

Recent advances in contraception

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Abstract

Focusing on intrauterine contraceptives (IUC), contraceptive implants, and emergency contraceptives, we review recent advances in contraceptive development and discuss progress in policies to improve access to the most effective methods. We report on the shift in practice towards routinely providing IUCs and implants to young and nulliparous women, prompted in part by the reduced diameter of the insertion tube for the Mirena IUC and the development of a smaller IUC called Skyla. Additionally, we describe the new SCu300A intrauterine ball and the development of an implant called Nexplanon, which comes with a preloaded inserter. We also discuss the efficacy of ulipristal acetate versus levonorgestrel for emergency contraception, especially for women who weigh more than 75 kg. Finally, in light of the increasing interest in providing IUCs and implants to women in the immediate postpartum and post-abortion periods, we consider the rationale for this change in practice and review the progress that has been made so far in the United States.

Introduction

In this short report, we review recent advances in the development of highly effective reversible methods of contraception (intrauterine contraceptives and implants) and emergency contraception. We also discuss policy advances in improving provision of the most effective contraceptive methods in the early and immediate post-abortion and postpartum periods.

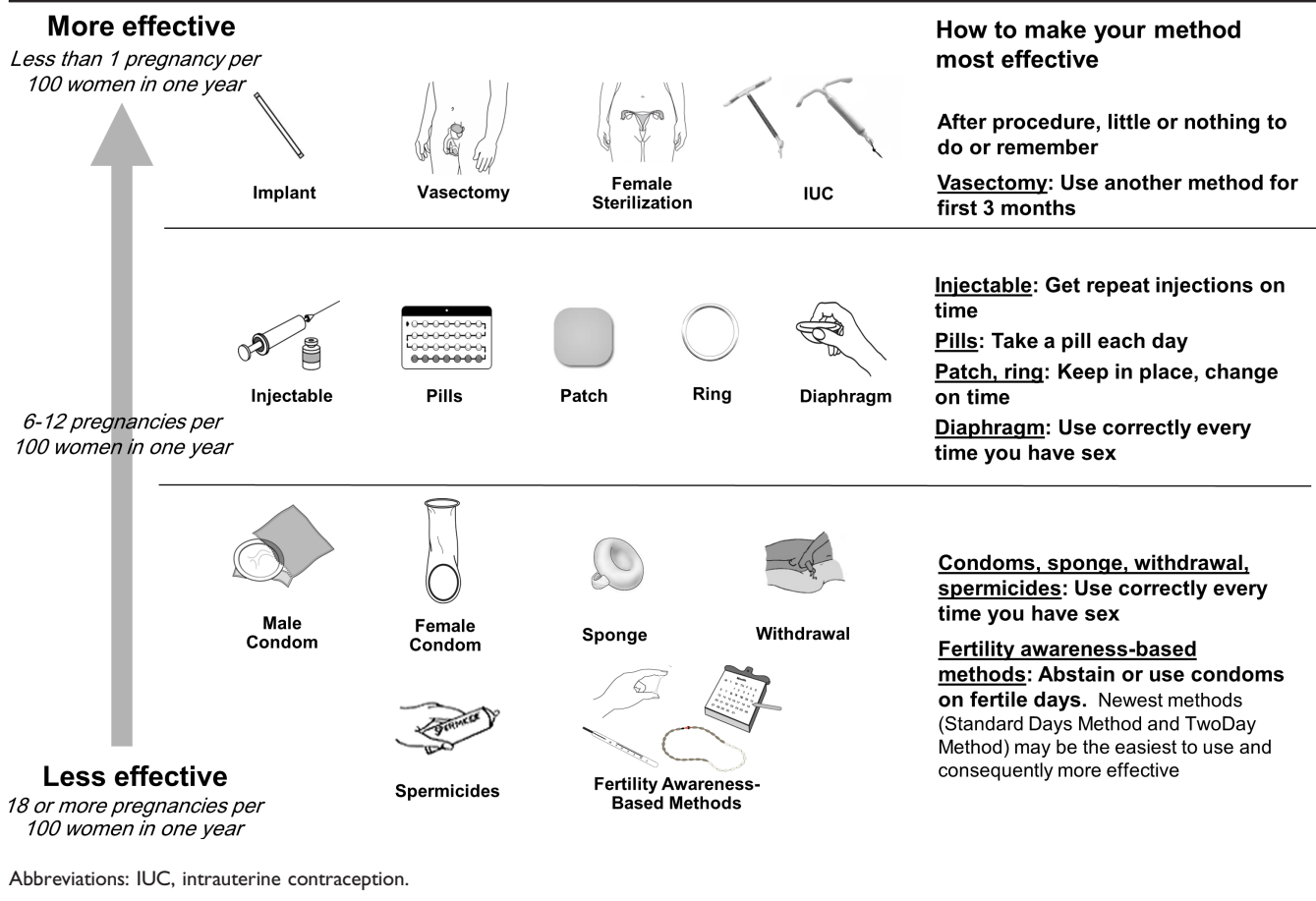
Intrauterine contraceptives

IUCs are in the top-tier effectiveness category of contraceptives (see Figure 1[1]) because they require no adherence on the part of the woman; hence they are sometimes referred to as "forgettable". There are two types of IUC: those containing copper on the arms and/or stem (which are labeled for use for 5 or 10 years, depending on brand) and those containing progestin in the form of levonorgestrel. The levonorgestrel IUC Mirena® (Bayer) contains 52 mg of levonorgestrel, which is released at an initial rate of 20 µg per day and lasts for five years. Where women have a choice between levonorgestrel and copper IUCs, the majority choose the former [2], most likely because of its lack of negative side-effects and the

associated beneficial reduction in dysmenorrhea and menstrual blood loss. At least 30% of women stop bleeding altogether by the end of the first year of use [3] and, among women with heavy menstrual bleeding, overall blood loss drops by at least 90% [4]. Mirena® has been marketed in Europe since 1990 and is the only 52 mg levonorgestrel-dose IUC available in the United States (US). However, a clinical trial of another levonorgestrel IUC produced by Medicines 360 is underway. In some European countries, the levonorgestrel IUC Levosert™ (Mithra) is available. Levosert™ provides the same levonorgestrel dose as Mirena®. A randomized controlled trial (RCT) comparing the two IUCs found no differences in menstrual blood loss over a one-year period and no differences in expulsion rates or major complications such as uterine perforation [5].

