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Female contraception over 40

The ESHRE Capri Workshop Group[1,†]

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BACKGROUND: The majority of women 40–49 years of age need an effective method of contraception because the decline in fertility with age is an insufficient protection against unwanted pregnancy. Although pregnancy is less likely after the age of 40 years, the clinical and social consequences of an unexpected pregnancy are potentially detrimental. No contraceptive method is contraindicated by advanced reproductive age alone; thus there is a need to discuss the effectiveness, risks and non-contraceptive benefits of all family planning methods for women in this age group.

METHODS: MEDLINE searches were done by topic (epidemiology, age and reproduction, sexual function, delayed childbearing and specific contraceptive methods). The topic summaries were presented to the Workshop Group and omissions or disagreements were resolved by discussion.

RESULTS: The decline in fecundity in the fifth decade is insufficient for contraceptive purposes. Thus a family planning method is needed. Sterilization is by far the most common method in several countries. Copper intrauterine devices and hormone intrauterine systems have similar effectiveness, with fewer than 1% failures in the first year of typical use. Special considerations in this age group include the frequency of menstrual irregularity, sexual problems and the possibility of menopausal symptoms, all of which may respond to hormonal methods of contraception.

CONCLUSIONS: Women should be advised to continue with a contraceptive method until they have reached the menopause with its natural state of sterility.

Key words: ageing / contraception / family planning / sterilization / premenopause

†A meeting was organized by ESHRE (August 1–September 1, 2008) to discuss the above subjects. The speakers included: D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), C. Castelo-Branco (Institute Clinic of Gynecology, Obstetrics, and Neonatology, Hospital Clinic, Faculty of Medicine, University of Barcelona, Barcelona, Spain), J. Collins (McMaster University, Hamilton, Canada), J.L.H. Evers (Dept. Obstet. Gynecol., Academic Hospital Maastricht, The Netherlands), A. Glasier (Family Planning and WW Services, Edinburgh, UK), C. La Vecchia (Istituto Mario Negri, Milano, Italy), H. Leridon (Director of Elfe Projet, INED, Paris, France), D.R. Mishell, Jr. (Dept. Obstet. Gynecol., Keck School of Med., U.S.C., Women's Hospital, Los Angeles, USA), K. Wellings (Sexual and Reproductive Health Research, Department of Public Health and Policy, LSHTM, London, UK). The discussants included: E. Arisi (Dipartimento Materno-Infantile, Trento, Italy), G. Benagiano (Dipartimento di Scienze Ginecologiche, Università di Roma, Italy), J. Bitzer (Universitätsspital Basel, Frauenklinik, Abteilungsleiter Gyn. Sozialmedizin und Psychosomatik, Basel, Switzerland), P.G. Crosignani (Fondazione Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milano, Italy), E. Diczfalusy (Karolinska Institutet, Stockholm, Sweden), A. Lanzone (Clinica Ostetrica e Ginecologica, Policlinico A. Gemelli, Roma, Italy), S.O. Skouby (Department of Obstetrics and Gynecology, University of Copenhagen, Denmark) G. Stock (President, Berlin-Brandenburg Academy of Sciences and Humanities, Berlin, Germany) and A. Volpe (Dipartimento Integrato Materno Infantile, Università di Modena, Italy). The report was prepared by J. Collins and P.G. Crosignani.

Introduction

The potential demand for all kinds of reproductive health services depends first on the absolute number of women in the respective reproductive age group. The total number of women aged 40–49 years increased substantially in the decades between 1950 and 2000 in developed countries by 58% and by 32% in Europe. The rise was especially high in Eastern and Southern Europe. This rise has stopped or will stop soon in most parts of Europe: a 5% decline in the number of women in this age group in Europe is expected between 2000 and 2020. The future decline in women aged 40–49 years in Europe reflects the end of the baby boom: women reaching the age of 40–49 years in 2000 were born in 1950–1960, the last years of the baby-boom in most countries (United Nations Population Division, 2007).

The decrease in fertility with age is not sufficient to protect couples wishing to prevent pregnancy. Although the occurrence of pregnancy is less likely after the age of 40 years, the clinical and social consequences of an unexpected pregnancy are potentially detrimental (Dutch Central Bureau of Statistics CBS, http://www.cbs.nl; UK Central Health Statistics, 2006, http://www.statistics.gov.uk). Thus effective contraception is needed to avoid unintended and unwanted pregnancies. In the UK in 2007–2008, 74% of women age 40–44 and 69% of women age 45–49 were using a method of contraception (Lader and Hopkins, 2008). Women more than 40 years of age may consider all methods of contraception as no method is contraindicated by older age alone. Thus they should be advised of the risks and non-contraceptive benefits of all contraceptive methods (Faculty of Family Planning and Reproductive Health Care, 2005).

Methods

Searches were done in Medline and other databases by individual subjects (epidemiology, age and reproduction, sexual function, delayed childbearing and specific contraceptive methods). The highest quality articles most relevant to clinical practice were selected. Each subject summary was presented to the Workshop Group, where omissions and disagreements were resolved by discussion.

Ovarian ageing and reproduction

Loss of fecundity

The reproductive system does not escape the ravages of ageing which occurs in every tissue in the body (Kirkwood, 1998). The ovary is particularly vulnerable because unlike the testis no new gametes are formed after birth (Gosden, 1985). It is hardly surprising therefore that the most prominent feature of reproductive ageing is a decline in the quality and number of oocytes leading to their exhaustion at the menopause (Baker, 1963). In the absence of acquired disease such as fibroids or pelvic inflammatory disease, the uterus and tubes show very little decline in reproductive function. The overwhelming influence from age of the oocyte on reproductive potential is illustrated by the fact that there is no decline in pregnancy rate when donor oocytes are placed in the uterus of older women (ESHRE Capri Workshop Group, 2004).

In most developed countries the Total Fertility Rate (number of births per woman) in the age group 40–49 has declined between 1975 and 2005. The decline was due to the postponement of births to later ages and was the main cause of overall reduction of the final number of births per woman. The mean age at birth of the first child rose by about 4 years in Europe, from around 25 years to around 29 years, a rather rapid change that might continue in the immediate future. The reduction in the final number of children is due mainly to a striking decrease in the proportions of births of order 3 and more. As a consequence, fertility rates at 40–44 years decreased quickly, despite the postponement of births. The fall was quite rapid and in most European countries the rate was between 15 and 30 around 1985 (Fig. 1). Then rates started to rise again, but at a very slow pace so that the rates in 2005 remain well below the values observed in 1960. At age 45–49 years rates have always been low and remain so: around 2/1000 women in most countries.

