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Family planning 2011: better use of existing methods, new strategies and more informed choices for female contraception

The ESHRE Capri Workshop Group[†]

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BACKGROUND: This paper explores recent developments in female contraception, using them to illustrate how adaptation of existing methods, improved service delivery and understanding contraceptive behaviour might increase contraceptive uptake and correct and consistent use, and how the development of new methods holds some promise for capitalizing on the potential non-contraceptive benefits.

METHODS: Searches were performed in Medline and other databases. Selection criteria included high-quality studies and studies relevant to clinical reproductive medicine. Summaries were presented and discussed by the European Society of Human Reproduction and Embryology (ESHRE) Workshop Group.

RESULTS: The topics discussed include: adapted regimens for combined oral contraceptive pills, non-invasive methods of female sterilization, the need to improve the awareness of pregnancy risk to increase the use of emergency contraception, improvements in the evidence base for the safety and service delivery of intrauterine methods, emphasis on the potential benefits of combined oral contraceptives for women with hirsutism and acne, the potential of female sterilization to prevent ovarian cancer, and the promise of anti-progesterones and new approaches to dual protection.

CONCLUSIONS: Although great strides have been made in recent years in increasing contraceptive use among women in many countries where contraceptive prevalence is low or there is a high unmet need for contraception, much more can, and needs to, be done.

Key words: family planning / contraception / sterilization / anti-progestins / ovarian cancer

[†] List of the ESHRE Capri Workshop Group participants is given in the Appendix.

Introduction

Throughout history, couples have tried to limit their family size. Until the 20th century, this was achieved largely by abstinence, infrequent coitus, coitus interruptus condoms, breast-feeding and induced (often illegal) abortion. Modern methods of contraception have only been around for some 100 years and hormonal contraception for only 50. Despite a wide range of methods with different delivery systems and regimens, contraceptive uptake by women in some parts of the world remains low, and even where it is high, unintended pregnancy remains common. This European Society of Human Reproduction and Embryology Capri workshop set out to discuss the need to continue to develop new methods of contraception as well as interventions aimed at improving contraceptive use while waiting for those new methods to reach the market. Using a number of examples from recent research findings, adaptations of existing methods, efforts at understanding contraceptive behaviour and strategies to improve services are discussed.

Methods

Searches were performed in Medline and other databases by individual participants in the workshop. Selection criteria included high-quality studies, and studies relevant to clinical reproductive medicine. Each subject summary was presented to the European Society of Human Reproduction and Embryology (ESHRE) Workshop Group where omissions or disagreements were resolved by discussion.

Results

Why more contraceptive are methods

The last 50 years have witnessed a massive increase in the use of contraception, which rightly could be described as one of the public health successes of the 20th century. Overall, in developing countries, contraceptive prevalence increased from a mere 10% in the early 1960s to some 60% by 2009, a level approaching the over 70% rate of developed countries. When only modern methods are considered, the current difference in rates between developing (55%) and developed (61%) countries is even smaller (United Nations, 2011). Given these figures, it seems reasonable to ask whether there is, in fact, a need for the expensive and time-consuming research and development (R&D) of new family planning methods. The answer to that question is an unambiguous 'Yes' for at least three reasons.

First, existing contraceptive methods (apart from sterilization, implants and intrauterine devices, IUDs) are associated with relatively high user-failure rates, reflecting the difficulties that many couples have with correct and consistent use of many of the currently available methods. If the typical-use failure rates of the various contraceptive methods as measured in the USA are applied to the whole world, it can be calculated that, each year, over 30 million women experience an unintended pregnancy during the first year of contraceptive use; this number represents nearly 40% of the 85 million unplanned and unintended pregnancies occurring annually throughout the world (World Health Organization, 2011a, b).

Second, substantial numbers of couples discontinue their method soon after initiation either because of contraceptive failure or because of method-related reasons (including side-effects, health concerns, inconvenience or husband's dislike of the method). For example, 15% or more of couples who start using periodic abstinence or withdrawal no longer use these methods after 12 months because they experienced an unplanned pregnancy (United Nations, 2004). In addition, by 12 months after starting, between 40 and 50% of couples discontinued the use of injectables and condoms for method-related reasons, and some 35% stopped using oral contraceptives (OCs). Obviously, many couples dislike the methods and run the risk of unplanned pregnancy because of method discontinuation and delayed switching to another mode of contraception.

Third, although the use of contraception has significantly increased, the global figures mask important regional differences, with Africa, and particularly sub-Saharan Africa, well behind the other world regions. In 2009, for example, prevalence of modern contraceptive methods was 22% for Africa as a whole and 16% for sub-Saharan Africa, when compared with 60% for Asia and 67% for the Latin American and Caribbean region (United Nations, 2011). Causes underlying the low use of contraception in sub-Saharan Africa are manifold and include, among others, problems of accessing services (due to geographical or financial barriers); personal, religious or cultural objections to contraception; previous experience or fear of side-effects associated with contraceptive use; and logistical failures resulting in products being out of stock. Although couples in most sub-Saharan African countries continue to desire larger families compared with other areas of the world, the unmet need for contraception as measured by the proportion of sexually active women who do not wish to become pregnant, yet are not using any form of contraception, is high. In developing countries, one in four sexually active women who want to avoid becoming pregnant have an unmet need for modern contraception (Darroch *et al*., 2011). Using nationally representative data from Demographic and Health Surveys and other sources for countries in sub-Saharan Africa, South Central Asia and Southeast Asia (which together account for the majority of women in developing countries with an unmet need), Darroch *et al*. found that the reasons women most often give for not using a method are concerns about health risks or side-effects (23%), infrequent sex (21%), being post-partum or breast-feeding (17%) and opposition from their partners (10%). They concluded that new methods with negligible side-effects, those that are appropriate for breast-feeding women and those that could be used on demand would have the greatest impact on contraceptive use in the developing world.

