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Biopanic, advanced maternal age and fertility outcomes

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BIOPANIC

Although obesity and smoking are the most obvious public health effects of the numerous social changes occurring in the late 20th and early 21st centuries, a new epidemic is extending across the Western world and leading to a considerable burden on health resources as well as enormous personal suffering. This new scourge is that of aging motherhood. In modern society, the pressure of achieving financial, career and relationship fulfillments, whilst ensuring a spontaneous conception, which has least impact on the conceptus, optimum pregnancy outcome and a capacity to withstand demands of the baby and child, has led to the coining of the term 'biopanic'.

Importance of biopanic

Whereas less than 5% of women below the age of 25 fail to conceive naturally, this rate increases to 30% after the age of 35[1]. Moreover, the likelihood of a successful response to ovarian stimulation resulting in egg retrieval decreases as the woman ages and this, compounded by the fact that older women have a poor ovarian response, makes women aged 35 years or older less than ideal candidates for *in vitro* fertilization (IVF)[2]. For example, the embryo implantation rate is around 6% for women over 40, with a live birth rate around 3.5% in those aged over 45, and a cumulative live birth rate of 14.4% after five IVF attempts in women over 40 in contrast to 45% for those under age 35. Diminished embryo implantation combined with the steep rise in the rate of miscarriage account for the substantial decline in fertility noted after the age of 45[3–6]. According to the UK Office of National Statistics (Figure 1), over the past several years the largest increase in conception rates has occurred in women aged 40 and over, and this trend has persisted with no sign of decline. However, this change is juxtaposed against the biological irony of a significant reduction in fertility after the age of 35, which clearly cannot change[8].

The same picture holds true for the USA, which also has seen a remarkable shift in the

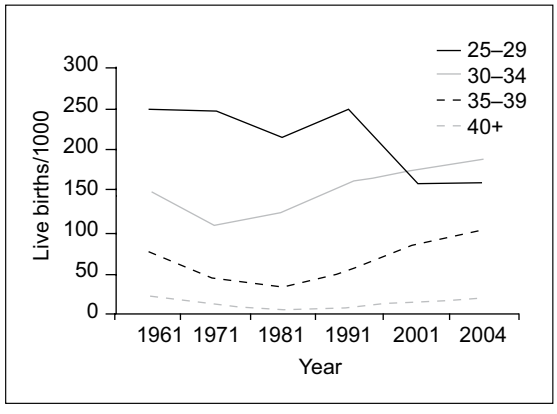

Figure 1 Maternal age groups at childbirth in England and Wales, 1961–2004. (Office for National Statistics, UK[7])

demographics of childbearing. The number of first births per 1000 women 35–39 years of age increased by 36% between 1991 and 2001, and the rate among women 40–44 years of age rose by a remarkable 70%[9]. The average age of women seeking IVF treatment according to the Human Fertilisation and Embryology Authority (HFEA) of the UK has risen in the 14 year interval between 1992 and 2005 from 33.8 years to 34.9 years, respectively, as is shown in Figure 2[10].

The age of menarche has decreased over generations, and life span has increased, but the age of the menopause has remained unchanged. The loss of female gametes with age is both quantitative and qualitative. The sense of urgency to conceive in the time when the number of gametes available is likeliest to result in a successful spontaneous pregnancy with a low chance of chromosomal abnormalities, and without encountering any obstetric or medical complications, is a pressure felt by a large number of women in modern day society. At the same time as they are pursuing their career, they desire to achieve successful pregnancy outcomes which creates a situation of 'biopanic'.

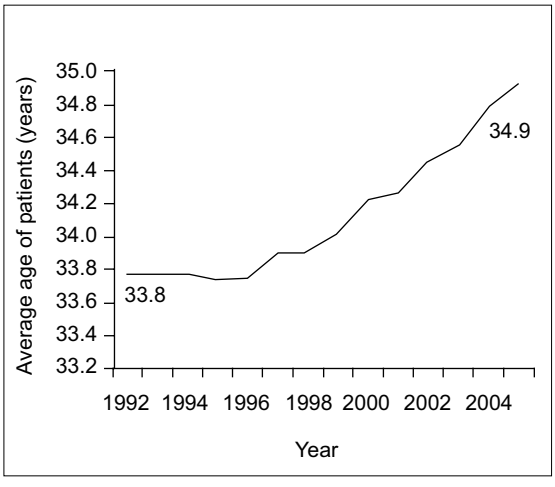

Figure 2 Trends in average age of patients requesting *in vitro* fertilization 1992–2005. (Reproduced with permission from Human Fertilisation and Embryology Authority[10])

ADVANCED MATERNAL AGE

Advanced maternal age (AMA) is defined as age 35 or more for the mother at the time of delivery of her baby.

Advanced maternal age predisposes to Down's syndrome (trisomy 21). The risk of having a Down's syndrome baby rises with maternal age, essentially doubling from 1 in 725 at maternal age 32 to 1 in 365 at maternal age 35. This risk continues to climb and is 1 in 32 at maternal age 45.

Importance of advanced maternal age

The effect of maternal age on the outcome of pregnancy may be best assessed by examining specific factors that can negatively affect the desired outcome of a pregnancy: declining fertility, miscarriage, chromosomal abnormalities, hypertensive complications, stillbirth and maternal mortality.

Fertility rate and maternal age at conception

Figure 3 shows the effect of maternal age on the average rate of pregnancy, calculated on the basis of ten different populations living between the 17th and 20th centuries that did not use contraceptives. Fertility remains relatively stable through to 30 years of age, at more than 400 pregnancies per 1000 exposed women per year, and then begins to decrease substantially. By 45 years of age, the fertility rate is only 100 pregnancies per 1000 exposed women[11]. Figure 4[9] and Table 1[12] depict the effect of age on the spontaneous miscarriage rate.