Most women do not want to conceive beyond age 40, or even 35, but if they do try to have a child, it may take longer to conceive, because fecundity declines with age. The monthly chance of conceiving declines from around 20% at age 25–30 to a significantly lower 8% at age 40 and is even more reduced at older ages (van Noord-Zaadstra *et al.*, 1991). The proportions of women permanently sterile (i.e. trying but unable to start a pregnancy) are 17% at age 40 years, 55% at age 45 and 92% at age 50 (Leridon, 2008). In addition, 24% of pregnancies started after age 40 and 33% started at age 45 will not end in a live birth (Leridon and Slama, 2008). Thus, the age-related decline in fecundity may severely limit the choices of women who are trying to conceive. The likelihood of pregnancy does not decline, however, to the levels associated with effective contraception, and therefore the decline in fecundity is insufficient to avoid the need for contraception among older women who do not wish to conceive (Dutch Central Bureau of Statistics CBS, http://www.cbs.nl; UK Central Health Statistics, 2006, http://www.statistics.gov.uk).

Changes in menstrual cycles

Recruitment from the pool of primordial follicles continues throughout life from birth until the menopause (Gougeon *et al.*, 1994). After establishment of menses at puberty the length of the menstrual cycle remains fairly constant until a few years before the menopause (Treloar *et al.*, 1967). There is a significant shortening of the cycle with age due to a decrease in the length of the follicular phase. This change in menstrual pattern signals the start of the 'menstrual transition' and coincides with a significant decline in fertility (ESHRE Capri Workshop, 2005).

In the normal cycle the follicle which will eventually ovulate is recruited from 2 to 5 mm follicles which are present in the ovaries at the end of the previous luteal phase (Baird and Mitchell, 2002). The levels of progesterone, estradiol and inhibin A fall with regression of the corpus luteum and the secretion of FSH and LH rise reaching maximum levels about day 3–5 of the cycle. It is this rise in FSH which stimulates the growth of the healthy small follicles, as reflected in the rise in the concentration of inhibin B (Klein *et al.*, 1996). The largest healthy follicle amongst this group is able to benefit most from this trophic effect of FSH and within a few days rapidly increases in size and secretes increasing amounts of estradiol and inhibin A. These hormones suppress the level of FSH below the concentration required to sustain the growth

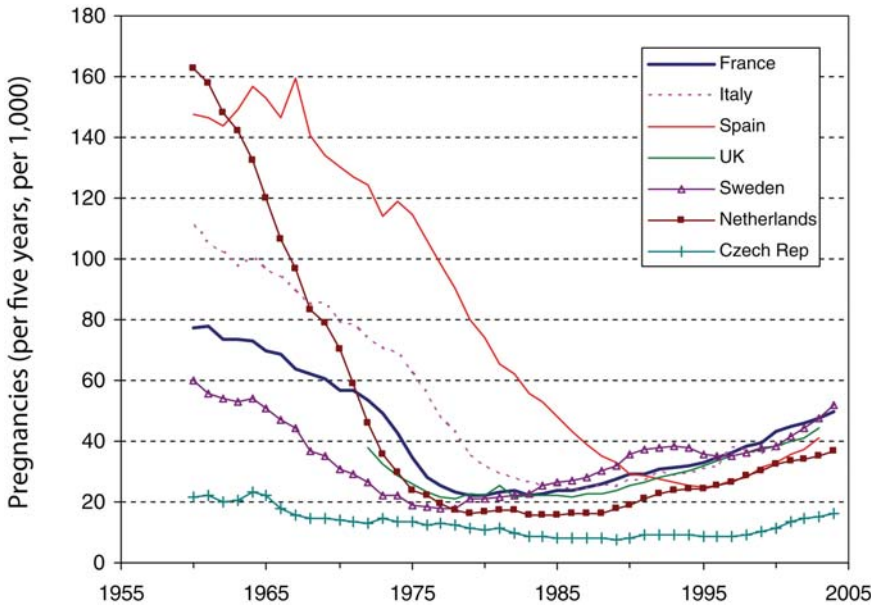

Figure 1 Trends in fertility rate at age 40–44 years [Source: Council of Europe, 2005 (H. Leridon, personal communication)].

of follicles other than the chosen one. In this way the follicle which is destined to ovulate maintains dominance over the other follicles.

It is likely that the dominant follicle continues to grow in the face of falling levels of FSH by becoming increasingly sensitive to FSH due to the action of local paracrine factors such as insulin-like growth factor (McGee and Hsueh, 2000; Webb and Campbell, 2007). In addition, by the mid-follicular phase the dominant follicle acquires LH receptors on the granulosa cells and hence can use LH as a partial surrogate for FSH. Ovulation occurs in response to the mid-cycle surge of LH induced by the rising levels of estradiol. After ovulation the corpus luteum secretes increasing amounts of progesterone, estradiol and inhibin A which combine to suppress the levels of FSH and LH to very low levels well below the threshold required to initiate and sustain follicle growth beyond 5 mm.

The cessation of cyclical ovarian function occurs at menopause defined as the last menstrual period (Gosden, 1985). Menopause is usually preceded by a period of about 5 years when signs and/or symptoms of incipient ovarian failure are present (Burger *et al*., 2007).

Endocrine changes during the menopausal transition

The first sign of imminent onset of the menopause is an elevated level of FSH and decrease in inhibin B in the follicular phase of the cycle (Sherman *et al*., 1976; Klein *et al*. 1996). The levels of estradiol and inhibin A which are secreted by the dominant follicle remain normal. The normal intercycle rise in FSH may persist into the follicular phase of the cycle although it is suppressed to normal levels by the time of ovulation. This rise of FSH is associated with lower levels of inhibin B, a hormone which arises mainly from the small antral follicles. The low levels of inhibin B reflect the reduced number of small follicles, which are the major source of this hormone. Recently further evidence to support this hypothesis has been provided from counts of the number of small antral follicles, using high resolution ultrasound, and from the concentration of the more stable anti-Müllerian hormone (AMH) (De Vet *et al*., 2002). The concentration of AMH declines with age and correlates closely with the number of small antral follicles as measured by ultrasound (van Rooij *et al*., 2000). These endocrine changes probably explain the significant shortening of the follicular phase of the cycle with age and the increased incidence of dizygotic twinning (Lambalk *et al*., 1998).

Trends in ovarian volume changes (Wallace and Kelsey, 2004) and in FSH, inhibin B and AMH concentration also correlate with the time of the final menstrual period (Sowers *et al*., 2008).

Although many women have regular monthly periods up until the menopause, in most menses may become less frequent and irregular during the late transitional phase (Burger *et al*., 2007). Many of these cycles are anovulatory (Metcalf *et al*., 1982; Landgren *et al*., 2004).