The case then for R&D of new and improved methods of contraception seems clear. In the last 15 years, however, very few really new methods of contraception have become available, much to the disappointment of those working in the field as well as those concerned with preventing unintended pregnancies. This is to some extent due to the time and cost involved in the R&D of new methods. However, in the medium-term, adaptations of existing methods can make these contraceptives more acceptable and easier to use. Efforts in the short-term should be directed towards giving women more information about the risk of pregnancy and about contraceptive methods, encouraging uptake and correct and consistent use of available methods and improving services for delivery.

Adaptations and improved regimens for the use of available methods

Combined oral contraceptives

Arguably the best-known, certainly the best-researched, and in many European countries the most widely used, method of contraception is OCs. In Great Britain, in 2008/2009, 54% of women aged 20–24 years had used the pill in the last year (Lader, 2009). Introduced in the 1960s, much of contraceptive development in the subsequent 30 years has focused on strategies designed to reduce the pill's unwanted side-effects. These strategies included the reduction of steroid content, the development of more specific progestogens and the use of phasic regimes. With lowering of the steroid dose (to as low as 15 mcg of ethinylestradiol, EE), the risk of escape ovulation, and subsequent contraceptive failure, became a concern. In recent years, therefore, there has been a re-examination of the 7-day pill-free interval (PFI) as a means of balancing any potential reduction in efficacy of the lower dose approaches.

It has long been known that ovarian activity occurs throughout the PFI and may result in the development of a dominant follicle approaching the stage of maturity required for ovulation by the start of the subsequent pill packet (Molloy *et al*., 1985). The risk of the presence of a fully mature follicle at the end of the PFI is greater in some women than in others, particularly if pills are missed during the treatment period. Such follicles have been shown to be capable of ovulation when subjected to a suitable ovulatory trigger (Killick, 1989). There is extensive evidence that reducing the PFI reduces the mean and maximum size of ovarian follicles (Sullivan *et al*., 1999; Christin-Maitre *et al*., 2011). A prospective randomized double blind study (Klipping *et al*., 2008) has addressed the issue of missed pills in regimens with reduced PFIs. When 21/7 and 24/4 regimens using pills containing 3 mg drospirenone and 20 mcg EE were compared, even with three consecutive pills deliberately missed, the 24/4 regimen demonstrated greater follicular suppression.

There is evidence that this reduced follicle development leads to increased contraceptive protection. The International Active Surveillance Study of Women Taking OCs has reported observational data on 21/7 and 24/4 regimens of pills containing 3 mg drospirenone and either 30 or 20 mcg EE (Dinger *et al*., 2011). Outcome data from 52 218 USA and 58 674 European participants have been published. The Pearl Index in the USA for the 24/4 preparation was 1.6 compared with 2.2 for the 21/7 preparation (Dinger *et al*., 2011). Most failures for all regimens were, of course, user failures. Although European failure rates were much lower than those in the USA, the differences between the two regimens persisted. In an randomized controlled trial, comparing cyclic administration of levonorgestrel (LNG) 100 mcg/EE 20 mcg with continuous administration of LNG 90 mcg/EE 20 mcg, there were no pregnancies among women taking the continuous regimen while the cyclical regimen was associated with a Pearl Index of 1.91 (Teichmann *et al*., 2009).

Concern has been expressed that the increased exposure to estrogen by regimens involving a shorter PFI might increase the potential for venous or arterial side-effects. Reassuringly, Endrikat *et al*. (2001) were unable to detect any significant differences over a 6-month period between a 21/7 regimen and a 23/5 regimen with regard to markers of cardiovascular disease, including haemostatic variables, carbohydrate or lipid metabolism. Data from the active surveillance study are also reassuring in this respect (Dinger *et al*., 2007), as the sample size of that study was sufficient to detect a clinically significant increase in myocardial infarction, stroke or thromboembolism. It will be several years however until any difference, or a lack of difference, in the risk of cancer becomes apparent.

As well as the move towards shorter PFIs, the last 10 years have seen an interest in extended pill regimens. Regimens consisting of 3 or 4 months of continuous low-dose pill use, usually followed by a standard 7-day PFI, have been prescribed for many years for patients with perimenstrual symptoms such as menstrual epilepsy and migraine, and premenstrual syndrome. Observational (Goretzlehner *et al*., 2011) and randomized (Kwiecien *et al*., 2003) studies have reported significant reductions in bleeding, bloatedness, skin problems and pain as well as benefits regarding the perimenstrual condition. Extended and continuous cycle OCs are as effective in preventing pregnancy as traditional OCs. These new regimens also have similar adverse effects, but they are associated with more breakthrough bleeding and spotting than the traditional 21/7 approach. A recent trial reported on the results from 320 women using a 91-day OC extended-regimen for up to 4 consecutive years, with 116 women completing the study (total exposure equivalent to 8292 28-day cycles). Participants reported no thromboembolic events and no unanticipated adverse events, and unscheduled bleeding and spotting diminished during the course of the trial (Davis *et al*., 2010).

