risk.

Late pregnancy/intrapartum complications

Obstetric intervention

The overall Caesarean rate for nulliparous women less than 35, 35–39 and >40 years old is 21%, 38% and 50%, respectively. The Caesarean rate for nulliparous women in labour (both spontaneous and induced) at term, excluding breech presentation, is 22.8% among women 35–39 years of age and 27.4% among women aged 40 years or older (unpublished data, Scottish maternities 2004–2008). In nulliparous women, the relationship between maternal age and delivery by emergency Caesarean is linear, which suggests a biological effect of advancing maternal age on labour performance, rather than simply obstetrician or maternal preference. Smith et al investigated this possible biological effect of advancing maternal age on myometrial contractility further. They took uterine biopsies from the upper edge of the lower segment uterine incision from 62 women at the time of their elective caesarean section between 38 and 40 weeks' gestation. The myometrial tissue was dissected into longitudinal strips and examined *in vitro* for its inherent contractility. They found a non-significant trend towards a reduction in frequency of spontaneous contractions in myometrial fibres with advancing maternal age. Overall, they found a significant reduction in spontaneous contractile activity with maternal age and this effect persisted when the results were adjusted for advancing gestational age and number of previous vaginal deliveries. The risk of operative vaginal delivery also increased linearly with maternal age in nulliparous women. The rates of operative vaginal delivery in women <35, 35–39 and >40 years were 23.5%, 36.9% and 43%, respectively.

When the length of labour was examined in over 120,000 women who had a singleton, term, live, cephalic birth and who reached 10 cm dilatation for both nulliparous and multiparous women the duration of the first stage of labour decreased with advancing maternal age, and the duration of the second stage in nulliparous women increased with advancing maternal age.

Perinatal death

Perinatal death refers to the death of a fetus or a newborn in the perinatal period that commences at 24 completed weeks' gestation and ends before seven completed days after birth. It therefore includes stillbirth (antepartum and intrapartum) and early neonatal death.

Stillbirth accounts for 67% of all perinatal deaths; excluding intrapartum causes, antepartum stillbirth accounts for 61% of all perinatal deaths and is by far the commonest cause of perinatal death at term. Antepartum stillbirth is particularly important in women over 40 years of age because they are less likely to have future pregnancies. Female fecundity (the ability to produce offspring) declines with age, with monthly fecundity gradually decreasing from the mean age of 30 years onward. If the mean rate of fecundity per cycle for women aged 20–30 years is scaled as 1, for a woman aged 33 years of age the relative rate is 0.75. In addition to the reduction in natural fertility with increasing age, there is a significant decrease in the chance of having a healthy child after the age of 30. Beyond 30 years of age the chance of a 'healthy baby' decreases by 3.5% each year. Assisted reproductive technologies cannot entirely counteract nature, the live birth rate for IVF/ICSI among women less than 39 years is 27.3% whereas for women aged between 40 and 42 years this rate is 11.1%, decreasing to 4% in women over 44 years of age.

Maternal age 35 years and over is associated with a 65% increase in the odds of stillbirth and accounts for over 4000 stillbirths in high income countries each year. The increasing average age at first childbirth may be contributing to the static rates of antepartum stillbirth in the UK over the last 20 years. One possible strategy to consider is an earlier induction of labour for women of advanced maternal age.

Antepartum stillbirth

Choosing the correct denominator

Traditionally, the risk of perinatal death at term was expressed as the perinatal mortality rate (the number of all perinatal deaths divided by the number of births in a given week). However, when considering antepartum stillbirth, Smith et al suggest that the population of babies at risk at any given gestational week are not only the babies born that week, but all babies yet to be delivered. Therefore it is important to consider the cumulative risk of stillbirth at any gestational age (the number of antepartum stillbirths at a given gestational week divided by the number of ongoing pregnancies at that gestational week). Although the perinatal mortality rate is lowest at 41 weeks, the gestational age associated with the lowest cumulative risk of perinatal death is 38 weeks.

The risk of antepartum stillbirth at term

The overall cumulative risk of antepartum stillbirth throughout gestation (from 20 to 41 completed weeks) for women of all ages is 6.5 per 1000 pregnancies. The cumulative risks of stillbirth for women younger than 35 years, 35–39 years and older than 40 years old, were 6.2, 7.9, and 12.8, respectively.

The largest increase in cumulative risk of stillbirth for women over 35 years of age starts at 39 weeks and peaks at 41 weeks. Women over 40 years old have a similar stillbirth risk at 39 weeks as women who are between 25 and 29 years old at 41 weeks, and once they pass 40 weeks' gestation their risk of stillbirth exceeds that of all women <40 years old at term. To quantify that risk, the risk of stillbirth between 37 and 41 weeks for women aged 35–39 years old is 1 in 382 ongoing pregnancies (RR 1.32), and for women 40 years or older 1 in 267 ongoing pregnancies (RR 1.88). If this is expressed as a risk per 1000 ongoing pregnancies, 2.6 in 1000 for women 35–39, and 3.7 in 1000 for women aged 40+, then comparisons with the routine practice of offering induction of labour postdates can be drawn, due to a 2–3 in 1000 risk of stillbirth for women of all ages.

It is a widely accepted practice in the UK to offer induction of labour for a pregnancy that continues beyond 41 weeks, termed a postdates pregnancy. This is because the rate of stillbirth

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