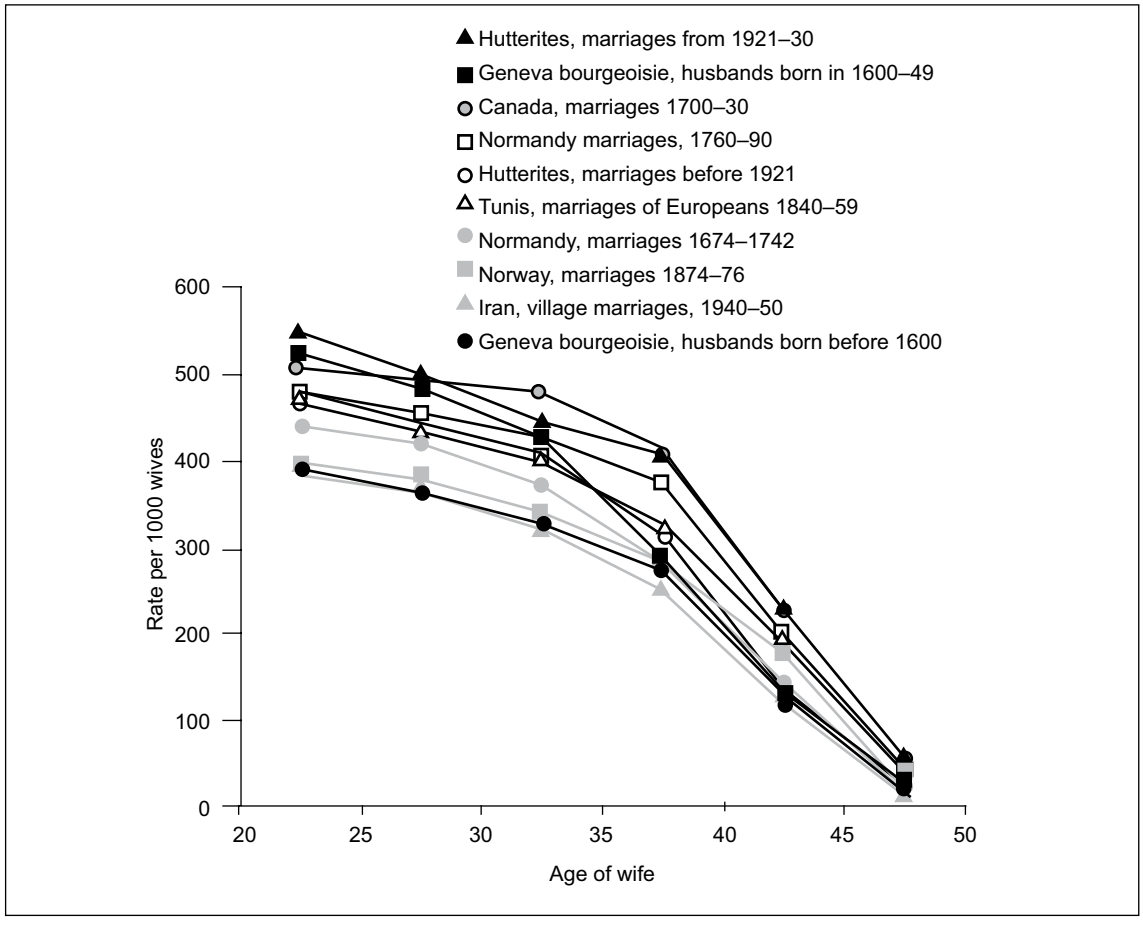

Figure 3 Fertility rates and advanced maternal age. (Reproduced from Menkel *et al.*, 1986[11], with permission from American Association for the Advancement of Science)

Reproductive issues

Fertility, defined as the natural ability of a woman to reproduce, declines gradually over the woman's life span[13]. Although this decline seems to begin at about age 30, it is more obvious between 35 and 40, and increases dramatically thereafter. The possibility of a spontaneous pregnancy occurring is less than 2% around the age of 42 and almost 0% after 45 years[14–17]. In actuality, fertility reaches its nadir after the age of 40. Thus, the overall contribution to the total number of births in a given population from 40-year-old women is 1%, and from 47-year-old women 0.01%[14]. The implantation rates also decline dramatically as menopause approaches, dropping from 20% at the age of 30 to less than 4% at the age of 40 years[13]. Accordingly, birth rates decrease significantly with advancing maternal age, presenting a drop of 95% at the age of 45, and of almost 100% around menopause[2,13,14]. However, age 41 is generally considered to be the point when fertility stops and subfertility starts. Therefore, menopause in reality occurs approximately 10 years after the substantial loss of conception potential[2,14] (Figure 5).