Ageing and sexual function

In a survey of Australian women between 44 and 49 years of age, 32% had intercourse once a week, 25% several times a week and 22% once a month. Also, 12% had intercourse one to six times a year, and 6% were not currently having intercourse. Only 3% of couples were having sexual intercourse daily (Deeks and McCabe, 2001). A recent US survey showed relatively high levels of sexual activity amongst men and women age 57–85, but there was a marked difference between men and women (Lindau *et al*., 2007).

Clearly sexual intercourse is important to most couples in this age group and sexuality may be a critical issue for women after 40. On the other side there is a significant decline in sexual function—in desire,

arousal, activity and satisfaction associated with ageing. The proportion with a notable or severe problem in desire, arousal, activity or satisfaction ranges from 19 to 25% (Fig. 2) (Addis *et al*., 2006).

A number of biological, psychological and environmental factors occurring in mid life may adversely affect sexual response. Biological or social-related events affect the integrity of multiple biological systems involved in the normal sexual response of women, including the hormonal environment, neuromuscular substrates and vascular supplies. Sex hormones, mainly low levels of estradiol, physical and mental well-being and feelings for her partner have an impact on women's desire and sexual responsiveness. Illness and its treatment increase in prevalence at this time of life and may affect sexual function. Women for the most part are less adversely affected by peripheral arterial disease than men (McCall-Hosenfeld *et al*., 2008), but the associated physiological changes increase their susceptibility to intercourse-related urinary tract infection (Moore *et al*., 2008). With increasing age too, sexual function and lifestyles may be markedly affected by changes in social circumstances (Guay, 2001).

Where children are still living at home they may be in the more difficult stages of adolescence, and where they have left the women may find difficulty in coping with the 'empty nest'. At this time of their lives, some women find themselves without a sexual partner and more middle aged women than men are not in a sexual relationship.

All these factors may greatly influence the perception of the sexual problems (Gallicchio *et al*., 2007; Gracia *et al*., 2007; Ferenidou *et al*., 2008). Nevertheless where prospective, population-based studies, using validated measure of sexual functioning and concurrent hormonal sampling, have been carried out they show an age-related decline in sexual functioning but an added incremental decline associated with the ovarian ageing (Dennerstein *et al*., 2003). More studies with this design are needed to properly understand the relative contribution of lifestyle, physiological and hormonal factors to the quality of sexual function during the menopausal transition. Satisfactory sex life may be even more important than prevention of pregnancy and practitioners should be aware of these additional needs above only contraception.

Delayed childbearing and fertility intentions

An increasing number of women remain childless by the age of 45. In the UK 10% of women born in 1945 and 5% born in 1960 have no children; and this figure is forecast to rise to around 22% among women born in 1990 (Smallwood and Jeffries, 2003). Throughout Europe women who do have children are increasingly having their first child later in life; in 2005, for the first time ever, British women in their early thirties had higher fertility rates than women in their late twenties (Office for National Statistics, 2008). Delaying childbearing inevitably means that some couples will have fewer children than they want, and some will have none (Smallwood and Jeffries, 2003). In an analysis of interview data from the British Household Panel Study investigating fertility intentions of childless women in their 30s, 44% of women aged 35–39 who had intended having children remained childless (Berrington, 2004).

There are many reasons for postponing childbearing and these have been widely discussed (Berrington, 2004; Bewley *et al*., 2005; Dixon and Margo, 2005; Gillan, 2006). It has been suggested that women postpone childbirth although they progress in their chosen careers and achieve a high standard of living (Bewley *et al*., 2005; Gillan, 2006). The costs of having children and the loss of income incurred as a result of early childbearing are significant. A change in the ideals and aspirations of women in the developed world towards 'post-materialist values' in which people lead more individualistic lives and prioritize personal freedom has also been suggested as a common reason for delaying childbearing (Dixon and Margo, 2005). The popular media tends to emphasize the problems people have in finding a suitable partner with whom to start a family (Brooks, 2006).

It has been said that the decision to postpone childbearing is not fully informed and that even when women are aware of their declining fertility, they rely on the success of assisted conception technologies (Bewley *et al*., 2005; Dixon and Margo, 2005; Maheshwari *et al*., 2008). In a recent study of male and female Swedish university students in their early 20s, around half the women wanted to delay

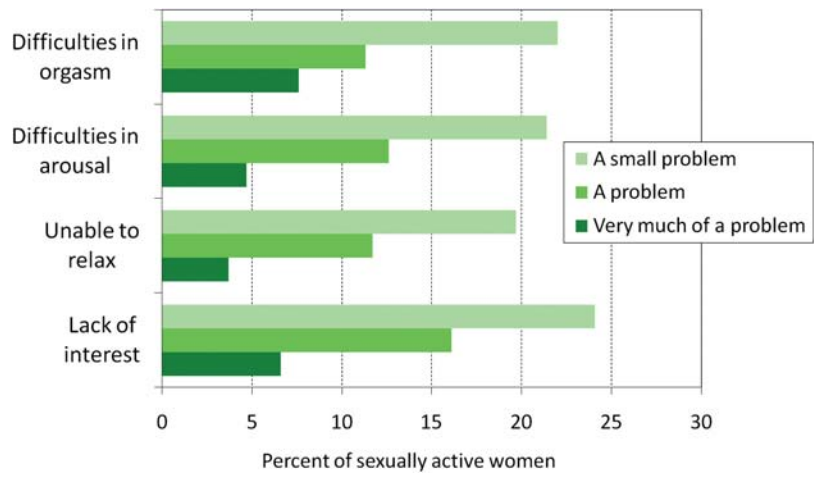

Figure 2 Sexual dysfunction among sexually active women aged 40–69 (adapted from Addis *et al*., 2006).

having children until after 35, and they were not well informed of the decline in fertility at this age (Lampic *et al*., 2006).

A number of studies have investigated women's fertility intentions and reasons for postponing childbearing. In a survey of German university staff aged 27–61, 67% of women delaying childbearing cited socio-economic reasons for doing so and only 18% the lack of a partner (Kemkes-Grottenhaler, 2003). In contrast, in an interview study of 45 childless US women in their thirties, over half cited the lack of a suitable partner, and only 11% financial reasons, as the reason for remaining childless (Robinson *et al*., 1987).

