

IPPF Medical Bulletin

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IMAP Statement on Contraception for women aged over 35 years

Introduction

Women over the age of 35 constitute at least 20 per cent of contraceptive users. The period from age 35 to menopause can be referred to as the transition years. Although fertility is reduced in women of this age group, higher rates of complications make unintended pregnancies potentially more hazardous. The risks of congenital and chromosomal abnormalities, pregnancy complications, and maternal morbidity and mortality increase for women over the age of 40 years.

As age increases, fertility decreases for women and to a lesser degree for men. Intermittent ovulation and anovulation occur, and therefore effective contraception is required for sexually active women, to prevent unintended pregnancy.

There are no contraceptive methods that are contra-indicated on the basis of age alone. For a woman of any age, continuation and efficacy of contraception are optimized if she is using her own choice of method. Communicating the benefits and risks associated with contraceptive use involves an exchange of clear, accurate information in order to enable clients to make informed decisions. Factors that may affect the choice and use of contraceptive methods include the achievement of desired family size, lifestyle and relationship issues with partner(s), and physical status, such as obesity, diabetes mellitus, hypertension, and smoking habits. The choice of method is also affected by the woman's previous contraceptive experience, frequency of sexual intercourse, sexual function and concurrent medical condition, as well as the desire for non-contraceptive benefits, which can include the treatment of peri-menopausal symptoms such as menstrual irregularity. All methods can be considered, after proper health screening and discussion of their benefits and risks.

The service provider should take a clinical history (including sexual and reproductive history) to assess medical eligibility for contraceptive use, taking into account current malignancies such as breast and liver cancer, cardio/cerebrovascular diseases and risk

factors (such as stroke, heart attack, blood clot and diabetes) all of which may increase with age. A sexual history can assist in gauging the risk of sexually transmitted infection (STI).

Choice of Methods

Hormonal Contraception

Combined hormonal contraception

Combined hormonal contraception is available as combined oral contraceptives (COC), injectables, patch or vaginal ring. There may be an increased risk of cardiovascular disease with COC use in women over 35 years of age. The increase is very slight in non-smokers who have no other risk factors, such as hypertension or diabetes. Therefore, low-dose COCs may be used by women over 35, as they provide contraception and prophylaxis against irregular, heavy anovulatory bleeding and the risk of hyperplasia and neoplasia of the endometrium.

Combined once-a-month injectable contraceptives (CICs) may be an option for healthy women over 35. Laboratory studies have shown that they have no, or very little, effect on coagulation factors and metabolism. However, there are no epidemiological data on the effect of CICs on the risk of cardiovascular disease. By extrapolation from the COC studies, any possible increase of risk, among women who do not smoke and have no other risk factors (e.g. hypertension or diabetes mellitus), is expected to be slight.

The annual risk of breast cancer rises with age regardless of hormone use. By the age of 35 years a woman has a 1 in 500 risk of developing breast cancer. The risk is 1 in 100 by the age of 45 years. The advantages and disadvantages of COCs for older women should be set against those of other contraceptives which are available and acceptable to the client, and against the risks associated with unintended pregnancy.

Smoking is an independent risk factor for cardiovascular disease. Women over 35 years of age, with no other risk factors, and who have stopped smoking for more than a year, may consider using combined hormonal contraception. The elevated risk of myocardial infarction associated with smoking, among users of combined hormonal contraception, falls significantly one year after cessation of use and is gone after another three to four years, regardless of the amount of tobacco smoked. The use of combined hormonal contraception for women over 35 years who currently smoke is not recommended.¹

Progestogen-only contraception (POC)

POC is available as pills, injectables, implants and the levonorgestrel-releasing intrauterine system (LNG-IUS). POC offers the advantage of freedom from the oestrogen-related side-effects which can occur with combined hormonal methods such as COCs. The high, and long-term, effectiveness of injectables and implants and the levonorgestrel-releasing intra-uterine system (LNG-IUS) may be especially attractive to women aged over 35. Bleeding problems could occur, masking or simulating that bleeding which is a symptom of gynaecological disease.

A possible hypo-oestrogenic effect of progestogen-only injectables may result in an accelerated loss of bone tissue. Long-

term use of progestogen-only injectable contraception, in particular depot medroxyprogesterone acetate (DMPA), is associated with a reduction in bone mineral density but it returns to normal levels gradually after cessation of contraception use. There is currently no evidence of any relationship between bone mineral densitometry and fracture risk in women over 35 years who use injectable POC^{2,3}. As stated in the WHO Medical eligibility criteria, the benefits of using DMPA in women aged over 45 outweigh any risks.