There are 4–7 million primary oocytes in the ovaries of a 20-week-old female fetus, but this number is halved at birth. By puberty there are

only 400,000 oocytes available in the ovaries, but only 400–500 eventually undergo ovulation[13]. From puberty onward, the loss of follicles is continuous throughout the woman's reproductive life (Figure 6). The phenomenon of oocyte depletion happens even under conditions of ovarian suppression, as is the case in pregnancy or with the use of combined oral contraceptives. The depleted oocytes undergo atresia through apoptosis or necrosis[18,19]. Because the ovarian pool of follicles declines exponentially with advancing age, from the age of 35 there is an accelerated loss of follicles, so that at 38, a woman may have only 25,000 follicles available, at age 40, 15,000, at age 45, her reserve may have declined to 5000, and in her early 50s, only a few hundred remain (Figure 6)[20]. Under these circumstances, IVF, a procedure selected by approximately 20% of

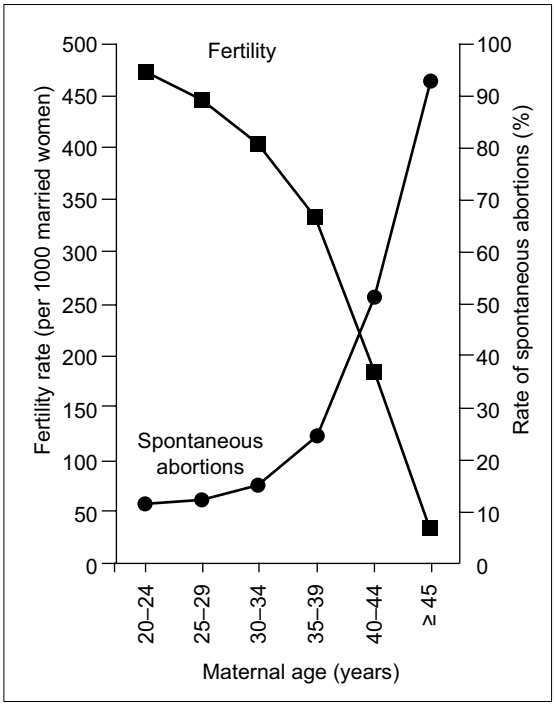

Figure 4 Fertility and miscarriage rates as a function of maternal age. (Reproduced from Heffner, 2004[9], with permission from Massachusetts Medical Society)

Table 1 Incidence of miscarriage by different age groups. (Reproduced from Madankumar *et al.*, 2003[12], with permission from Elsevier)

Maternal age (years)	*Miscarriage rates*
<19	10.3%
20–29	9.7%
30–34	11.5%
35–39	21.1%
40+	42.4%

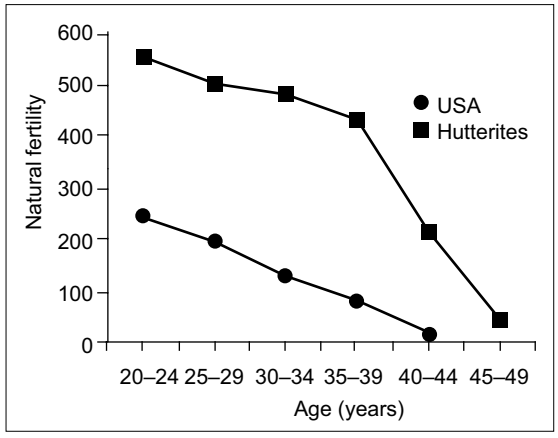

Figure 5 Natural fertility according to age in different populations

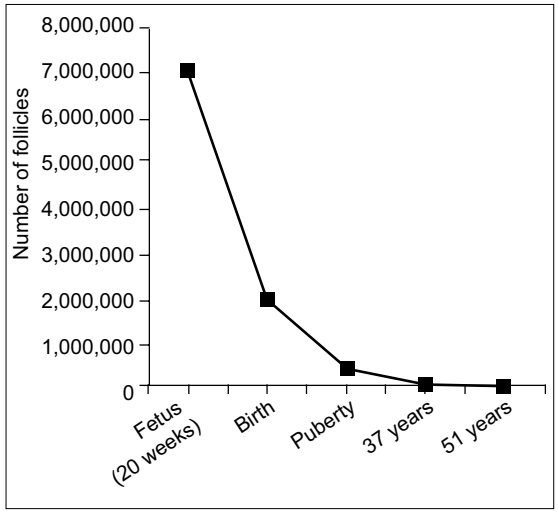

Figure 6 Number of follicles in the ovaries during a woman's life

women between the ages of 35 and 44 wishing to conceive, has a much less successful outcome with advancing age, as the number of gametes available is much lower (Table 2).

Compiled data from IVF programs since their inception show that whereas outcomes have improved for those aged under 35, no significant increase in those aged 35 and over has been seen. Moreover, the natural effect of biology on declining fertility is compounded by pathology, by which many older women have more time to accumulate detrimental medical conditions including diabetes and increased body mass index (BMI), which, although varying with age, are more common on average for older women, with trends being apparent through the childbearing years as shown in the Confidential Enquiries into Maternal and Child Health, 2007 (Table 3). Other accumulated conditions include sexually transmitted infections and their consequences, uterine fibroids, endometriosis, tubal damage, cervical disease and acquired thrombophilias, all of which can compromise fertility.

Table 4 shows the risks of Down's syndrome and any chromosomal abnormality according to 5-year increments of maternal age[24]. Advanced paternal age, which is frequently associated with advanced maternal age, increases the risk of autosomal dominant diseases, such as

Table 2 Pregnancy success rates in 2007. (Reproduced from Centers for Disease Control and Prevention, 2009[21], with permission)

	Age of women			
Type of cycle	*<35*	*35–37*	*38–40*	*41–42*
Fresh embryos from non-donor eggs				
Number of cycles	42,127	23,504	20,612	9535
Percentage of cycles resulting in pregnancies	45.7	37.2	28.1	18.4
Percentage of cycles resulting in live births	39.6	30.5	20.9	11.5
Percentage of retrievals resulting in live births	42.9	34.2	24.4	14.0
Percentage of transfers resulting in live births	45.9	36.9	27.1	16.0
Percentage of transfers resulting in singleton live births	29.9	25.7	20.6	13.6
Percentage of cancellations	7.6	10.8	14.1	17.8
Average number of embryos transferred	2.2	2.5	2.8	3.1
Percentage of pregnancies with twins	33.2	28.2	21.6	14.0
Percentage of pregnancies with triplets or more	3.5	4.5	4.0	2.5
Percentage of live births having multiple infants	34.9	30.4	23.9	15.4
Frozen embryos from non-donor eggs				
Number of transfers	10,518	5388	3518	1126
Percentage of transfers resulting in live births	33.6	29.9	25.0	20.9
Average number of embryos transferred	2.2	2.2	2.4	2.5
	All ages combined			
Donor eggs	*Fresh embryos*		*Frozen embryos*	
Number of transfers	10,321		5633	
Percentage of transfers resulting in live births	55.1		31.9	
Average number of embryos transferred	2.2		2.3	