In a questionnaire survey of 234 nulliparous women aged 34 and over attending a family planning clinic in Scotland for contraception and asked about fertility intentions (Proudfoot *et al*., 2009) almost half (49.6%) definitely, or possibly, wanted children and (50.4%) definitely did not. Of the women who had not ruled out childbearing, 53% were concerned, and 18% very concerned about their future fertility and 96% of them felt they had passed the ideal age for first childbirth. Most were realistic about how long it may take to become pregnant. Among women who may/definitely want children but wished to delay childbearing, 74% gave reasons to do with their relationships. The second most frequent reason was having other distractions in life. Only 34% of them reported that work/training issues had caused them to delay childbearing (Proudfoot *et al*., 2009). In a large study which unusually sought the opinions of men, among 500 childless men and 1006 childless women in Alberta (Canada), the top four factors that influenced timing of childbearing were similar for men and women. These were financial security (85%), partner suitability to parent (84%), own interest/desire for having children (77%) and partner's interest/desire for having children (79%) (percent of women citing reason) (Tough *et al*., 2007).

In contrast to what many suggest, older women in developed countries who want children are quite realistic about their potential fertility and are aware that they are risking remaining childless if they wait too long. However for many of them it appears to be the lack of the 'perfect partner' which accounts for the delay and it is hard to understand reasons to alter this circumstance.

Births after age 40

Due to the delayed age of childbearing, the proportion of live births to women aged 40 or more is rising dramatically. In Sweden, the number of live births to women between 40 and 44 years of age increased from 5.0 to 10.3 per 1000 women from the early 1980s to 2001 (Jacobsson *et al*., 2004). In the USA, the number of first births after age 40 per 1000 increased by 70% between 1991 and 2001 (Heffner, 2004). From 1982 to 2002 the proportion of all live births in Canada to women aged 40 or more years rose from 0.6 to 2.6% (Joseph *et al*., 2005). In France, out of a total of 761 464 live births in 2003, births in women aged 40–44 accounted for 3.4% of the total births. Births in women aged 45–49 accounted for only 0.17% of all births, and only 4.8% of births were to women over 39 years. There were only 41 births at 50 years or more, accounting for 0.15% of births over 39 years (Beaumel *et al*., 2005). The oldest woman giving birth was with natural conception was 57 years of age (Glasier and Gebbie, 1996).

In The Netherlands, in 2006, 2% of first born children were born to women of 40 years of age and above (Table I).

Unwanted pregnancy is not uncommon in women over 40 years of age. In The Netherlands, the number of voluntary abortions in women over 40 years of age was 26 per 100 known pregnancies compared with 6 per 100 at 30–34 years of age (Dutch Central Bureau of Statistics CBS, http://www.cbs.nl). Comparable data for elective abortions have been reported from the UK: in 2006 there were 13 elective abortions per 100 recognized pregnancies in the 30–34 years age group and 32 per 100 in the over 40 age group (http://www.statistics.gov.uk). Thus there is clear evidence that declining fertility is an unreliable means of contraception in women over 40 years.

Risks associated with pregnancy in women over 40

Miscarriage

The likelihood of miscarriage before 20 weeks gestation rises from about 10% at 20 years of age to 50% at age 40–44 and more than 90% for women 45 years of age or older (Andersen *et al*., 2000). Oocyte aneuploidy leading to mal-development of the embryo is the most likely cause. In women 35–41 years of age undergoing pre-implantation genetic screening after *in vitro* fertilization more than 60% of embryos were aneuploid (Staessen *et al*., 2004) and about two thirds of the products of conception after miscarriage had abnormal karyotypes (Heffner, 2004).

Chromosome abnormalities at birth

The frequency of any chromosomal abnormality at birth for mothers at age 40 years is 1.5% and at age 45 4.8% in the absence of prenatal screening (Heffner, 2004). A meta-analysis of five published articles and 13 EUROCAT registries reported that trisomy 21 aneuploidy rose from 0.26% of births at age 35 to 0.94% at age 40 and 3.4% at age 45 (Morris *et al*., 2005).

Maternal complications in pregnancy and maternal mortality

Large studies reporting pregnancy complications in women 40 or more years of age include: (1) the American First and Second Trimester Evaluation of Risk (FASTER) trial, which involved more than 35 000 women, of whom 1364 (4%) were age 40 years and older (Cleary-Goldman *et al*., 2005); (2) a Swedish cohort study which involved 1 566 313 births from 1987 to 2001 including 32 867 women (3.6%) age 40 or more years (Jacobsson *et al*., 2004); and a Canadian cohort study of 157 445 singleton births from 1988 to 2002 which included 1822 mothers (4.9%) who were 40 or more years of age (Joseph *et al*., 2005). The comparison groups in the three studies were women aged <35, 20–29 and 20–24 years, respectively.

Gestational diabetes and placenta previa were increased in the Swedish, Canadian and American studies (Table II). Pregnancy hypertension was increased in the Swedish and Canadian studies, but not in the American trial with OR = 1.0 (0.8, 1.4). Placental abruption and severe pre-eclampsia also were significantly increased in women aged 40 years or more in the three studies. The baseline rates in the three studies varied because of different ages in the reference groups, and there were different definitions of morbid conditions.

Table I Births according to maternal age (Dutch Central Bureau of Statistics CBS, 2006; http://statline.cbs.nl/StatWeb/publication)

Age group	Number of firstborn children	Percent
<15	28	<1
15–20	2301	3
20–25	13 075	16
25–30	29 669	36
30–35	26 973	33
35–40	9532	12
40–45	1257	2
>45	42	<1

Nevertheless, the risk ratios were similar among the studies except in the case of pregnancy hypertension.

The likelihood of operative vaginal delivery did not increase with maternal age, but the likelihood of Caesarean section was in older women 2- to 3-fold higher than the younger ones in each of the three studies (Jacobsson *et al*., 2004; Cleary-Goldman *et al*., 2005; Joseph *et al*., 2005).

From 1991 to 1999 in the USA there were 4200 maternal deaths corresponding to 11.8 deaths per 100 000 births (Chang *et al*., 2003). The rate was less than 10/100 000 for women younger than 30 years, and 12.0, 21.6 and 45.4 for women 30–34, 35–39 and 40 or more, respectively. The mortality rate for women aged 40 or more was 5.3-fold higher (95% CI, 4.2–6.6) compared with women younger than 20. Among women 40 or more years of age, the mortality rates were 8.1 and 30 per 100 000 for white and black women, respectively.

Neonatal complications

Pre-term delivery prior to 37 weeks was 1.4-fold more likely (95% CI, 1.1–1.7) and birthweight <2500 g) was 1.6-fold more likely (95% CI, 1.3–2.1) in women 40 or more years of age compared with those <35 years of age (Cleary-Goldman *et al*., 2005). Risk of pre-term birth before 32 weeks for women in their fifth decade was 1.66-fold higher compared with women in their third decade. The risk was at least 1.9-fold higher that the newborn would be below the 3rd percentile of weight for gestational age (Jacobsson *et al*., 2004; Joseph *et al*., 2005).