In 2013, the US Food and Drug Administration (FDA) approved Skyla® (Bayer), the first new IUC to be approved in 12 years. Skyla® (called Jaydess® in Europe and Canada) contains a lower dose of levonorgestrel (13.5 mg) and is approved for up to 3 years of use [6,7]. It is primarily marketed for use in adolescent and

Figure 1. Contraceptive failure rates during typical use



nulliparous women, having been designed with a smaller size compared to existing IUCs, in terms of the transverse arms and vertical stem. The diameter of the insertion tube is also smaller, at 3.8 mm. It has a silver ring to distinguish it from Mirena® on ultrasound and to enable visualization by x-ray. Use of Skyla®/Jaydess® makes initial placement easier and less painful for women; bleeding profiles are similar [8]. A new insertion tube for Mirena® was introduced in 2012, with the diameter reduced from 4.8 mm to 4.4 mm. Clinical practice restrictions on the placement of IUCs in nulliparous women have been eliminated, and both nulliparous and young women are now generally considered good candidates for any type of IUC.

Despite the excellent safety record of the levonorgestrel and copper IUCs, uterine perforation on placement, malposition, and expulsion are possible risks. Perhaps the most innovative recent advance in intrauterine contraception has been the development of the SCu300A intrauterine ball (IUB), which is a three-dimensional, spherical copper IUC. It is inserted and removed in the

same fashion as two-dimensional T-shaped IUCs, but its spherical shape may help to reduce the likelihood of perforation, malposition, and expulsion [9]. A prospective, randomized, single-blind study of the safety and efficacy of the IUB (220 women) in comparison to the TCu 380 (110 women) is now underway in Romania and Bulgaria. OCON Medical recently received CE approval (signifying compliance with European Union regulations), so that the IUB™SCu300A can be marketed in over 30 countries including all European Union member states.

Progestin implants

The contraceptive implant is also in the top-tier effectiveness category of contraceptives (see Figure 1 [1]) and, like IUCs, is not dependent on daily or pre-coital adherence on the part of the user. The implant takes the form of a small (40 mm), flexible tube that is inserted subdermally in the upper arm and releases 68 mg of progestin in the form of etonogestrel. Despite their safety and efficacy, the main difficulty with providing implants (besides cost and an adequate supply of trained providers) is ensuring

correct subdermal placement by the provider [10]. In 2010 (Europe) and 2011 (US), the original implant, Implanon® (Merck), was replaced by the second-generation Nexplanon®, in some countries named Implanon NXT®. These devices contain the same dose of etonogestrel but come with an improved pre-loaded inserter, which makes correct subdermal placement easy [11]. Correct placement is essential for easy removal. The core contains barium sulphate detectable by x-ray, allowing providers an additional option to check for correct positioning if palpation fails. Use of the older 2-rod levonorgestrel-releasing implants Jadelle and Sino-Implant (II) is still prevalent in lower-income countries.