Table 3 Trends in body mass index (BMI) expressed as percentage by age, England. (Reproduced from Confidential Enquiry into Maternal and Child Health, 2007[22], with permission)

	BMI					
Year	*18.5 or under*	*18.6–25.0*	*25.1–30.0*	*30.1–40.0*	*Over 40*	*All*
1993	1.9	49.5	32.2	15.0	1.4	100.0
1994	2.2	49.1	31.4	15.7	1.6	100.0
1995	2.2	47.4	32.9	16.1	1.4	100.0
1996	2.0	46.0	33.6	17.0	1.4	100.0
1997	1.9	45.6	32.8	17.4	2.3	100.0
1998	2.1	44.6	32.1	19.3	1.9	100.0
1999	1.8	44.3	32.8	19.2	1.9	100.0
2000	1.8	43.1	33.8	19.1	2.3	100.0
2001	1.6	41.9	32.9	21.0	2.5	100.0
2002	1.9	41.6	33.7	20.2	2.6	100.0
2003	1.9	41.3	33.4	20.6	2.9	100.0
2004	1.7	39.8	34.7	21.3	2.6	100.0
2005	1.6	40.7	32.9	19.0	2.9	100.0

Table 4 Risk of Down's syndrome and chromosomal abnormalities at live birth, according to maternal age[23]

Maternal age at delivery (years)	*Risk of Down's syndrome*	*Risk of any chromosomal abnormality*
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21

achondroplasia and Marfan's syndrome, that appear to result from new genetic mutations[9].

It is not just defects resulting from chromosomal anomalies which are more prevalent in the offspring of the older age group, but also non-chromosomal congenital abnormalities such as cardiac defects, club foot, spina bifida, diaphragmatic hernia and limb defects[24]. Whereas the baseline risk of congenital malformation for women aged under 25 is around 3.5%, this risk increases by an additional 1% and 2.5% when the woman is over 35 and over 40, respectively[25].

Preimplantation genetic screening for aneuploidy

Preimplantation genetic screening (PGS) refers to techniques whereby certain categories of patient thought to be at a higher than average risk of conceiving chromosomally abnormal embryos have their embryos tested (by blastomere or polar body biopsy) to determine whether specific abnormalities are present.

The purpose of preimplantation screening for aneuploidy is to help those seeking assisted conception treatments for infertility to achieve a successful pregnancy and to reduce their risk of miscarriage. Whilst it helps to identify chromosomally abnormal embryos, aneuploidy screening (PGS) does not necessarily identify normal embryos. In some cases, information

discovered through preimplantation testing may help those who have been unable to conceive to identify the underlying basis of their infertility.

It is anticipated that PGS for aneuploidy has a role in the treatment of the following categories of patient:

1. Women over 35 years of age;
2. Women with a history of recurrent miscarriage not caused by translocations or other chromosomal rearrangements;
3. Women with several previous failed IVF attempts where embryos have been transferred[10].

All the above, either alone or in combination, may be present in patients with AMA.

Medical disorders associated with advanced maternal age

Hypertension

The incidence of pregnancy induced hypertension is doubled by the time a woman reaches 35, compared to its incidence in the preceding decade[26]. This fact, along with the observed reduction in arterial compliance seen with aging, accounts for the increased incidence of cardiovascular disease in older gravidas, as well as the increased morbidity and mortality affecting this age group[27].

Vascular reserve capacity is likely to be compromised by the increased prevalence of chronic hypertension in older age. Compared to controls, chronic hypertension is increased fivefold in older nulliparas and ninefold in older multiparas[28]. Pre-eclampsia may complicate chronic hypertension which then results in complications, such as fetal growth restriction and placental abruption[29]. The rate of pre-eclampsia in women aged over 35 was almost three times that in younger women, this being a direct consequence of a greater preponderance of hypertensive disease in the older age group[30]. If pre-eclampsia does occur, it is likely to be severe[31].

Diabetes

The incidence of type 2 diabetes increases with age. This condition is a state of relative insulin deficiency which results because of either a reduced production of insulin from the pancreatic islet cells or a reduced sensitivity to the effects of insulin within the body. Both phenomena decline as aging proceeds[32]. With older age, the production of insulin is diminished[33]. Up to 16% of women of AMA have a positive glucose tolerance test. The increase in gestational diabetes amongst older mothers may be due to progressive endothelial damage or to the onset of obesity, also observed in this group[34].

Obstetric issues

The increased occurrence of uterine fibroids can lead to obstetric complications such as placental abruption, fetal malpresentation and dysfunctional labor[35].

Women aged more than 40 years have a poor chance of a successful pregnancy, irrespective of their reproductive history. A large scale study from Denmark over a period of 15 years (1978–1992) involving a total of 634,272 women and 1,221,546 pregnancies demonstrated that the overall risk of fetal loss was 13.5%. The risk of fetal loss according to maternal age at conception followed a J-shaped curve, with a steep increase after 35 years of age (Figure 7). More than one-fifth of all pregnancies in 35-year-old women resulted in fetal loss, and at 42 years of age more than half of intended pregnancies (54.5%) resulted in fetal loss. The risk of spontaneous abortion varied from a minimum of 8.7% at the age of 22 years to 84.1% by the age of 48 years or more[36].