In the FASTER trial, perinatal mortality was 0.3% in women 35–39 years and 0.7% in women age 40 or more years (Cleary-Goldman *et al*., 2005). In the Swedish cohort study perinatal death occurred in 0.5, 1.0 and 1.4% of women 20–29, 40–44 and 45 years or older, respectively (Jacobsson *et al*., 2004). In the Canadian study perinatal death rates excluding congenital abnormalities were 0.6, 0.7 and 1.1% in women, 20–24, 35–39 and 40 years or older, respectively (Joseph *et al*., 2005). This evidence from different settings and study types consistently indicates that for women in their fifth decade perinatal mortality is approximately 2-fold higher than in the third decade.

Table II Pregnancy complication risks for women more than 40 years of age

Pregnancy risks	US Cleary-Goldman *et al*. (2005)	SW Jacobsson *et al*. (2004)	CAN Joseph *et al*. (2005)
odds ratios			
Gestational diabetes	2.4	3.5	3.4
Placenta previa	2.8	4.5	5.9
Hypertension	1.0	3.4	3.6

Use of family planning methods over 40

Given that the number of women aged 40–49 years has increased, and that fewer of them want children, the demand for contraception in this age group has certainly increased. The data to show this trend are, however, rather limited. Data on contraceptive use are sparse in developed countries although in developing countries, Demographic and Health Surveys and other surveys have generated a large amount of information in the last three decades, especially on age of contraceptive users. Unfortunately, surveys that do exist are often performed at such long intervals that cannot be evaluated reliable trends (Leridon, 2006); and they are sometimes limited to eliciting recall from women when they are 45 or more years of age.

In most countries, among couples where the woman is aged 40–45 years, by far the most frequently used method of family planning is sterilization. The proportions of women who were sterilized (most often for contraceptive reasons) range from 7% in Italy to 53% in Canada. The proportion of vasectomized men is over 20% in countries such as The Netherlands, UK, USA and New Zealand. Other common methods include oral contraceptives (OCs) (up to 28% of women in France), the intrauterine device (IUD) (up to 30% in France), the condom (up to 22% in Greece and 21% in Spain), or natural methods such as fertility awareness or withdrawal (up to 27% in Greece). Among these methods, there is special concern about the fertility awareness methods (such as sympto-thermal) because their efficacy depends on the presence of regular cycles, of which the incidence decreases with increasing age. Fortunately, few women in this age group use this technique (<5%) (Table III).

Overall between 66 and 90% of women aged 40–44 years use some method of family planning. The situation is similar at 45–49 years, where between 50 and 82% use a method of family planning.

Trends can be seen in data from France, the UK and the USA, countries where two surveys or more were carried out among women who were at least at 40–44 years of age. These data indicate that use of sterilization has decreased in the more recent survey in the UK and the USA, where the prevalence was especially high. Use of OCs is increasing in all three countries.

The dominant trend in reproduction among women more than 40 years of age is the decline in fecundity. Although the risk of pregnancy is lower in this age group, the acceptability of pregnancy

among most women over 40 is also lower, requiring the use of contraception until the menopause (Dutch Central Bureau of Statistics CBS, http://www.cbs.nl; UK Central Health Statistics, 2006, http://www.statistics.gov.uk).

Hormonal contraception after 40

The most common type of hormonal contraception are OCs which combines various forms of estrogen and progestin. The proportion of women aged 40–44 using an OC was 11% in the USA in 2002 and of British women aged 40–44 in 2007–2008 was 13% (Kaunitz, 2008; Lader and Hopkins, 2008) (Table IV). Other hormonal contraceptive methods also combine estrogen and progestin or rely on progestin alone. Combined hormone methods, besides the OC, are injectable suspensions medroxyprogesterone acetate (MPA + ethinyl estradiol (EE)), the transdermal patch (norelgestromin + EE) and the vaginal ring (etonogestrel + EE). A further method for emergency contraception sometimes involves use of combined OC pills (ESHRE Capri Worlkshop Group, 2002). Progestin only hormonal contraceptive methods include oral tablets, three monthly injections of depo-medroxyprogesterone acetate (DMPA), an intrauterine system that releases levonorgestrel [LNG-intrauterine system (IUS)] or a subdermal implant. The latest United Kingdom Contraception and Sexual Health survey indicates that OCs, DMPA and the LNG-IUS account for virtually all use of hormonal contraceptive methods in women aged 40–49 years. Use of the LNG-IUS by 5% of women in this age group may reflect the non-contraceptive indications for excessive bleeding.

Little is known about the pregnancy rate of hormonal contraception in women age 40–49 because reports involve average rates for all ages and women over 40 constitute a minority of users. Over all ages, with perfect use of OC only 0.3% of women would have a pregnancy in the first year of use, but this rises to 8% with typical use. Pregnancy rates are similar for the patch and ring. Typical first year pregnancy rates are 3% with injectable methods and 0.1% with the LNG-IUS (Trussell, 2004).

Typical pregnancy rates in women over 40 using contraception would be lower than these average rates for all ages because pregnancy rates decline with increasing age. The decline probably reflects a combination of declining fertility and declining frequency of coitus (Trussell, 2004). Also, women in this age group are more likely to be experienced previous contraceptive users who are in a steady relationship, factors which reduce pregnancy rates. Theoretically, because women more than 40 years of age have lower fertility, low dosage OCs may be the most appropriate choice, and continuous regimens may be more acceptable, but there are no data to support these choices.

As noted in a following section, hormonal contraception is associated with non-contraceptive benefits such as a reduction in risk of ovarian and endometrial cancer. Some non-contraceptive

Table III Use of family planning methods among women aged 40–44 years (%)

	Year	Sterilization			OC	IUD	Condom	Rhythm	Other	All
		Female		Male						
		a	b		c				d	
Canada	1995	29.5	23.6	17.6	1.2	1.9	6.7	0.5	2.8	84
Czech Repub.	1997	16.8		0.0	12.5	13.7	11.8	3.1	7.8	66
France	1994	6.9	5.9	0.1	20.3	25.5	3.7	7.8	7.4	78
France	2000	16.3		0.0	28.0	29.6	6.7	1.7	4.6	87
Greece	1999	10.0		0.0	1.1	4.5	21.8	2.6	24.7	65
Italy	1996	7.3		0.0	9.2	8.2	13.5	4.4	17.5	60
Netherlands (e)	1993	17		25	18	5	6		6	77
New Zealand	1995	22.0		31.0	10.0	4.5	6.4	1.6	1.9	77
Portugal	1996	16								n.a.
Spain	1995	19.6		12.0	5.1	8.5	20.7	3.0	15.7	85
Switzerland	1995	28.4		12.2	25.6	6.5	10.0	3.2	4.1	90
UK (f)	1993	25		23	7	7	14	1	3	79
UK (f)	2002	17	4	22	11	5	13	2	5	78
USA (f)	1988	51		22	3	4	11		4	66
USA (f)	2002	34.7		13.9	7.9	0.8	9.3	2.3	4.5	69