Although data are limited, there is no apparent increase in risk of cardiovascular disease or stroke with POC. For women with current venous thromboembolism (VTE), the risk of using POC outweighs the benefits. Those with a history of ischaemic heart disease or stroke should be advised that the risk of initiating a progestogen-only injectable method (POI) outweighs the benefits. However, the benefits of initiating progestogen-only pills (POPs), implants or the LNG-IUS, outweigh the risks for most women. There is no evidence to suggest a significant increase in the risk of breast cancer associated with POC. In addition to the contraceptive benefits, progestogen-only methods may reduce the risk of endometrial and ovarian cancers.⁴

Emergency contraception (EC)

The use of the dedicated emergency contraceptive pill (LNG-only) is safe for women over 35 years. LNG EC pills have been in use for several decades and current research shows no association with increased risk of cancer.⁵ The most convenient regimen is a single dose consisting of 1.5 mg levonorgestrel taken as soon as possible after unprotected intercourse. It provides maximum protection if taken within 72 hours (3 days) of unprotected intercourse and some protection up to 120 hours (5 days), although efficacy is much reduced. The duration of use of ECPs is shorter than that of the regular use of COCs or POPs, and thus has a smaller clinical impact, so its use by women with migraine and hypertension is not contraindicated. While oestrogens contained in many contraceptives pills are associated with some (very low) risk of stroke and venous thrombo-embolism, especially in women over 35 who smoke, no such risks are associated with levonorgestrel. Repeated use of ECP is not recommended; not because of the level of hormones ingested, but rather because repeated use during the cycle may lead to irregular bleeding or unpredictable cycles. The combined oestrogen-progestin regimen for emergency contraception consists of two 50 µg ethinyl estradiol/0.25 mg levonorgestrel pills, or four 30 µg ethinyl estradiol/0.15 mg levonorgestrel pills, taken as soon as possible within 72 hours after unprotected intercourse, followed by a second, similar dose 12 hours later. This method shows little efficacy after 72 hours. Service providers and pharmacists should give contraceptive counselling to clients seeking ECP, to support them in making an informed choice for regular contraception. ECPs do not protect against STI/HIV.

Intrauterine devices

The copper T intrauterine device (CuT IUD) and LNG-IUS are among the most effective contraceptives. The CuT IUD is a long-acting, effective method with no systemic effects. A non-contraceptive benefit of the LNG-IUS is that it is associated with the reduction of the heavy bleeding that may become increasingly common during the perimenopause. Any increased risk of pelvic infection with contemporary IUDs is limited to the insertion procedure and the subsequent transportation of pathogens to the upper genital tract. Careful screening for STIs and the use of good aseptic technique are very effective in minimizing this risk. Women should be informed that menstrual abnormalities, including spotting, light bleeding, heavy or longer menstrual periods, are common in the first three to six months of CuT IUD use. They should be advised to seek medical advice to exclude infection and gynaecological pathology, if menstrual abnormalities occur after the first six months of use.

Contra-indications to the use of IUDs include fibroids or other

uterine abnormalities with known distortion of the uterine cavity, undiagnosed abnormal vaginal bleeding and current cervical or endometrial cancer before treatment. Fibroids, which impede the correct placement of a device, are more common in the over-35 age group. While diabetes mellitus becomes more prevalent with age, no increase in adverse event has been observed for CuT IUD use in women with either insulin-dependent or non-insulin-dependent diabetes at any age.

For women with heavy menstrual periods, the LNG-IUS can be a good alternative to a copper-bearing device, because it may reduce the volume of bleeding, aside from the contraceptive effects. The LNG-IUS may help reduce the risk of pelvic infection. It is effective in protecting the endometrium against hyperplasia (abnormal thickening of the uterine lining) in women using tamoxifen or postmenopausal oestrogen. The LNG-IUS can also be used to treat endometrial hyperplasia. Despite the protective mechanism of the LNG-IUS, service providers should manage unusual bleeding with care and consider referral to rule out endometrial carcinoma.

Barrier methods

Barrier methods include male and female condoms, and the diaphragm or cervical cap. They have no known significant side-effects, but are coitally-dependent. Barrier methods are generally less effective than hormonal methods and intrauterine devices, but they provide protection, especially when used consistently and correctly.