While some development is possible with reference to the pattern of pill use, further changes in pill composition are now difficult to justify. Many experts agree that OCs containing levonorgestrel (i.e. the 'second generation pill' of the 1970s) have lower thromboembolic risk than 'third generation' (desogestrel and gestodene) and 'fourth generation' (drospirenone) containing OCs (La Vecchia and Franceschi, 2002; Lidegaard *et al*., 2009, 2011; Van Hylckama *et al*., 2009; Hannaford, 2011). Indeed, the US Food and Drug Administration (FDA, 2011) has recently reviewed the evidence on combined hormonal contraception and venous thrombo-embolism with particular reference to drospirenone. The FDA concluded that the more recently developed combined hormonal combinations did not have be removed from the market, but that manufacturers did have to improve labelling and patient counselling around venous thromboembolism. Most information on OC use and the favourable effect on ovarian and endometrial cancer risk is also based on levorgestrel-containing OCs (Cibula *et al*., 2010). Thus, OCs containing levonorgestrel should be preferred to other compositions, in the absence of specific medical indications (i.e. treatment of acne and hirsutism).

Female sterilization

Sterilization arguably prevents most pregnancies worldwide (Table I). In 2002, worldwide, over 222 million women were protected from unintended pregnancy by sterilization, either of the female (180 million) or the male partner (42 million; Anonymous, 2002). Although vasectomy remains popular in some, especially developed, countries, e.g. The Netherlands (where in 1998, 2003 and 2008, respectively, 19, 18 and 19% of couples at the age of 40–45 years relied on male sterilization), female sterilization appears to be losing out (12, 10 and 8% in the same years) to long-acting reversible methods (De Graaf, 2009). Easily applicable, safe and reliable methods of permanent female contraception became widely available, first, in the 1960s, by (mini)

Table I Method mix among 1.1 billion women practicing contraception in 2007 (Population Reference Bureau World Population Data Sheet, accessed 24.10.2011).

Female sterilization	20%
Intrauterine device	16%
Oral contraceptive	9%
Condom	6%
Male sterilization	3%
Injectable hormone	3%

laparotomy, then, in the 1970s, by laparoscopy. In recent years, a gradual switch from laparoscopic to transcervical approaches, i.e. hysteroscopic surgical methods, has occurred (Smith, 2010).

Electrocautery, chemical and mechanical devices have all been investigated as means of producing tubal occlusion by hysteroscopy. Many years ago, in a series of 350 women from Mexico, Quiñones *et al.* (1975) performed hysteroscopic tubal electrocoagulation. After 1-year hysterosalpingography showed 87.8% with bilateral block, 11.4% with one open tube and 0.8% with two open tubes (Quiñones *et al.*, 1975). In a follow-up study of 1200 cases, no pregnancies occurred in the first year in 513 patients with a bilateral block at Hysterosalpingogram (HSG). However, in 423 patients of these patients, monitored for 5 years, pregnancies occurred in 3.8% of women (Smith, 2010).

Much debate has occurred, and still occurs, about the use of chemical devices to occlude the tubes. Quinacrine instillation has been applied on a wide scale. More than 100 000 women have been treated in this way, mainly in Vietnam and other low-income countries (Zipper and Kessel, 2003). Failure rates are two to four times higher than with laparoscopic procedures and disagreement exists about local toxicology and carcinogenicity (Cancel *et al.*, 2010). In 2006, these factors together led the manufacturer to abandon further development of quinacrine pellets for contraceptive use. Previous tube-occluding methods have included silicone plugs (Ovabloc); a hydrogelic compound, co-polymerized by gamma radiation (P-block); and several plastic devices, e.g. nylon and teflon plugs. Because they migrated too frequently and gave rise to pregnancy rates of up to 10 per 1000 and even more, the development of most of them has been discontinued.

In a long development line of mechanical devices, the Adiana and Essure systems emerge as the only two that offer a satisfactory safety profile (Adiana®, Hologic Inc., Bedford, MA, USA; Essure®, Conceptus Inc., Mountain View, CA, USA).

Application of the Adiana device involves a three-step hysteroscopic procedure. First, a superficial lesion is created in the intramural portion of the Fallopian tube by local application of low-level bipolar radiofrequency waves. Then, a silicone polymer matrix is inserted. Finally, tissue in-growth will occur in the matrix, creating tubal blockage. Clinical trial data show that of 570 women relying on Adiana for permanent contraception (each showing bilateral blockage after 3 months at HSG), 12 conceived in nearly 5 years of collected data—giving an estimated cumulative 5-year failure rate of 21.2/1000 women (Basinski, 2010). The application of the Essure device involves also a hysteroscopic procedure. The conjoint delivery and release catheters are placed under direct hysteroscopic guidance in the intramural portion of the Fallopian tube, the catheters are retracted, and the coil of the device expanded to anchor itself in the tube. The polyethylene terephtalate fibres inside the device elicit an inflammatory response and tissue in-growth occurs, creating tubal blockage. Clinical trial data show that of 643 patients relying on Essure for permanent contraception, none conceived in 9 years of collected data (Basinski, 2010; Table 2). In their present stage of development, both non-invasive methods require a skilled provider, multiple trips to a clinic to ensure that complete blockage has occurred, and a supplementary contraceptive method is required for up to 3 months (as with vasectomy). At present, these approaches to female sterilization are not available in low-resource settings.