Emergency contraception

There are two types of emergency contraception: IUCs containing copper and emergency contraceptive pills (ECPs). ECPs are available containing both progestin and estrogen, containing only progestin, and containing an antiprogestin (either mifepristone or ulipristal acetate). Dedicated ECPs containing progestin and estrogen are no longer marketed (though regular oral contraceptives containing levonorgestrel and ethinyl estradiol can be used for emergency contraception; see <http://www.not-2-late.com>) because they are less effective and cause more side effects.

More than 7,000 postcoital insertions of copper-bearing IUCs have been reported in the literature since the practice was introduced in 1976. With only 10 known failures, this approach has a pregnancy rate of 0.1% [12]. The effectiveness of using the levonorgestrel-20 intrauterine device (IUD) for emergency contraception is currently being studied (see <http://clinicaltrials.gov>).

In a Cochrane Review of 20 Chinese randomized trials, 25 mg or 50 mg of mifepristone had a lower failure rate than did levonorgestrel. Mifepristone was tolerated more easily but the delay in menses was greater in 13 trials that reported side effects [13]. Low dose (<25 mg) mifepristone was more effective than levonorgestrel in a meta-analysis of nine Chinese, one UK [14] and one multinational [15] randomized trials, but mifepristone was not superior in the only four high-quality studies [13]. Mifepristone is not widely used outside China and Russia for political reasons; in larger doses (200 mg), it can be used with misoprostol to induce abortion. Therefore, efforts to develop a new ECP have focused on another antiprogestin.

In 2009, ellaOne® (HRA Pharma), containing a 30mg single dose of the second-generation antiprogestin ulipristal acetate (UPA), became available in Europe, and the same pill ella® was approved by the FDA in 2010. These are the most effective ECP options in the US and Europe.

In one randomized study, UPA prevented significantly more pregnancies than did levonorgestrel when the ECPs were taken 72-120 hours after unprotected intercourse [16]. Another randomized trial compared the efficacy of levonorgestrel and UPA when taken up to 72 hours after unprotected intercourse [17]. When data from these two trials were pooled, UPA was found to have lower failure rates: odds ratio for pregnancy was 65% lower in the first 24 hours, 42% lower up to 72 hours, and 45% lower up to 120 hours for UPA compared with levonorgestrel [18]. The reason seems to be that when ovulation is imminent, UPA is more effective than levonorgestrel in delaying it. By the time the leading follicle reaches 15–17 mm, follicular rupture is prevented within 5 days of administration no more often after levonorgestrel administration than after placebo administration [19]. In contrast, when taken when the leading follicle reaches 18–20 mm (and ovulation should occur within 48 hours) and the probability of conception exceeds 30%, UPA prevents follicular rupture within 5 days of administration in 59% of cycles, compared with 0% in placebo cycles [20]. The antiprogestins UPA and mifepristone are probably equally effective.

Further analysis of data from the two randomized trials of UPA and levonorgestrel showed a rapid decrease of efficacy with increasing weight, reaching the point where it appeared no different from pregnancy rates expected among women not using emergency contraception (EC) at 70 kg, compared with 88 kg for UPA [18]. The label for NorLevo (a 1.5 mg levonorgestrel EC product available outside the US) was changed in Europe in November 2013 to reflect findings from further analyses of these data; the label states: "In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more, and levonorgestrel was not effective in women who weighed more than 80 kg" [21]. However, the European Medicines Agency, after reviewing additional data from three World Health Organization (WHO) trials [22–24] that did not find reduced efficacy with increasing weight or body mass index (BMI), removed that statement from the Norlevo label in July 2014 [25].

Post-abortion contraception

There is now convincing evidence that immediate post-abortion placement of IUCs and implants leads to a reduction in subsequent unintended pregnancies [26,27] and repeat abortions [28–30]. At the time of the abortion procedure, many women may be highly motivated to obtain a highly effective method and prevent another unintended pregnancy, and the timing is convenient for both the woman and provider. The 2010 US Medical Eligibility Criteria (US MEC) for Contraceptive Use classifies placement of levonorgestrel-releasing implants

as category 1 (no restrictions on use) immediately following first and second trimester abortion, and levonorgestrel-releasing IUCs and copper-IUCs as category 1 following first trimester abortion and category 2 (advantages outweigh theoretical or proven risks) following second trimester abortion [31]. For women undergoing medical abortion, immediate provision of IUCs is not possible, but it has recently been demonstrated that early insertion (5–9 days post-mifepristone administration) does not result in a higher incidence of expulsion compared to delayed (routine) insertion at 3–4 weeks. Women were also more likely to return for early as opposed to delayed insertion [32].