Table. First year failure rates for barrier methods in USA⁶

Method	% failure with perfect use	% failure with typical use
Male condoms	2	17.4
Female condoms	5	27
Diaphragm	6	16
Cervical cap. Nulliparous	9	16
Parous	26	32

When counselling clients, it should be emphasized that improper or inconsistent use of these methods is associated with high failure rates. Both male and female condoms provide dual protection against STIs and unintended pregnancy. The female condom is an effective, woman-controlled contraceptive method; its disadvantages are limited acceptability and high cost.

Pregnancy rates for diaphragm use range between 4 and 18 per 100 women per year. The current recommendation is to use the diaphragm in combination with a spermicide. Clients should be advised that, although the diaphragm offers some defence against upper genital tract STIs, its ability to protect against HIV is unknown.

Relative contra-indications for the use of diaphragms include allergic reactions to latex, repeated urinary tract infections, and conditions that prevent adequate fitting (such as uterine prolapse).

Spermicides, because of their low effectiveness, should be used mainly in conjunction with barrier methods. The lubricating effect of spermicides may be an advantage to women in this age group, for whom dryness of the vagina can cause discomfort during sexual intercourse. For women who are at high risk of HIV, repeated and high-dose use of the spermicide nonoxynol-9 has been associated with increased risk of genital lesions, which may augment the risk of acquiring HIV infection.

Fertility awareness methods

Fertility awareness methods of family planning involve identification of the fertile days of the menstrual cycle, whether by observing fertility signs such as cervical secretions and basal body temperature, or by monitoring cycle days. These methods can be used in

combination with barrier methods, or with periodic abstinence, during the fertile time.

Despite their relatively low use-effectiveness, methods based on periodic abstinence may be more acceptable to women over 35 than to younger women. Older couples are more likely to follow the instructions for identifying the fertile phase of the cycle and to abstain from intercourse when necessary.

Fertility awareness methods can be used by women in this age group, but with special counselling and extreme caution. In pre-menopausal women with irregular menstrual cycles, periodic abstinence techniques are unsuitable, whether based on changes in cervical mucus (interpretation of which becomes more difficult towards the end of fertile life) or basal body temperature (because biphasic changes are absent in anovulatory cycles). If couples rely on the basal body temperature method, long periods of abstinence will be necessary.

Coitus interruptus

Women with conditions which make pregnancy an unacceptable risk should be advised that coitus interruptus (withdrawal) may not be appropriate for them, because of its relatively high typical-use failure rates. A further disadvantage is that it does not protect against STI/HIV.

Surgical sterilization

Women who do not want to have children may choose sterilization. Globally, sterilization is the most common method of contraception: female sterilization accounts for 34% and vasectomy 5.6% of all contraceptive use.⁷ The individual seeking sterilization (or the couple, as appropriate) needs to be given adequate knowledge and counselling before an informed decision is made. Careful counselling is needed on the permanence of the procedure and the availability of long-acting, reversible methods of contraception as an option for long-term protection against unwanted pregnancy. Vasectomy carries a lower failure rate and there is less risk related to the surgical procedure. For women, it may be important to weigh the risk of complications, or the risks associated with the surgical procedure, against the number of years for which the contraceptive protection will be needed. Women should be counselled that female sterilization does not cause menstrual problems and that menses will continue as they were, prior to sterilization.

Before operating, service providers should exclude the possibility of uterine disease or other gynaecological disorders that might necessitate additional surgery in the future. Hysterectomy should not be performed for the sole purpose of sterilization. The risk of tubal sterilization failure may be higher with certain techniques (spring-clip application and bipolar coagulation). However, the overall risk of tubal sterilization failure is very low. Pregnancies can occur even many years after tubal sterilization, and a high proportion of these are ectopic, which would require serious medical and surgical interventions. However, there is a lower risk of both pregnancy, and ectopic pregnancy, among women who have the sterilization procedure at an older age.

Male and female sterilization procedures and the associated risk are discussed in more detail in the IMAP Statement on voluntary surgical sterilization.

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Prevention of sexually transmitted and reproductive tract infections (STIs/RTIs)

It is important to note that, for all contraceptive methods, correct and consistent use of condoms is recommended to avoid acquisition of STIs/RTIs (including during pregnancy or postpartum), either alone or with another contraceptive method. Male latex condoms and female condoms are proven to protect against STI/HIV.