Table II Essure and Adiana failure rates compared with other forms of female sterilization (*n* failures/1000 women/5 years) (Peterson *et al.*, 1996; Ligt-Veneman at al., 1999; Levy *et al.*, 2007; Arjona *et al.*, 2008; Vancaillie *et al.*, 2008; Basinski, 2010).

Contraceptive Device	*n* failures/1000 women/5 years
Spring clip	31.7
Adiana	21.1
Bipolar electrocoagulation	16.5
Interval salpingectomy	15.1
Falope silicone ring	10.0
Post-partum salpingectomy	6.3
Unipolar electrocoagulation	2.3
Essure	1.6

Awareness of pregnancy risk and correct use of existing methods

As discussed earlier, even when oral contraceptive pills are taken continuously or with shorter PFIs, unintended pregnancies still occur, most as a result of user failure. Most people find it difficult to take medication consistently and correctly even when not doing so threatens survival (e.g. patients with organ transplants taking immunosuppressive drugs). Many women miss oral contraceptive pills on a regular basis, putting themselves at risk of pregnancy (Hou *et al.*, 2010). If women recognize that they have missed pills, pregnancy may be prevented by using emergency contraception (EC). Hormonal emergency contraception is now widely available throughout the world and in the vast majority of countries in Europe, can be acquired without the need to see a doctor. Although a new and apparently more effective emergency contraceptive preparation (Ulipristal acetate UPA, EllaOne® HRA Pharma, Paris) has been marketed in most of Europe in the last 2 years (Glasier *et al.*, 2010a, b), in reality the biggest challenge relating to EC is its underuse. Trussell and Stewart (1992) estimated that if every woman in the USA had used EC every time that it was indicated, 2.3 million pregnancies could be avoided each year, 1 million of them ending in abortion.

Among women in Great Britain, where use of EC is among the highest, in 2008/2009 only 7% of women under 50 years of age had used it in the previous year (Lader, 2009). Condom failure was the most common reason for EC use, with 36% of women citing this. EC use was highest at age 16–19, with 14% using EC once in the last year and 3% using it three or more times (Lader, 2009).

The most relevant data on use of EC come from women requesting abortion. In the UK in 2006, 12% of women had used EC to try to prevent an unwanted pregnancy, compared with 9% in France (in 2006) and 3% in Sweden (in 2002; Glasier, 2006). The reasons for non-use of EC vary, but fall into four broad categories: lack of knowledge, the stigma associated with use, difficulty with access and lack of recognition of the need for EC. In middle- and low-income countries, lack of knowledge among potential users is common. In India, for example, only 6% of women attending family planning clinics had heard of EC and none had ever used it (Arora and Mittal, 2005). In many African countries, EC is the preferred hormonal method of contraception as a back up to condoms. However, even when knowledge is good, access is limited by the need to use EC within 72 h of intercourse and, in many countries, the need to get a prescription from a doctor. The negative attitudes of some health providers may also limit access (Glasier *et al*., 2010b), but potential users themselves may be deterred by the moral overtones associated with EC. In a US interview study of teenagers, despite knowing about EC, most adolescents did not think there was anything they could do to prevent a pregnancy after unprotected sex. They also believed that easier access to EC would encourage promiscuity and misuse and felt prevented from using it themselves by the views of their family about EC (Johnson *et al*., 2010).

Since the late 1990s, EC has been deregulated in much of Europe and so is now generally available without prescription. Even then, increased use does not always seem to follow. In the years following deregulation in the UK, the number of women using EC remained quite constant, rather the effect being a change to the preferred provider (Marston *et al*., 2005). Studies in the UK (Glasier *et al*., 2004), China (Hu *et al*., 2005) and France (Moreau *et al*., 2005) have all demonstrated that the commonest reason for not using EC when it might prevent pregnancy is the lack of recognition (or acknowledgement) of the need for it. It is likely that it is for this reason that studies of advanced provision of hormonal EC have failed to demonstrate any effect on abortion rates (Polis *et al*., 2007). To increase the use of EC and, arguably to improve consistent and correct use of all methods which rely on compliance for their effectiveness, couples need to be made aware of the risks of pregnancy associated with non-use or imperfect use of contraception. Were this achieved, more effective methods that prevent or delay ovulation even when the LH surge has started would fulfil their potential in reducing unintended pregnancies (Brache *et al*., 2010).

Improvements in service delivery

Service delivery varies considerably worldwide, and different approaches suit different settings. As strategies to improve accessibility of services (and cut costs), task-sharing and task-shifting are increasingly being explored. However, contraceptive services are delivered, they should be of the highest quality. Initiatives designed to improve the quality and cost-effectiveness of care, such as ensuring the use of internationally recognized evidence-based guidelines, particularly the World Health Organization Medical Eligibility Criteria, and Selected Practice Recommendations for Contraceptive Use (WHO, 2002, 2008), are beyond the scope of this paper. As high user-failure rates are associated with use of contraceptive methods which rely on the user doing something with every act of intercourse (condoms) or taking a pill every day, and as EC does not appear to be the solution to the difficulties people have with using these methods, strategies to reduce unintended pregnancies must include increased use of long-acting reversible methods of contraception (LARC). Falls in teenage pregnancy rates in the USA have been attributed to increased use of the long-acting progesterone injectable contraceptive Depo Provera (Darroch and Singh, 1999). Similarly, there is some evidence that use of the contraceptive implant Norplant led to a reduction in teenage childbearing also in the USA (Darney *et al*., 1999). However, worldwide, the copper IUD is the most commonly used LARC (United Nations, 2011). In Europe, too, intrauterine contraception (IUD and the intrauterine system releasing levonorgestrel, IUS) is the most commonly used LARC with 20–25% of women relying on an IUD or IUS in Scandinavia (Haimovich, 2009). Service delivery issues and misconceptions among both providers and potential users hamper the wider use and acceptability of intrauterine methods. Their insertion requires a degree of skill, and over the years concerns have been expressed about their association with pelvic infection and doubts have been cast on their suitability for nulliparous women and for women with coexisting medical conditions (ESHRE Capri Workshop Group, 2008).