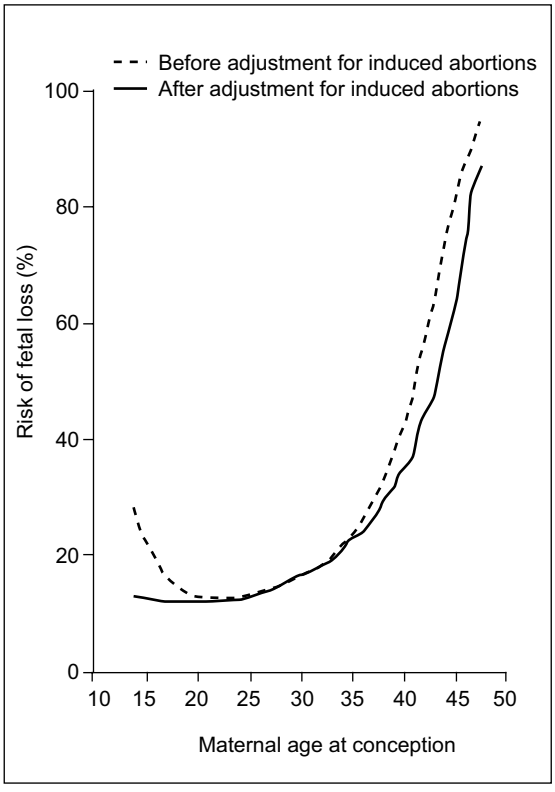

Figure 7 Risk of fetal loss from spontaneous abortion, ectopic pregnancy and stillbirth according to maternal age at conception. (Reproduced from Nybo Andersen *et al.*[36], with permission from BMJ Publishing Group Ltd)

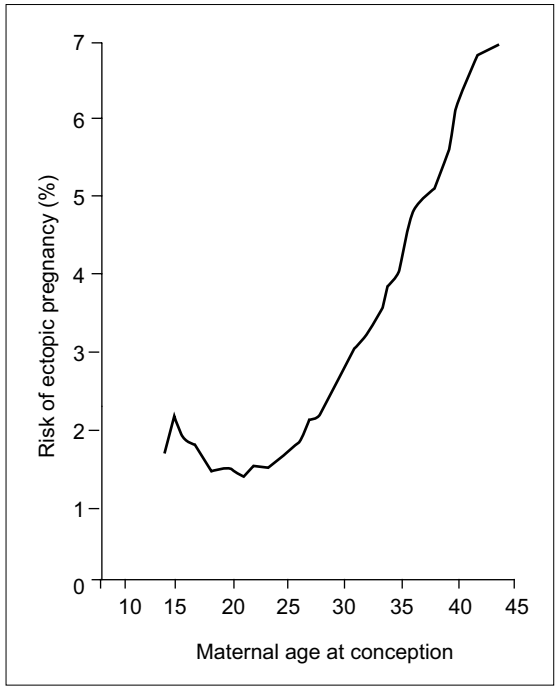

Figure 8 Risk of ectopic pregnancy rate according to maternal age. (Reproduced from Nybo Andersen *et al.*[36], with permission from BMJ Publishing Group Ltd)

It is difficult to understand the effect of age alone on the rate of miscarriage, as multiple confounding factors are involved, including chromosomal alterations, reduced fertility, coexisting disease and a greater number of conceptions initiated by assisted reproductive techniques.

The incidence of ectopic pregnancy showed a steady increase with increasing maternal age at conception from 1.4% of all pregnancies at the age of 21 years to 6.9% of pregnancies in women aged 44 years or more[36] (Figure 8). This change may be secondary to an increased prevalence of risk factors such as sexually transmitted and pelvic inflammatory disease or due to the effect of reducing tubal motility with increasing age.

A few studies have shown a lower mean gestational age at delivery in older women, with an increased incidence of preterm delivery at under 28 and 32 weeks of gestation[37]. Increasing maternal age shows an association with intrauterine growth restriction[38,39]. Figure 9 shows the association of AMA and adverse perinatal outcomes.

Stillbirth rate

Whereas women under the age of 30 have the lowest rate of fetal death, this rate increases with advancing maternal age, with women age 40 or older having twice the fetal death rate of women younger than 30 (Figure 10)[40]. Although the absolute rate of fetal death has