For further information on safe contraception for women with medical conditions, see the IMAP Statement, published in the IPPF Medical Bulletin, March 2010: “New recommendations on the safety of contraceptive methods for women with medical conditions: World Health Organization’s Medical eligibility criteria for contraceptive use, fourth edition”. Statement by the International Medical Advisory Panel (IMAP), 1997 revised in 2009. IPPF reserves the right to amend this statement in the light of further developments in this field.

Breakthrough in Microbicides Development

Naomi Rutenberg and John Townsend

Globally, the majority of new HIV infections are in women, underscoring that current prevention strategies are not always feasible for them and there is an urgent need for woman-initiated prevention strategies. A microbicide could be formulated as a gel, ring, film or suppository designed to be inserted into the vagina or rectum. It would provide protection by directly inactivating HIV, preventing HIV from attaching, entering or replicating in susceptible target cells (cells containing a type of protein which attracts the virus), or averting the dissemination of the virus from the target cells present in semen, or the host cells that line the vaginal or rectal walls. Microbicides are being developed primarily as woman-initiated methods to reduce male-to-female transmission of HIV, and possibly other sexually transmitted infections, during vaginal intercourse. However, microbicides (in forms other than rings) could also be inserted in the rectum and used to prevent HIV transmission during anal intercourse among heterosexual couples, as well as men who have sex with men. Finally, microbicide products could deliver or have contraceptive properties offering protection against unwanted pregnancies.

Six microbicide products with varying mechanisms of action, though none containing an antiretroviral compound, have failed in

Phase 3 trials to be effective and/or safe for users exposed to the risk of HIV acquisition. Thus the results of the CAPRISA (Centre for AIDS Programme of Research in South Africa) 004 trial announced in July, 2010 represent a significant breakthrough for microbicides development. CAPRISA 004 is the first completed trial to evaluate the effectiveness of an ARV-based candidate microbicide gel for the prevention of sexually transmitted HIV infection among women. The CAPRISA 004 trial tested a microbicide gel that contained a 1% concentration of the antiretroviral (ARV) drug tenofovir in a gel formulation. Tenofovir is an ARV drug that is used as an oral treatment for HIV in many countries and is licensed for use as an HIV treatment in South Africa. In vitro and in vivo assessments and monkey challenge studies of the 1% concentration of tenofovir in a gel formulation demonstrated its potential as a microbicide. In early stage clinical trials, tenofovir gel was well tolerated in both HIV- negative and HIV- positive women, and use of the gel, both daily and coitally-related, was found to be acceptable and safe.

The CAPRISA study, which started in May 2007, enrolled 889 sexually active, HIV-uninfected women at two sites in South Africa. The women were randomly assigned to one of two study groups - placebo gel with no active ingredient, or tenofovir gel - and instructed to use the study product before and after sex, but not to exceed two doses in a 24-hour period, regardless of the frequency of intercourse. All participants received condoms, intensive counselling, and other routine interventions for reducing HIV risk

throughout the time they were in the trial. The trial was conducted by CAPRISA in partnership with the US-based organizations FHI and CONRAD with funding from USAID. Gilead Sciences donated the active ingredient for the manufacture of the tenofovir gel.

The microbicide gel containing tenofovir reduced sexual transmission of HIV infection by 39%. At the end of the CAPRISA 004 trial, 38 new HIV infections had occurred among women who received 1% tenofovir gel plus the standard prevention package, and 60 new HIV infections among women who had received the placebo gel plus the standard prevention package. The 95 per cent confidence interval associated with the point estimate of 39 per cent effectiveness was 6 to 60, and the p-value was 0.017. The 95 per cent confidence interval reflects a plausible range for the true effectiveness of one per cent tenofovir gel in the study population. Simply put, the CAPRISA statistics say that the trial conclusion, that 1% tenofovir gel provides some protection against HIV, is highly likely to be true. However, the level of protection could be at any point from 6 to 60 per cent, so it is likely that another confirmatory trial will be required.