While there have been no major new technical developments in intrauterine methods in the last few years, a series of Cochrane reviews has brought together the evidence required to support better evidence-based delivery of these methods and hopefully dispel many of the myths, thereby widening access. Eleven reviews of intrauterine contraception are registered in the Cochrane Library. Of most practical benefit is the recommendation that the IUD is effective for up to 10 years (Grimes *et al*., 2007), that the Copper T380A is the most effective copper device available (Grimes *et al*., 2007), and that insertion of an IUD immediately following both childbirth (Grimes *et al*., 2010a) or surgical abortion is safe and practical and, after abortion, results in higher continuation rates compared with interval insertion (Grimes *et al*., 2010b). With respect to concerns about the risk of sexually transmitted infection (STI), of vital importance in many developing countries, prophylactic antibiotic administration at the time of insertion of IUDs is unwarranted except in populations with a high prevalence of STIs (Grimes *et al*., 2007; ESHRE Capri Workshop Group, 2008).

In most of Europe, the IUD has been replaced by the IUS as the most popular long-acting contraceptive. It is the most effective LARC, as effective, and in some studies, more effective even than female sterilization, with cumulative pregnancy rates at 5 years of $<0.5\%$ (Thonneau and Almont 2008; Mansour *et al*., 2010). In recent years, the safety of the IUS has been assessed among women with a number of pre-existing chronic medical conditions, including diabetes mellitus (Rogovskava *et al*., 2005), HIV infection (Heikinheimo *et al*., 2011) and congenital haemostatic disorders (Lukes *et al*., 2008) and among women on anticoagulant therapy (Pisoni *et al*., 2006; Kilic *et al*., 2009), thus improving contraceptive choices for these women for whom pregnancy prevention can be vital to

health. Recent research has also demonstrated that, contrary to popular belief, insertion of a second consecutive IUS is easy and both avoids the initial period of irregular bleeding and maintains amenorrhoea during long-term use (Gemzell-Danielsson *et al*., 2010; Heikinheimo *et al*., 2010a). The safety and efficacy of the IUS in nulliparous women have also recently been confirmed (Marions *et al*., 2011). While cervical priming with misoprostol has been shown to aid the provider's experience of IUD insertion in nulliparous women (Sääv *et al*., 2007), misoprostol priming does not alleviate the pain of insertion or improve the ease of placement in repeat consecutive insertions (Heikinheimo *et al*., 2010b).

It is anticipated that a smaller IUS, which is easier to insert, will become available in the next few years.

Recognition and promotion of health benefits beyond contraception

Just as opinion leaders recognize the advantages of LARC, so too they emphasize the need to inform women about the non-contraceptive benefits of existing methods as a mean of encouraging uptake and improving use (ESHRE Capri Workshop Group, 2005, 2008). The benefits of combined OCs for the treatment of common gynaecological conditions such as endometriosis and premenstrual syndrome are well known and the IUS is licensed, and in many countries recommended, as first-line treatment for heavy menstrual bleeding (HMB; National Institute for Health and Clinical Excellence, 2007).

In recent years, the benefits of the combined OC have been formally recognized in the clinical guidelines produced by both the Endocrine Society (Martin *et al*., 2008) and the Androgen Excess and PCOS Society (Escobar-Morreale *et al*., 2012) concerning the management of women with symptoms of hyperandrogenism and/or polycystic ovarian syndrome.

Hirsutism, defined as excessive male-pattern terminal hair growth in women, is the most commonly used clinical diagnostic criterion of androgen excess. Other clinical androgen excess signs include acne and androgenic alopecia (Yildiz, 2006). The most common hyperandrogenic disorder is polycystic ovary syndrome (PCOS) with ~80–85% prevalence among women with androgen excess (Azziz *et al*., 2004). OCs suppress the secretion of LH, and decrease ovarian androgen production. The estrogenic fraction of the pill increases the levels of sex hormone-binding globulin, which, in turn, results in a decrease in free testosterone levels. OC also decreases adrenal androgen production by a mechanism yet unclear, possibly involving a decrease in adrenocorticotrophic hormone levels (Yildiz, 2008).

OCs are the mainstay of the chronic treatment of PCOS for women not seeking pregnancy (Vrbikova and Cibula, 2005). They ameliorate hyperandrogenic skin manifestations, regulate menstrual cycles thereby protecting from the risk of endometrial carcinoma, and provide effective and safe contraception. Several studies in women with PCOS have demonstrated that OC use improves hirsutism and acne (Fig. 1). OCs containing progestins with anti-androgenic activity, rather than second- and third-generation OCs containing progestins with varying androgenic activity, appear to be an appropriate alternative in the treatment of hirsutism (Yildiz, 2008; Escobar-Morreale *et al*., 2012).

Concerns have been expressed about the safety of the OC in obese women and in those who have increased risks of diabetes and cardiovascular disease (Yildiz, 2008). However, the conclusions of a recent Cochrane review comparing OC with metformin in PCOS are reassuring (ESHRE Capri Workshop Group, 2005; Costello *et al*., 2007).