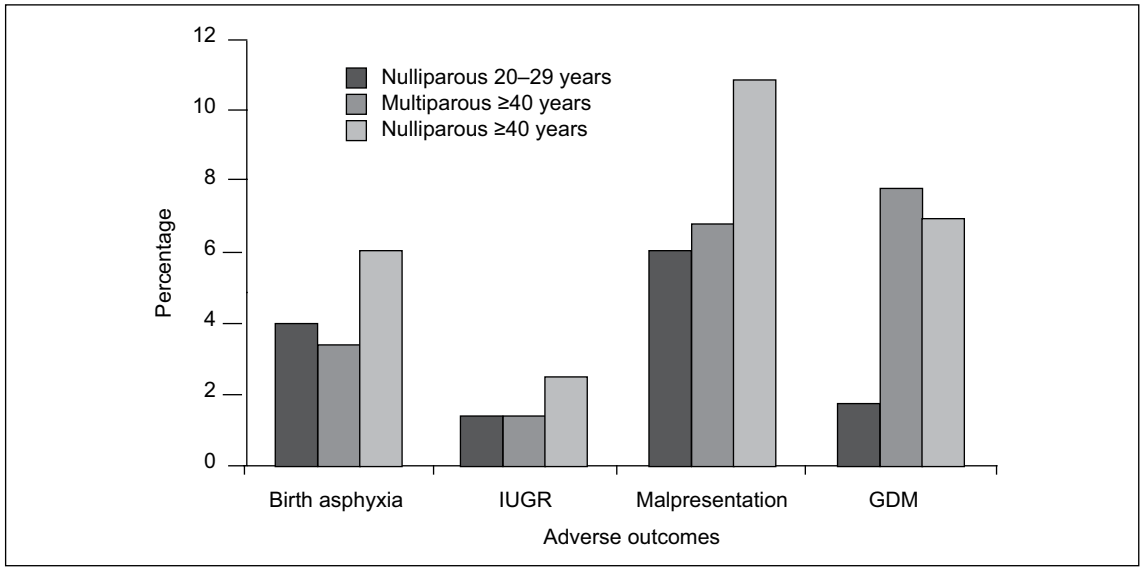

Figure 9 Adverse outcomes associated with advanced maternal age and parity. IUGR, intrauterine growth retardation; GDM, gestational diabetes mellitus. (Data from Gilbert *et al*.[28])

declined significantly for women of all age and parity groups since 1968 as compared to 1978, older women nevertheless remain at higher risk for fetal death, even after controlling for common diseases associated with older age, such as diabetes and hypertension, and complications of pregnancy such as abruption, all of which are also associated with increasing maternal age. Exactly why AMA is an independent risk factor for fetal death remains unexplained.

The increased incidence of obstetric complications is intimately associated with the incidence of cesarean section, which is far greater in women who are older[41,42]. Women aged 35 and over are 1.5 times more likely to undergo operative delivery compared to their younger counterparts[31]. Primary reasons include fetal distress, malpresentation secondary to pelvic pathology, and protracted labor. The latter is thought to be as a result of an age related decline in myometrial gap junction deficiency or a reduced sensitivity of myometrial oxytocin receptors[34,43]. In addition, an age related decline in pelvic elasticity[44,45] and myometrial

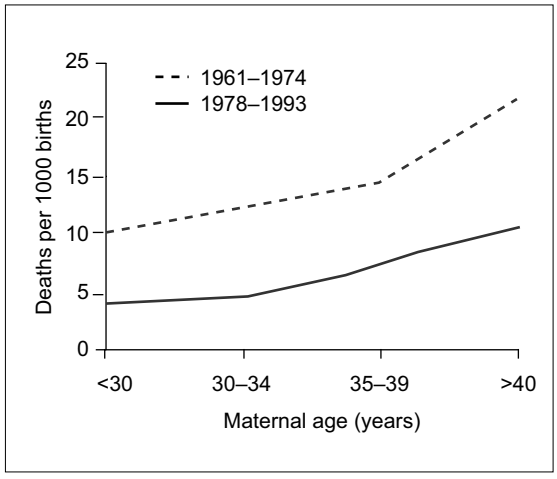

Figure 10 Increased maternal age and the risk of fetal death. (Reproduced from Fretts *et al*.[40], with permission from Massachusetts Medical Society)

function of the reproductive tract, along with fibrosis of the myometrial arteries, make normal vaginal delivery more difficult in older women and contribute to the prevalence of operative deliveries[44–46]. According to some reports, cesarean section rates in women aged

over 35 range between 21% and 52% (Figure 11)[26,28,47].

Cesarean rate and advanced maternal age

The concept of having a 'premium baby', the higher incidences of abruptio placentae, placenta previa, preterm labor, multiple pregnancy and malpresentation, as well as the widely held personal conviction that the index pregnancy may be the last chance to achieve a successful pregnancy, act in isolation or in combination and contribute to the excessive cesarean rate observed in the AMA group. Other factors also are operational, including induction of labor especially if the pregnancy exceeds 41 weeks[46], and antepartum hemorrhage from either placental abruption or placenta previa[34]. This latter risk is substantially greater with a 23% increase of placental abruption in women aged 35–49, in particular those with twin pregnancies, compared to pregnancies in women of younger age, although the risk of placenta previa in older nulliparous women is lower (around eight times higher than the baseline risk)[28].

Neoplastic disorders associated with maternal age

The older mother also runs a risk of developing certain cancers if she delays childbearing until a later age[48] (Figure 12), and numerous reports document AMA women becoming pregnant whilst being investigated or treated for cancerous conditions. To avoid the effects of radiation and cytotoxicity on embryo/fetus, it is crucial to offer effective contraception and also to make the patient aware of its availability. The commonly encountered cancers