Table III References: Bajos *et al.* (2004), de Guibert-Lantoine and Leridon (1999), Martin and Wu (2000), Office for National Statistics UK (2004), Office of Population Censuses and Surveys UK (1995), United Nations Economic Commission for Europe. Fertility and Family Surveys: standard Country Report, U.S. Department of Health and Human Services (2006), Mosher (1990). OC, oral contraceptive; IUD, intrauterine device.
(a) Sterilizations 'for contraceptive reasons' only when available.
(b) Sterilizations 'for medical reasons' when available. Other 'infecund' not included.
(c) Including implants, patches, injectables.
(d) Withdrawal, douche, diaphragm, foam.
(e) 40–42 years.
(f) Multiple use excluded from total.

benefits of hormonal contraception are specific to the perimenopausal age group. Dysmenorrhea and acne are less common in this group of age, but menstrual irregularity or excessive bleeding are more common, compared with younger women. Menstrual irregularity can be improved although using hormonal contraception as can excessive bleeding, and the latter is especially responsive to the LNG-IUS (ESHRE Capri Workshop Group, 2008). Hormonal contraception also is effective in controlling vasomotor symptoms.

Effects of contraception on bone health may be of interest for women with high risk of osteoporosis. Bone mineral density (BMD) normally decreases in women during the later reproductive years (Kaunitz, 2008). A 2000 systematic review and a 2006 trial comparing three low dose OCs indicate that BMD increases with OC use in this age group (Kuohung *et al*., 2000; Gambacciani *et al*., 2006). BMD is a surrogate outcome, but hip fracture risk also may be reduced. Among post-menopausal women (130 hip fracture cases and 562 population controls) in Sweden, the odds ratio for hip fracture with OC use was 0.75 (95% CI, 0.59–0.96) (Michaëlsson *et al*., 1999).

Age alone is not a contraindication to the use of hormonal contraceptive methods (Faculty of Family Planning and Reproductive Health Care, 2005).

Estrogen and progestogen combinations are contraindicated, however, if there exist risk factors for arterial or venous thromboembolic disease, and many of these risk factors increase with age (excess weight, smoking, hypertension, hyperlipidemia, diabetes, migraine). Also, base line rates of most cardiovascular and neoplastic conditions are higher in 40-year-old than 20-year-old women. The effect of hormonal contraception on such conditions is considered in a following section.

Appropriate advice requires clinicians to take a history that will allow assessment of medical eligibility. Helpful guidelines for medical eligibility have been published by the World Health Organization (2004). Especially when considering estrogen-containing contraception, the history of venous thromboembolism in the patient and her family is important as is obesity.

Table IV Current use of hormonal contraception by UK women using at least one method (Table adapted from Table 2.3 in Lader and Hopkins, 2008)

	Age (years)					
	20–24	25–29	30–34	35–39	40–44	45–49
OC pill	67	57	42	26	13	8
Injection	9	3	1	3	3	1
Implant	3	3	1	1	1	0
Patch	0	–	1	1	–	–
Hormonal IUS	1	4	2	7	7	3
Emergency contraception	3	0	–	2	–	–

Where no answers for a particular response were given are indicated in the table by '–'.
OC, oral contraceptive; IUS, intrauterine system.

Cardiovascular and cancer risk of hormonal contraception in women more than 40 years of age

Cardiovascular disease

Studies conducted in the 1960s and early 1970s showed a strong association between first generation, high estrogen and progestogen OCs and the risk of thromboembolic disease, myocardial infarction and (mainly ischemic) stroke. Most of the excess risk has later been avoided by reducing the hormone levels in OCs, as well as by avoiding OC use for women above age 35 who are smokers or hypertensive. The use of OC in women of older reproductive age is however still of possible concern, given that over 10% of women between 40 and 44 years of age in the USA reported using OC in 2002 (Kaunitz, 2008).

The issue of smoking is now much better quantified: the health risks of smoking are so large that smoking cessation is the first priority. Thus the advice given in the past to restrict OC use in smokers should be reversed, that is, first all women should stop smoking. Hypertension can now be better controlled.

Newer OCs are remarkably safe in young women, and only a blood pressure measurement is required for their use in women below age 35. OC use is associated, however, with a relative risk (RR) of the order of 1.5 to 3 of venous thromboembolisms, myocardial infarction and (ischemic) stroke (World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1997; La Vecchia and Franceschi, 2002). There is no indication that the RR differs in various age groups, but the absolute risk (incidence) of vascular disease increases substantially with age, increasing the impact of the association. Venous and arterial thromboembolism rates are similar between standard products and relatively recent products such as drospirenone (Dinger *et al*., 2007).

Thus, OC use in women above age 40 and, particularly, above age 45, when cardiovascular diseases are no longer extremely rare events in women, should be considered in terms of risks and benefits, and discussed with the woman before prescription.

Cancer

Reasoning about the balance of risks and benefits also applies to cancer risk in this age group. Current OC use has been associated with a moderate excess risk of breast and cervical cancers. There are scanty data on the risk of these neoplasms among older women who are recent or current users, but they do not indicate substantial differences in the RR as compared with younger women (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; International Collaboration of Epidemiological Studies of Cervical Cancer, 2007). Thus, as for vascular disease, since cancer incidence increases with age, the absolute risk of current OC use on breast and cervical cancers would be appreciably larger above age 35 or 40 than in young women. However, at least in developed countries, invasive cervical cancer is avoided by adequate Pap smear screening, and hence the public health consequences of OC use in older women would be negligible in those countries (but not in low resource ones) (La Vecchia and Bosetti, 2003). Breast cancer is more difficult to

prevent, and consequently the moderate excess risk of breast cancer in current and recent OC users is an additional reason to restrict OC use in aged women, particularly in those with positive family history or high mammographic density.

OC use reduces the risk of ovarian and endometrial cancer. The protection for both these neoplasms appears to be long lasting, i.e. to last at least 15–20 years after stopping OC use (Fig. 3) (La Vecchia and Bosetti, 2004; La Vecchia, 2006, Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008). There is little indication, however, that the favourable effect of OC use on ovarian and endometrial cancers is appreciably influenced by age at use, i.e. that the protection is greater, in relative and absolute terms, for older women.

Ever use of OC is associated with an approximately 20% reduction in the risk of colorectal cancer, in the absence however, of a duration--risk relation. Data are inadequate for evaluation in older women (Fernandez *et al.*, 2001).