The benefits of combined oral contraception and the levonorgesterel IUS for the management of HMB are well recognized. While the latter is now licensed, it has taken a surprisingly long time for combined OCs to be licensed for this therapeutic purpose. In 2011, a

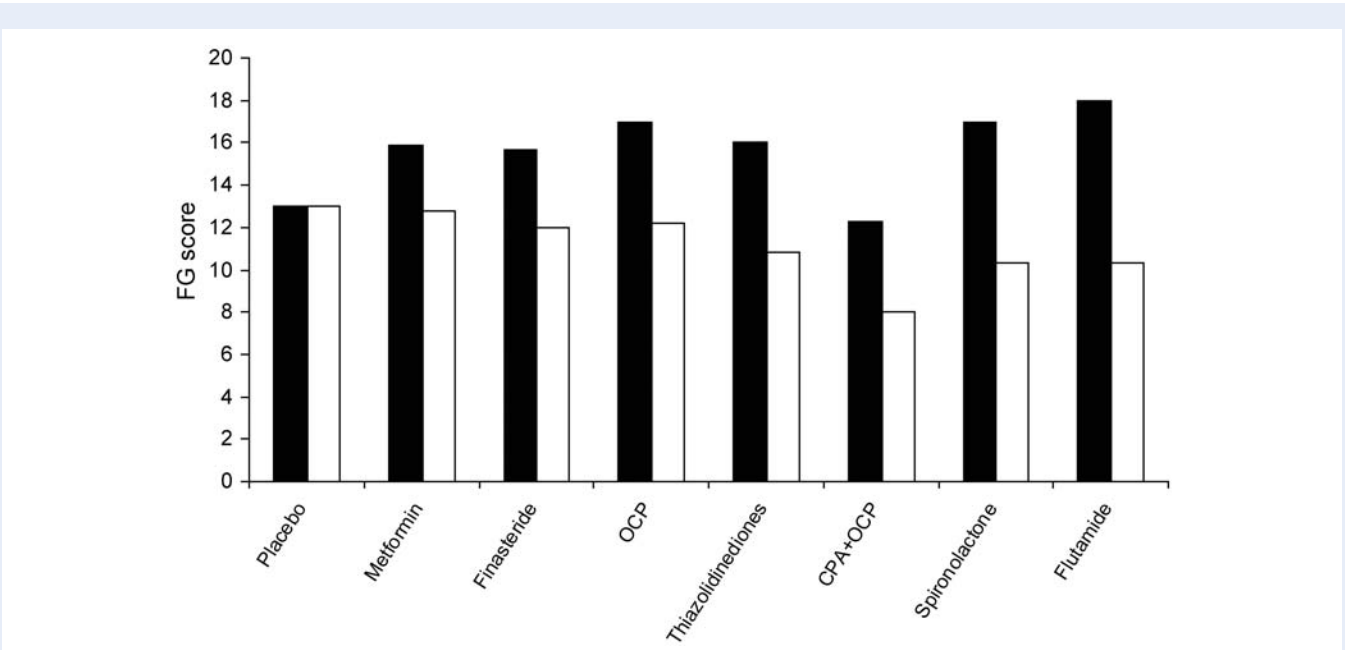

Figure 1 Combined mean values of Ferriman–Gallwey scores before (black bars) and after (white bars) 6 months of treatment in randomized controlled trials (modified from Koulouri and Conway, 2008).

randomized, placebo-controlled trial demonstrated a significant reduction in measured menstrual blood loss (mean reduction 69.4%) when women with HMB were treated with an OC containing estradiol valerate and dienogest (Fraser *et al*., 2011).

While the immediate 'side' benefits of contraceptives on conditions such as acne and HMB are of interest to individual women, arguably of much greater importance to public health are the effects of long-term use of contraceptives on the incidence of cancer. The significant effect of the OC on reducing endometrial and ovarian cancer is well recognized and indeed it has been suggested that the deaths from ovarian cancer prevented by OCs outweigh the concerns about any increased risk of breast cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008). The risk reduction of epithelial ovarian cancer is around 5% per year of OC use. This means that the overall risk is almost halved after about 10 years of OC use. Interestingly, this effect is long-lasting as it persists, although is progressively reduced, even after >20 years since last use of the OC (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; Hannaford *et al*., 2010; Vessey *et al*., 2010). Oral contraceptives and tubal ligation substantially reduce the risk of serous (80% of malignancies), endometrioid (10–25%), and clear cell ovarian tumours (5–10%), but have no significant effect on mucinous tumours, which probably follow a different oncogenic pathway (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; Cibula *et al*., 2010, 2011). The beneficial effect of the copper IUD use on endometrial cancer is less well known (Beining *et al*., 2008), but a recent publication has reported a reduced cervical cancer risk in IUD users (Castellsagué *et al*., 2011).