Currently, the major barrier to providing immediate post-abortion IUCs and implants in the US is Medicaid reimbursement policy. In many states, provider billing for method placement on the same day as the abortion procedure is not allowed, thus requiring women to return to the clinic on a different day for a separate visit [33]. Since up to 50% of women do not attend a scheduled follow-up appointment after an abortion [34], such a requirement may constitute a significant burden in terms of time and financial resources, while at the same time introducing inefficiency into the delivery of care. Should all states adopt a same-day Medicaid reimbursement policy for immediate post-abortion IUCs and implants, estimates suggest that the attributable reduction in unintended pregnancies could result in savings to Medicaid of \$70 million per year [35]. In the US and in other countries, investment in provider training, effective contraceptive counseling, and willingness to cover the costs of the devices are all necessary to make post-abortion provision of the most effective reversible methods possible.

Postpartum contraception

Early postpartum access to highly effective reversible contraceptives, both IUCs and the implant, is key to helping women prevent unintended pregnancy [36]. In light of recent evidence regarding the safety and efficacy of IUC and implant placement immediately postpartum [37,38], there has been much interest in increasing access to these methods prior to hospital discharge. The 2010 US MEC classifies immediate postpartum placement of levonorgestrel-releasing IUCs and implants among breastfeeding women as category 2. Implants among women not breastfeeding and copper-releasing IUCs are classified as category 1 [31].

Immediate postpartum placement is an attractive option for many reasons: high motivation to prevent repeat pregnancy or to space pregnancies optimally; convenient timing for the woman and the provider; and the ability to

overcome the logistical obstacles that arise following hospital discharge. In the United Kingdom, women are typically not provided with contraception before discharge and must wait until their postpartum checkup, typically six weeks after hospital discharge. By this time, many women will have resumed intercourse and, if ovulating, already be at risk for unintended pregnancy. In the US, there is the additional problem of some types of health insurance having a limited window of coverage following delivery. For women whose deliveries were covered by Medicaid, coverage expires 60 days post-delivery, leaving little time for contraceptive counseling, ensuring a method is available, and scheduling an additional appointment for placement. Immediate postpartum placement of IUCs and implants, in addition to being safe and effective, would circumvent these problems.

Despite these advantages, hospitals in the US have a financial disincentive to provide immediate postpartum IUCs and implants. For women whose deliveries are covered by private insurance or Medicaid, hospitals receive a global fee for all delivery-related care. While postpartum sterilization may be billed separately from the global fee, postpartum IUCs and implants are not eligible for separate reimbursement in most states. Since their provision would involve deducting between \$600 and \$775 (based upon wholesale costs) from the global fee, it is not in the financial interests of hospitals to provide them.

Yet, recent policy changes offer some hope for increasing postpartum access to the most effective methods in the future. To date, separate billing for postpartum implants and IUCs for women covered by Medicaid has been adopted in ten states (Colorado, Georgia, Iowa, Louisiana, Mississippi, New Mexico, New York, Oklahoma, South Carolina, and California). These progressive policy changes required only regulatory adjustments and short-term investments; no legislative action was necessary. It is hoped that the next advance in improving contraceptive access will be adoption of these policy changes across all forty remaining states. Such action would both save healthcare dollars and help women prevent future unintended pregnancies.

Conclusion

Recent advances in the development of highly effective reversible methods of contraception have focused mainly on improving the ease of device insertion and removal, making these methods more acceptable to young and nulliparous women. There is a compelling rationale for immediate postpartum and post-abortion access to IUCs and implants and policy progress towards

improving access in the US would require only regulatory changes at the state health services level. With regard to developments in emergency contraception, ulipristal acetate has been found to be more effective than levonorgestrel in delaying imminent ovulation, but copper IUCs are the most effective option for women who are willing to use them.













Abbreviations

EC, Emergency contraception; ECP, emergency contraceptive pill; FDA, Food & Drug Administration; IUB, intrauterine ball; IUC, intrauterine contraception; UPA, ulipristal acetate.

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