Most risk assessments for OC use in aged women apply to current or recent users. It is now known, in fact, that OC use is not associated in the long-term with overall increased risk of vascular disease or cancer, and indeed it may produce a net long-term reduction of overall cancer risk. After about 35 year follow-up in the Royal College of General Practitioner study the RR for all cancers in OC users compared with non-users was 0.88 (95% CI, 0.83–0.94) consistent with a public health gain (Hannaford *et al.*, 2007).

Non-hormonal contraceptive choices

Given the relationship between age and systemic diseases, non-hormonal methods of family planning may be preferred by older women. But since no such general preference exists, the over 40 woman asking for contraception should be provided with individualized advice. Table V shows the current use of non-hormonal contraception by women using at least one method in the over 40 age group.

As for hormonal contraception, reliable effectiveness data are not available by age group. Table VI shows the effectiveness of non-hormonal methods for users of average age.

As with hormonal contraception, failure rates may be lower after 40 years of age due to declining fertility and less frequent intercourse. Continuation rates for users of non-hormonal methods of average age are generally higher than 50% at 1 year, and may be higher still among women over 40 years of age.

Of the non-hormonal contraceptive methods, absolute age-related contraindications do not exist for the copper IUD, barrier methods, fertility awareness methods or male and female sterilization. Fertility awareness methods, of course, will be less reliable in premenopausal women with irregular menstrual cycles. Table VII shows relative age-related (or age-associated) contraindications for the use of non-hormonal contraception in women over 40.

Copper IUDs should not be used in women with a distorted uterine cavity and may be ill-advised in women on anticoagulants, but in these cases the relation with age is only indirect. Balancing these concerns, endometrial cancer risk is reduced by about half among women using IUDs (OR 0.5; 95% CI, 0.47–0.62) (Beining *et al.*, 2008).

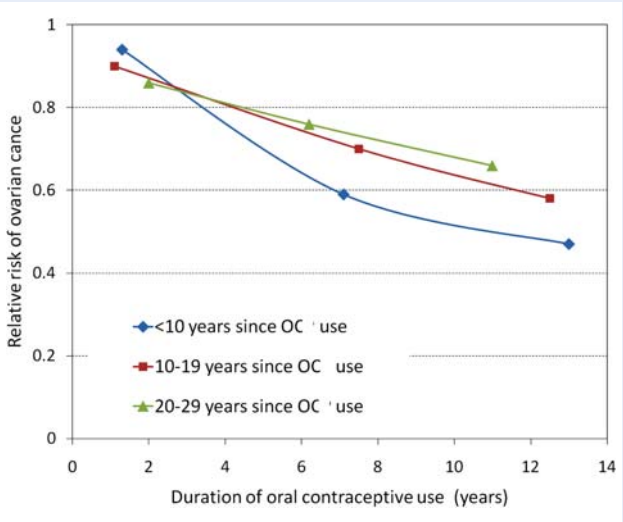

Figure 3 Relative risk of ovarian cancer associated with oral contraceptive (OC) use, plotted according to duration of use and time since last use.
Estimates stratified by age, parity and hysterectomy (adapted from Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008).

Contraception over 40: medical eligibility-discontinuation

The contraceptive method for a woman in her 40s should be individually tailored for an appropriate balance of effectiveness, non-contraceptive benefits and risks. Contraceptive failure is less likely because women over 40 are less fertile and more likely to be consistent and conscientious users (Trussell, 2004). Other special circumstances include the presence of hot flushes in women who have entered the perimenopause, which may suggest oral contraception for its beneficial impact (Blümel *et al.*, 2001). Infrequent sexual intercourse may indicate a barrier method such as the condom, with its freedom from systemic side-effects. Marital breakdown is not uncommon and new relationships may lead to increased risk of sexually transmitted infections and the need for condoms. Regardless of the special considerations, for most women aged 40 or more who are not in the menopause, contraception remains necessary.

The data in Tables V and VI show that the contraceptive options that are most widely used among women age 40–49 include male sterilization, tubal sterilization, male condoms, OC pills, withdrawal, intrauterine devices and the intrauterine system, in that order. Other theoretically effective methods are not in common use and need further testing in women who are more than 40 years of age. Examples are the monthly injectable system, the contraceptive vaginal ring and the transdermal contraceptive system. Effectiveness and major non-contraceptive benefits of the most frequently used methods are summarized in Table VIII.

Diaphragms with spermicide are more effective than natural methods and may be acceptable options in older couples when fertility is declining. Women using barrier methods should be counseled about emergency contraception when the method is not available or if failure occurs during use. Barrier methods do not mask the symptoms

Table V Current use of non-hormonal contraception by women using at least one method, 2006/2007 (UK Central Health Statistics, 2006, http://www.statistics.gov.uk)

Method	Current use (%)	
	Age 40–44 (n = 165)	Age 45–49 (n = 178)
Partner sterilized	30	28
Condom	20	16
Woman sterilized	18	29
Withdrawal	6	4
Intrauterine device (IUD)	6	7
Rhythm method	3	3
Female condom	1	–

Percentages sum to more than 100 as respondents could give more than one answer.

Table VI Unintended pregnancy during the first year of typical use or ideal use of non-hormonal contraceptive methods (Trussell, 2004)

Method	Pregnancy in first year (%)		Percent continuing use at 1 year
	Typical Use	Ideal Use	
Partner sterilized	0.15	0.1	100
Woman sterilized	0.5	0.5	100
Condom	15	2	53
Withdrawal	27	4	43
Copper intrauterine device	0.8	0.6	78
Rhythm methods	25	2–9	51
Female condom	21	5	49

associated with the menopause. Condoms are more effective than other barrier methods and have the added benefit of protection against sexual transmitted infections (STIs).

OC can be continued until the menopause in low risk women who do not smoke since recent epidemiological and clinical pharmacology studies have indicated the safety of extending the use of combined OCs beyond the age of 40 years (Faculty of Family Planning and Reproductive Health Care, 2005). It is important not to rely on menopausal hormone treatment for contraception, as the hormone dosage is lower and the level of effectiveness is not yet known. Women who have contraindications for estrogen use or personal reasons for avoiding OC can use barrier methods, progestogen-only contraceptives, including pills, LNG-IUS, depot injectables and implants. Implants combine high efficacy with a long-term effect. The World Health Organization Medical Eligibility Criteria for Contraceptive Use provides evidence-based recommendations to help to select the most appropriate method of contraception in women with potential medical barriers (World Health Organization, 2004).