Female sterilization (including tubectomy) is also now being promoted for ovarian cancer prevention (Cibula *et al*., 2011). Most serous ovarian cancers appear to originate from precursor lesions at the fimbriated end of the fallopian tube (Folkins *et al*., 2009; Salvador *et al*., 2009), whereas most endometrioid and clear cell cancers seem to derive from atypical endometriosis (Kurman and Shih, 2010). It has been suggested that serous, endometrioid, and clear cell cancers share a common pathogenic mechanism, i.e. iron-induced oxidative stress derived from retrograde menstruation (Vercellini *et al*., 2011). Fimbriae floating in bloody peritoneal fluid are exposed to the action of catalytic iron and to the genotoxic effect of reactive oxygen species, generated from haemolysis of erythrocytes by pelvic macrophages (Defrère *et al*., 2008). This would explain the distal site of tubal intraepithelial neoplasia. Collection of blood inside endometriotic cysts would lead to the same type of genotoxic insult as gonadal endometrial implants (Yamaguchi *et al*., 2008, 2010), which would explain why endometriosis-associated cancers develop much more frequently in the ovary than at extragonadal sites, despite the fact that endometriosis occurs just as frequently away from the ovary than on the ovary. Where appropriate, combined OCs have been recommended for prolonged periods of time, especially for women with endometriosis, a population at double the risk of gonadal malignancy (Modugno *et al*., 2004).

New developments in contraceptives for women

Selective progesterone receptor modulators

Progesterone is essential for the establishment and maintenance of pregnancy. Synthetic progestogens and estrogens have been the basis of methods of hormonal contraception which have been developed and widely used throughout the world in the last 50 years (Baird and Glasier, 1993). It has been clear however, for many years, that compounds which inhibit the synthesis of this vital hormone or interfere with its action would have anti-fertility properties (Pincus, 1965). Elucidation of the mechanisms by which steroid hormones exert their actions by interacting with specific receptors in target organs led to the development of synthetic analogues which have antagonistic as well as agonist activity (Baulieu, 1997). Hormone antagonists bind to the receptor but fail to initiate the chain of reactions which lead to transcription of DNA by the specific target organ characteristic of the natural ligand (Baulieu, 1997). Antagonists of androgens, estrogens and adrenal steroids have found an important place as therapeutic agents in oncology. While the theoretical potential of antagonists of progesterone has long been recognized, the discovery of the first potent antagonist of progesterone occurred by chance during the screening of compounds which were being developed for anti-glucocorticoid activity (Baird, 2001). Within 2 years of its synthesis, mifepristone was shown to terminate pregnancy in the first 3 months and, by inducing bleeding in the menstrual cycle, to have contraceptive potential (Herrman *et al*., 1982). Since then, mifepristone in combination with a suitable prostaglandin has been widely used as a medical alternative to vacuum aspiration for the termination of pregnancy (Baird, 2002). Subsequently, a number of antagonists of progesterone have been synthesized, but their full therapeutic potential had hardly been explored until recently. In the last 10 years, a number of studies have explored the contraceptive potential of various antigestogens (mainly mifepristone) but only one has been taken through to marketing.

Soon after its licensing as a medical abortifacient, mifepristone was shown to be highly effective at preventing pregnancy after unprotected intercourse (Glasier *et al*., 1992). Subsequent trials have demonstrated its effectiveness even in small doses (<30 mg) well below those necessary to induce abortion (Cheng *et al*., 2010). The high effectiveness is probably due to the fact that, unlike the widely used alternative (levonorgestrel), mifepristone can prevent follicle rupture and implantation as well as inhibit ovulation (Baird, 2009). Furthermore, the recently marketed ulipristal acetate is effective even when taken up to 120 h after intercourse (Glasier *et al*., 2010a).

Other types of contraceptives

Other contraceptives are at various stages of development as follow.

Continuous daily administration as an oral pill or vaginal ring. Doses as low as 2 mg/day of mifepristone inhibit ovulation while ovarian estrogen secretion is maintained. Suppression of ovulation as well as disruption of endometrial maturation is the basis of a highly effective daily contraceptive pill (Brown *et al*., 2002). Although for commercial and political reasons oral mifepristone has not yet been marketed outside China, ulipristal acetate with a similar structure and properties is under development in the USA and Europe as a continuous pill for the treatment of fibroids and endometriosis (Nieman *et al*., 2011).

Once-a-month/week contraception. Because antagonists of progesterone interfere with the initiation and establishment of pregnancy, they should prevent pregnancy when given at any stage of the ovarian cycle. Studies of women of contraceptive age in a range of countries

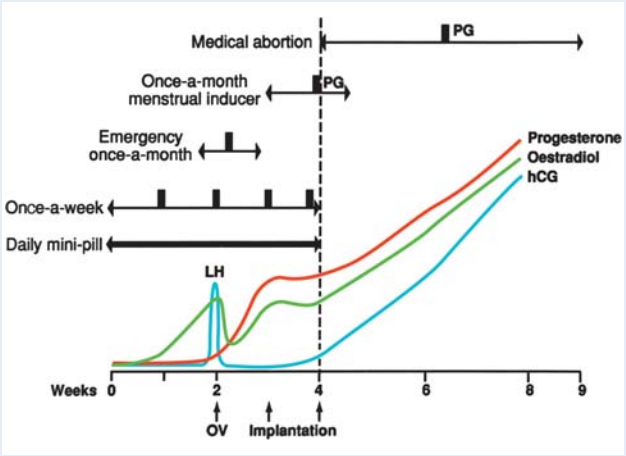

Figure 2 Potential for contraceptive activity of anti-progesterones in relation to the menstrual cycle.

worldwide have shown that for some women, this would be a very attractive option (Glasier *et al*., 1999). Unfortunately, the published trials failed to indicate a regimen which would be useful for regular contraceptive use either because the unplanned pregnancy rate is significantly higher than other comparable regular methods of contraception (e.g. OC) or because the disruption of menstrual patterns is unacceptably high (Bygdeman *et al*., 1997; Narvekar *et al*., 2006; Fig. 2).