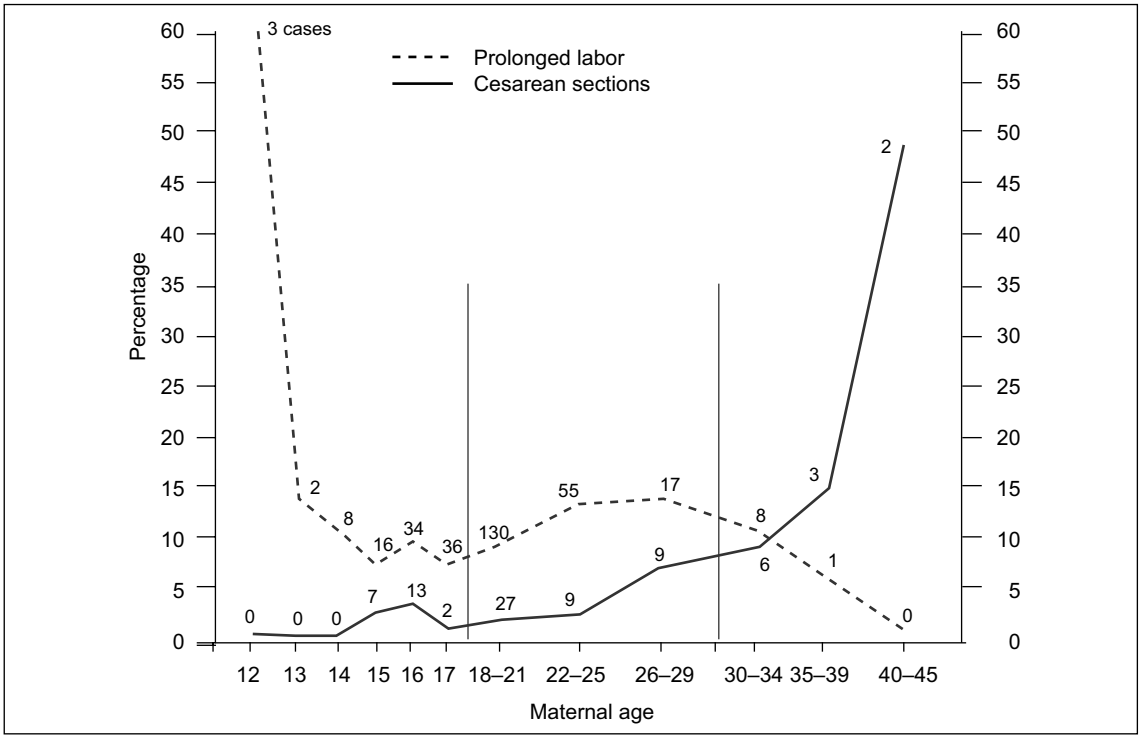

Figure 11 Maternal age, duration of labor and cesarean section rates. (Reproduced from Dodge *et al.*[47], with permission from Southern Medical Association)

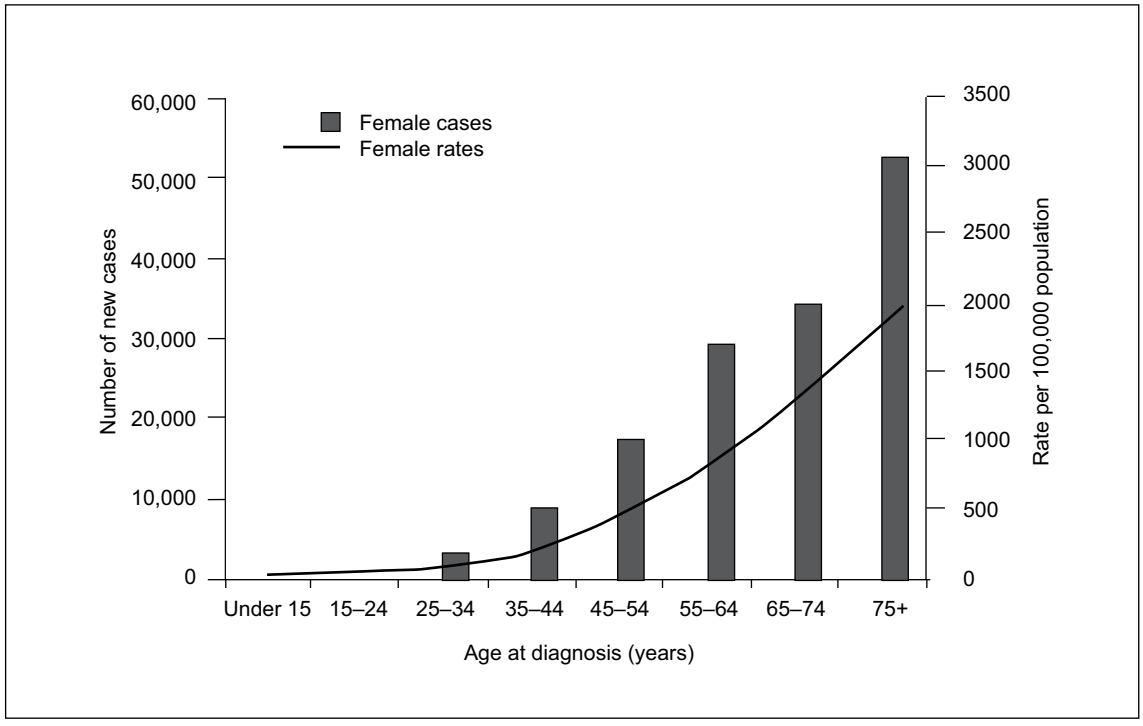

Figure 12 Number of new female cases and rates, by age, of all malignant neoplasms. (Office for National Statistics, UK, 2006[48])

include carcinoma of breast, lymphoma, carcinoma of cervix and ovarian tumors.

Maternal mortality and advanced maternal age

Modern day management of pregnant women who are older requires an understanding of the risks involved that result from the complex interplay between age, existing medical history and antenatal as well as perinatal complications. Maternal mortality is closely associated with maternal age. As shown in Figure 13, the highest mortality rates are among the oldest women as was evident in the Confidential Enquiry into Maternal and Child Health enquiries of 2003–2005, UK, in which the linear trend by age was statistically significant[22]. Stated another way, the average maternal mortality rate (MMR) increases as a function of age[38], and this increased risk is operational regardless of parity, time of entry into prenatal care and level of education.

Co-morbidities are also much more prevalent in older age, including cardiovascular disease, hypertension and multiparity, all of which directly contribute to the increase in MMR seen in older age[49]. These conditions also result in recognized complications of pregnancy, such as pregnancy induced hypertension, abnormal fetal growth, placental abruption and an increased rate of cesarean deliveries[49]. The risk of death from complications such as pregnancy induced hypertension, infection, embolism, hemorrhage and cerebrovascular disease is more than doubled in women over 30 compared to those who are younger[50]. In addition, psychiatric causes of death, such as postnatal depression, are more prevalent in women of older age.