Table VII Contraception in women over 40, eligibility criteria for non-hormonal methods (Adapted from: World Health Organization, Medical Eligibility Criteria for Contraceptive Use; Faculty of Family Planning and Reproductive Health Care, 2006, http://www.ffprhc.org.uk)

Methods	Remarks
Copper IUD	Advanced age is not a special risk factor and neither is parity. Smoking and body weight do not affect reliability. Arterial or venous thromboembolism are not contraindications, unless anticoagulants are used. Antibiotic prophylaxis during insertion is indicated in patients with artificial heart valves or previous endocarditis. Unexplained bleeding is an absolute contraindication against insertion as are genital cancers before being treated. A distorted uterine cavity, purulent cervicitis or pelvic inflammatory disease are contraindications. Being at risk of HIV/AIDS does not increase the risk of complications with insertion or with continuation of the IUD
Barrier methods/ spermicides	Advanced age is not a special risk factor. Weight increase of >3 kg may affect diaphragm fitting and reliability. Repeated use of high-dose nonoxynol spermicide may increase risk of genital lesions, which in turn may increase HIV risk. Because diaphragms and cervical caps do not protect against HIV and other sexually transmitted infections, condom use is also required
Fertility awareness	Advanced age is not a special risk factor, but menstrual cycle irregularity associated with age makes identification of fertile days of the menstrual cycle difficult. Combination with a barrier method is advised
Sterilization	Advanced age is not a special risk factor, but older women establish new relationships more frequently nowadays. Since sterilization should be considered irreversible, alternative long-acting reversible methods which are equally effective may be preferred since they offer additional benefits

Copper-releasing IUDs and the LNG-IUS combine the advantages of high efficacy and long-term effect. The reduced fecundity above the age of 40 can allow extending IUD or IUS use beyond the approved term, up to 1 or 2 years beyond the menopause without the need for replacement (Sivin, 2007). In some patients a copper-releasing device may exacerbate menstrual problems, but the LNG-IUS is highly effective in reducing the amount of menstrual bleeding (ESHRE Capri Workshop Group, 2008). Copper IUD use is associated with a significant 46% reduction in the risk of endometrial cancer (Beining *et al.*, 2008).

Male or female sterilization is an excellent contraceptive option, provided that this approach is culturally acceptable and available at reasonable cost and low risk. Sterilization methods have the lowest failure rates of any other methods (Trussell, 2004).

After a systematic consultation and according to each one's contraceptive needs, women should receive accurate individualized advice on the risks and benefits of contraceptive methods to cover the choice between the newer, effective, reversible methods and sterilization.

One further important issue to address is when to advise an older woman to discontinue hormonal or non-hormonal contraception. At some point, the unprotected pregnancy rate becomes lower than the failure rate with effective contraceptive methods in younger women. In a woman on hormonal contraceptives, the non-contraceptive benefits should be taken into account as well as her eventual interest in HRT. In non-hormonal contraception discontinuation of the contraceptive may be considered after 2 years of amenorrhea in women below 50, and after 1 year in women over 50 years of age. Ovarian exhaustion is likely if FSH, on two occasions, 6–8 weeks apart, is >30 IU/l (Bhathena and Guillebaud, 2006). After the age of 55 natural sterility can be presumed. After age 35 a copper IUD does not need to be replaced if it is not causing any problems (Faculty of Family Planning and Reproductive Health Care, 2005; Sivin 2007).

Conclusions

(i) Although risk of pregnancy is lower in this age group, the acceptance of pregnancy is also lower with more women having elective abortions, so there is a need for contraception.

(ii) Although all reproductive organs age, it is the ageing of the ovary that is dominant, so that some time between age 45 and 55 women become sterile, when the number and quality of the oocytes declines below a critical mass.

(iii) There is a need for studies of the potential for predicting the absolute size of the follicle pool, and thus the onset of menopause by means of estimations of FSH, inhibin B and AMH, of which the latter is the most precise predictor.

(iv) Reasons for delayed childbearing are complex, although studies indicate that the perception of the current relationship is the main reason. Women who reject future childbearing may consider definitive methods. Those considering possible future childbearing should avoid irreversible methods.

(v) Women may perceive that a satisfactory sex life is as important at this time of life as the prevention of pregnancy, and practitioners should be aware of these additional needs, over and above simple contraception. Although only 10% of women may need medical attention for sexual problems, the majority are not getting this attention.

(vi) With pregnancy in women aged 40 or over, increased aneuploidy rates lead to 5- to 8-fold increases in early pregnancy loss and chromosomal abnormalities at birth. Pregnancy complications, neonatal risks and perinatal mortality rise gradually with age and are up to 2-fold higher at age 40–44 than they are at age 35–39.

(vii) Non-hormonal contraception is the most common choice in women after age 40, with the majority relying on sterilization or condoms.

(viii) Combination OC pills are the most commonly used hormonal contraceptives in women after age 40. Failure rates decline with increasing age, reflecting a combination of declining fertility and declining frequency of coitus and the fact that older women are less likely to be first time users.

(ix) Current or recent OC use is associated with moderate increased risk of breast, cervical cancer and vascular disease. These excess risks are particularly relevant for women over 40 because their base line risks are higher than in younger women.

(x) Nevertheless, OC use is not associated in the long-term with an overall lifetime increased risk of vascular disease or cancer, and indeed it may produce a net long-term reduction of overall cancer risk, due to the long-term protection on ovarian, endometrial and probably colorectal cancers.

(xi) Special circumstances include the presence of hot flushes in women who have entered the perimenopause, the possibility that sexual intercourse may be infrequent and the frequency of irregular bleeding.

(xii) The contraceptive method for a woman in her 40s should be tailored to provide a balance of effectiveness, non-contraceptive benefits and risks.

(xiii) Hormone replacement therapy is not a reliable contraceptive and women should be advised to continue with a contraceptive method until they have reached the menopause with its natural state of sterility.

Table VIII Effectiveness and non-contraceptive benefits associated with various methods of contraception among women more than 40 years of age (Trussell, 2004)

Method	Effect*	Non-contraceptive benefits	Main risks
Natural	25–30		Failure
Barrier	16–20		Failure
Condom	15	STI prevention	Not available
OC	8	Reduces bleeding, bone loss, and ovarian and endometrial cancer risks	Arterial and venous thrombosis
Progestin only	8	Reduces ovarian and endometrial cancer risks	Irregular bleeding
Copper IUD	<1	Reduces endometrial cancer risks	Irregular bleeding
LNG IUS	<1	Reduces bleeding	Expulsion
Female sterilization	<1	Reduces ovarian cancer risk	Not reversible
Male sterilization	<1		Not reversible

*First year failure rate (%) with typical use. OC, oral contraceptive; IUD, intrauterine device; LNG IUS, levonogestrel releasing intrauterine system.

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