1% tenofovir gel had greater effectiveness in women who had high rates of consistent gel use. Adherence was calculated by looking at the number of used applicators each woman returned at a study visit and the number of sex acts she reported having experienced since the last study visit. Women were defined as *high adherers*, if they returned at least two gel applicators which had been used for more than 80 per cent of their reported sex acts. There were 54 per cent fewer infections among high adherers who received 1% tenofovir gel, compared to high adherers who received the placebo. This difference was statistically significant. Among *intermediate adherers*, women who used at least two applicators for 50–80 per cent of their sex acts, there were 38 per cent fewer infections among those who received 1% tenofovir gel, compared to those who received the placebo. Among *low adherers*, women who used at least two applicators for less than 50 per cent of reported sex acts, there were 28 per cent fewer infections among those who received 1% tenofovir gel, compared to those who received the placebo. However, neither of these differences was statistically significant.

Coitally-related tenofovir gel use in the CAPRISA 004 trial was safe. There was no increase in the overall rate of side effects among study participants in the tenofovir arm other than mild and self-limiting diarrhoea; this may have been due to a local tenofovir effect. There was no renal toxicity, which was the most important tenofovir-related safety concern, although it should be noted that the study excluded women with compromised creatinine clearance at enrolment. Increases in hepatic flares, which have been reported upon cessation of oral tenofovir use in hepatitis B-infected individuals, were not observed in this study, possibly due to the low systemic absorption of tenofovir from the gel formulation. No safety concerns were identified in the 22 women exposed to tenofovir gel in early pregnancy. No tenofovir-related resistance was found in the 35 women exposed to tenofovir gel early in acute HIV infection.

One unexpected and exciting finding from CAPRISA 004 was that, among women who were uninfected with herpes simplex virus type 2 (HSV-2) at the start of the trial, there was a significantly lower risk of acquiring HSV-2 for those who used 1% tenofovir gel, compared to HSV-2 negative women using the placebo. 29 out of 202 HSV-2 negative women using 1% tenofovir gel acquired HSV-2 during the trial, compared to 58 out of 224 HSV-2 negative women using placebo gel. This translated to a point estimate of effectiveness of 51 per cent protection against HSV-2. The 95 per cent confidence interval for this result was 21 to 70. This result was statistically significant. Reduction

in the risk of HSV-2 infection could be an additional benefit of using the gel. This effect could also enhance the HIV-prevention benefit of 1% tenofovir gel, since HSV-2 increases the risk of HIV infection among HIV-negative people.

CAPRISA 004 provides a proof-of-concept, but more information is needed about effectiveness, adherence strategies and other issues, to support registration and widespread introduction of 1% tenofovir gel. In addition, the trial was conducted among known high-risk populations based on the results of pre-trial feasibility studies. The HIV incidence rates in the trial - 5.6 per 100 woman years in the tenofovir gel arm, and 9.1 per 100 woman years in the placebo gel group - are very high. More data from additional sites are needed to generalize this result. A group of key decision makers met in South Africa in August, 2010 to develop a comprehensive research agenda to build on the results of the CAPRISA 004 microbicide gel trial. At that meeting, public health officials, researchers, and regulators developed a consensus plan for a set of studies aimed at confirming the CAPRISA 004 results, obtaining evidence on alternative dosing strategies such as a single coitus-dependent dose and daily dosing, and developing implementation strategies.

Additional microbicides in both gel and ring formulations, using a range of anti-viral agents, are under development in several sites around the world, and the CAPRISA 004 results offer the promise of new products in progress. For example, the Population Council and International Partnership for Microbicides (IPM), with funding from the Bill & Melinda Gates Foundation, have begun the development of a dual-protection vaginal ring, which is being formulated to protect women against both pregnancy and HIV infection.

What does this mean for IPPF in countries where HIV is endemic? Member Associations (MAs) should ensure that their medical and counselling staff are familiar with the development of HIV prevention and dual protection technologies. MAs might consider collaborating with development teams to test the efficacy and safety of new products, including the introduction of the new products in their national programmes. At the same time, it is clear that client counselling should include a range of prevention technologies until a highly effective HIV prevention is developed. Strategies for risk reduction, including partner reduction and consistent condom use for women, and the addition of circumcision for men, will remain key elements of any comprehensive prevention strategy.

Naomi Rutenberg, Ph.D. is Vice President and Director, HIV and AIDS Program

John W. Townsend, Ph.D. is Vice President and Director, Reproductive Health Program, Population Council

4301 Connecticut Ave NW, Suite 280

Washington DC 20008

Tel: 202-237-9400

Fax: 202-237-8410

Email: nrutenberg@popcouncil.org

Web: www.popcouncil.org <http://www.popcouncil.org/>

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