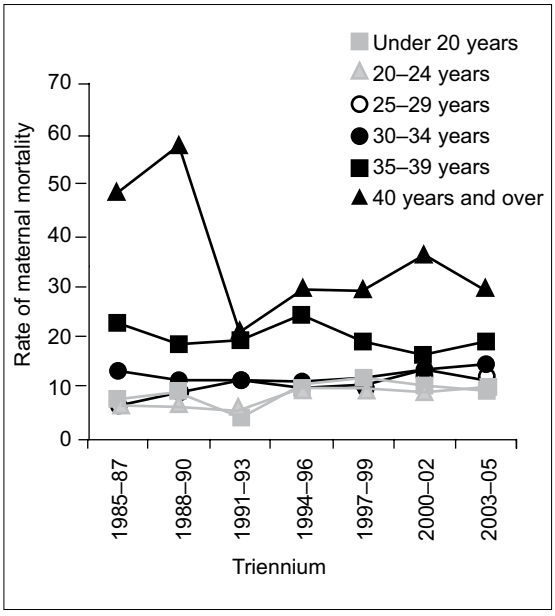

Figure 13 Maternal mortality and maternal age[22]

ETHICAL ISSUES AND OLDER PARENTS

Older age motherhood is generally associated with a greater level of educational achievement[51], and a large number of women presently elect to pursue educational programs and careers in fields that were conventionally occupied by men. In spite of this, it is not clear whether better educated women are delaying childbearing in order to reach a point of professional and financial security, or whether the pursuit of a better career leads to an unwanted but inevitable postponement of childbirth. With divorce figures on the rise, it is much more common for women to wed again in midlife, and then desire to have another child. Despite this growing trend, it will probably be another 15 years before information about both parents and children from the perimenopausal pregnancies becomes available to assess problems associated with facing retirement and adolescence at the same time.

When children face bereavement and orphanhood at a young age, emotional consequences may be devastating and potentially disabling. Even when the child does not have to face parental loss, the social stigma of being taken to and picked up from school by an uncharacteristically older parent may burden the child with psychological sequelae and prevent him/her from achieving an essentially normal childhood. Moreover, the inevitability of reduced stamina and energy which often accompanies older age may have a negative impact on the welfare of the offspring, as the older parent struggles to meet the demands of a growing child in its development.

Whilst a lot of women will already be aware of the significance of these potential problems, many still choose to attempt pregnancy at any cost, be it monetary, physical or psychological, despite the presence of significant co-morbidities. For some, the drive to have children is so strong that they willingly risk their livelihoods and even ultimately their own lives for the sake of bringing a child into the world and thus being a biological mother. This desire is undeniable and long has been defined as the very essence and meaning of womanhood.

Setting aside the emotional desire to have children, several objective reasons support childbearing at a later age and actually are of potential benefit in contrast to being a disadvantage. First, the financial security that an older parent has is undeniable. Second, an older parent typically experiences less pressure in the professional environment, being able to spend more time parenting, something that younger couples often find difficult and which accounts for the increasingly common circumstance in which young children are raised by their grandparents. Last, but hardly least, older parents often are better equipped with the emotional maturity required to raise a child and deal with the hurdles that child-rearing presents.

Age related attributes, often characterized merely as life experience and wisdom, may also mean that older mothers are more confident about their child-rearing skills and ability

to handle problems. In women who entered oocyte donation and IVF programs at later ages, there is evidence of a better relationship with their child and a greater degree of emotional involvement when the child is very young[52], as well as a considerably lower level of parenting stress[53]. Once the child reaches the age of 2, there appear to be no overt differences in parenting behavior compared to couples that conceived naturally[54].

CONCLUSION

In this age when women in Western societies seem to be able to have it all, there lies the untold truth about the private grief of older women, who for a number of reasons within and outside their control, have found themselves facing the prospect of childbearing in older age. The social and financial gains that come with women's new-found freedoms are tempered by the unrelenting biological decline of their fertility with advancing years, and this has forced many women into 'biopanic'.

As obstetricians and gynecologists, we have a duty to address the growing epidemic of aging motherhood and the complications that arise from this, as well as to inform women of the risks associated with delayed childbearing. Part of this duty includes trying to mount national and international efforts to facilitate childbearing with the option of career breaks, an ability to return to full- or part-time work after childbirth, and provision of adequate childcare and flexibility of working hours, among other possibilities.

Having said this, women should not be made to feel anxious or forced into childbearing when they may not feel prepared. They should not have to make a choice (however informed or ill-informed it may be) between having a career and reproducing within a safe biological window. For those women who desire to have children at an earlier age, they should not have to bear any adverse consequence from this decision, such as a diminution of their life plans and choices, nor should they be stigmatized for their decision or penalized in their professional spheres.

Society has a responsibility to make adequate provisions so that childbearing remains a free choice for women. Medicine, too, needs to realize that the persisting trend in older age motherhood is unlikely to be reversed and, should therefore, continue its present research into new methods of assisted reproduction, such as cryopreservation, to develop reliable means of reproduction for those women unable to conceive naturally, for those undergoing oophorectomy or chemotherapy for neoplastic disease, and for those wishing to conceive in older age for reasons both within and outside their influence.

Some women will inevitably fall outside of this range, for a number of personal and social reasons, and it will be up to us, as obstetricians and gynecologists to advise, as honestly and openly as possible, on the risks involved.

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