Intrauterine contraception. Although in the very early phase of development, work is underway to explore the potential of anti-progestogens in hormone-releasing intrauterine devices (Brenner *et al*., 2010).

In spite of the many possible ways of interfering with fertility, and the fact that mifepristone has many advantageous pharmacological properties (low toxicity, orally active, long half life), its full contraceptive potential has not been realized, despite its widespread clinical use as an abortifacient where its low toxicity in doses which are 20-fold higher than those which are contraceptives has been demonstrated (McKinley *et al*., 1993). While concerns have been raised about the effect of chronic administration of anti-progesterones on the histological appearances of the endometrium, actual cell proliferation appears to be extremely uncommon (Mutter *et al*., 2008). It is likely that this class of compounds will be very useful in the treatment of hormone-dependent conditions such as fibroids and endometriosis as well malignancies such as breast and uterine cancer. Due to its antiproliferative effect (Engman *et al*., 2008; shown in women) and thus its ability to reduce the lifetime risk of breast cancer (as shown in mice), antagonists of progesterone may indeed become extremely valuable methods of contraception (Poole *et al*., 2006).

New defences against sexually transmitted infections

The Millennium Development Goal target of universal access to reproductive health reaffirms the need for contraceptive options as well as access to other key reproductive health services, including prevention of STIs. In recent years, there has been great interest in agents that provide dual protection against pregnancy and STIs, especially HIV. A contraceptive method providing dual medical benefits might increase the motivation for consistent use, thus reducing contraceptive failures and unwanted pregnancies (Townsend *et al*., 2011). The future for dual protection is improving, new products are entering clinical trials in 2012 and there is ongoing work with regulatory agencies to facilitate the review of multi-purpose prevention technologies.

Hormonal contraception is often the first method used by young women in many high- and low-income countries, even though it does not provide protection against STIs as would barrier methods such as male and female condoms. Although providers are strongly in favour of long-acting methods of contraception, the acceptability for post-coital or peri-coital contraceptive methods seems to be as high as for regular methods if their use is indicative (Lader, 2009).

The levonorgestrel-only (LNG) emergency contraceptive pill is available in many countries. LNG can also be administered vaginally with similar effects on follicular development and ovulation and (such as oral LNG) no effect on endometrial development and markers of endometrial receptivity (Meng *et al*., 2010). Based on the possibilities of developing combinations of microbicides and hormonal contraceptives for dual protection, two clinical trials have focused on the effect of vaginal LNG combined with the Population Council's Carraguard (CARRA) vaginal gel (CARRA/LNG; Sitruk-Ware *et al*., 2007; Brache *et al*., 2007). Despite its apparent lack of effectiveness in preventing HIV transmission (Skoler-Karpoff *et al*., 2008), CARRA/LNG gel can sustain elevated serum levels of the contraceptive steroid for up to 96 h after a single application. The serum levels attained with the 0.75 mg LNG formulation are in the range expected to perturb the ovulatory process (Sitruk-Ware *et al*., 2007). In a small study, Carraguard vaginal gel containing 0.75 mg LNG (CARRA/LNG gel) was administered in a single dose at different stages of follicle development. No follicular rupture within 5 days following administration was observed in 74 and 30% of the CARRA/LNG and CARRA alone treatment cycles, respectively, while ovulation was documented in 4 and 61%, respectively. The overall proportion of cycles with a lack of follicular rupture or ovulatory dysfunction (follicle rupture preceded by an inadequate LH surge) was 96% for CARRA/LNG and 39% in the CARRA alone cycles (Brache *et al*., 2007).

Better news recently on microbicides (Abdool Karim *et al*., 2010) may extend the search for more reliable methods of dual protection. In 2010, results from the CAPRISA 004 study in South Africa were published (Abdool Karim *et al*., 2010). The study included 35 889 high-risk women who used an applicator that delivered 1% tenofovir gel into the vaginal vault up to 12 h before, and within 12 h after, intercourse. Investigators reported a 39% reduction in overall acquisition of HIV, and the maximum reduction was 54% in the most adherent women. HIV acquisition was inversely correlated with detection of tenofovir in the vaginal secretions, an indication of the strong association between product adherence and efficacy. Several ongoing trials evaluating oral or vaginal antiretroviral agents for pre-exposure prophylaxis are currently ongoing (Microbicide Trials Network, 2011).

Conclusions

Although great strides have been made in recent years in increasing contraceptive use in many countries where contraceptive prevalence has been low, many pregnancies are still unwanted and much still needs to be done. Adaptations of existing methods, improvements in service delivery and a better understanding of contraceptive

behaviour can and do increase contraceptive uptake and correct and consistent use, and we have illustrated some of these approaches in this review. While interest in developing new methods of contraception appear to have dwindled in the last 10 or 15 years, there clearly is scope for adding new methods to those already available, focusing arguably on particular needs that are presently poorly served, such as dual protection, and on the potential added value of methods which confer other health benefits.

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Conflict of interest

P.G.C. consulting work for Bayer-Schering, IBSA and Merck-Serono. A.G. consultancy with HRA Pharma Paris.

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Appendix

A meeting was organized by ESHRE (28–29 August 2011) to discuss the above-mentioned subjects. The contributors included: D.T. Baird (Centre for Reproductive Biology, University of Edinburgh, UK), J.L.H. Evers (Dept. Obstet. Gynecol., Maastricht University Medical Centre,

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