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Starting hormonal contraception after using emergency contraception: what should we recommend?

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By convention for many years oral contraceptive (OC) instructions have advised women to wait for the onset of their next menstrual period before starting the pills in order to be certain they were not already pregnant. Patient information leaflets (PILs) in the UK for both combined oral contraception (COC) and progestogen-only pills (POPs) still state that it is 'best' to take the first pill of the packet on the first day of a period (Bayer, 2014; Merck Sharp & Dohme Ltd, 2014). Recognizing that any fears about teratogenicity of hormonal contraceptive pills were without foundation, and that imposing any delay on starting contraception may well mean that some women will never start it. In 2002 Westhoff and colleagues introduced the concept of 'quick-starting' (Westhoff *et al.*, 2002). In this observational study in the USA, women starting an OC were encouraged to swallow the first pill of the packet in the clinic regardless of their menstrual cycle day. The authors reported that women who took the first OC immediately were much more likely to continue the method to the second packet compared with women who chose to delay starting. Quick-starting hormonal contraception has since become standard practice in many European countries as well as in the USA.

Women take emergency contraception (EC) at any time in their cycle, often around the middle when the risk of pregnancy is highest (Glasier, 2014). Over 90% of women who use EC do not get pregnant and remain at risk of conception from further acts of sexual intercourse unless they use another contraceptive method. Prior to 2005, the advice to women taking EC and wanting subsequently to start hormonal contraception was to abstain from intercourse or use a condom until the onset of menses when ongoing hormonal contraception should be started. Many women do not abstain from intercourse in these circumstances and many do not use a condom. In a pooled analysis of nine trials which collected data on sexual activity after EC use, 30% of women reported having sex in the same cycle after using EC (Cheng *et al.*, 2012). Although advised to use condoms (and in many instances provided with condoms as part of the study protocol) the risk of pregnancy among the women who admitted to having sex after EC use was significantly higher than among those who did not (Relative risk: 2.61; 95% confidence intervals: 2.00–3.41) suggesting that a number of pregnancies were conceived soon after EC had been used. Current national and international guidelines acknowledge this and now advise women using EC that if they wish to use an OC they can start immediately (FSRH, 2010; ICEC, 2012; CDC, 2013). This message seems to have been getting through to clinicians. In an audit of practice following publication of a UK guideline endorsing quick-starting contraception after EC use (FSRH, 2010), a clinic in Scotland reported a statistically significant increase in the practice (Simpson *et al.*, 2014). Moreover, there is some evidence that quick-starting hormonal contraception after EC use has advantages. A pilot study, also from Scotland, showed that giving women a supply of POP to take home with them to give them more time to arrange to see a doctor about ongoing contraception significantly improved effective contraceptive uptake 6–8 weeks later (Michie *et al.*, 2014).

Ulipristal acetate (UPA) was first marketed as an emergency contraceptive in Europe in 2009 (as ellaOne® HRA Pharma Paris, France). A selective progesterone receptor modulator, in theory UPA could alter the effectiveness of progestogen-containing contraception started immediately after EC. The results of a recently published pharmacodynamic study of the effect of UPA or placebo followed by quick-starting a combined OC pill were reassuring in that there was no difference in the timing of the onset of ovarian quiescence associated with starting the COC (Cameron *et al.*, 2015). A similar study published in this issue of *Human Reproduction* (Brache *et al.*, 2015) is likewise reassuring about the apparent lack of an effect of UPA on both ovulation and cervical mucus permeability when quick-starting a POP. Like the Cameron study of UPA and the combined pill, Brache's study suggests that UPA may not in fact have any deleterious effect on the contraceptive effectiveness of a 'quick-started' POP. Far more concerning, and arguably not foreseen, is the finding of Brache et al. (2015) that starting a POP significantly increased the chance of ovulating within 5 days of taking UPA when, in theory, sperm still present in the genital tract from the act of intercourse for which EC was used may fertilize the egg. While ovulation occurred in the first 5 days after EC use in only one of the 29 cycles (3%) when UPA was taken followed by a placebo, it occurred in 13 of 29 (45%) in the

cycles in which UPA was immediately followed by quick-starting the POP. Thus, the Brache study suggests the very real possibility that quick-starting a POP may jeopardize the contraceptive effectiveness of UPA itself, significantly reducing the chance of the emergency contraceptive preventing a pregnancy resulting from the act of intercourse for which it was taken in the first place. So, rather than providing effective contraception to prevent pregnancy from further acts of intercourse, quick-staring may enhance the likelihood of failure of UPA EC.

These are not easy studies to do and both are pharmacodynamic studies, involving relatively small numbers of women, with ovarian activity as their end-point rather than pregnancy. As ever, they raise more questions than they answer. Does quick-starting the combined OC pill—which contains estrogen as well as a progestogen—have the same effect on the ovulation inhibition associated with UPA? Or will the ethinyl estradiol in the combined pill suppress LH sufficiently to prevent ovulation? In their study, Cameron and co-workers (2015) did not address this issue; they looked at the effect of the emergency contraceptive on the efficacy of the quick-started pills, but not at the effect of the pills on the efficacy of the emergency contraceptive. What about progestogens other than desogestrel; will they have the same effect on UPA as Brache et al. (2015) have shown? What about other routes of administration? Would insertion, immediately after EC use, of a contraceptive implant containing etonogestrel (Implanon®) or levonorgestrel (Jadelle®) have a similar effect on the ovulation inhibiting effect of UPA? Lastly, many women present for EC after missing a few OC pills. Theoretically missing pills may result in ovulation but how many must be missed before ovulation occurs so that if the pill is re-started immediately after using EC (as is usually advised) the effectiveness of the EC is jeopardized?

Given the nature and size of the Brache and Cameron studies and the lack of any evidence of quick-starting on pregnancy rates, it may be tempting to regard the findings as inconclusive and inconsequential. This is what the European Medicines Agency did when presented with the data by the manufacturer in 2014—the PIL was left unchanged. Women are presently advised 'ellaOne may make regular hormonal contraceptives, like pills and patches, temporarily less effective. If you are currently taking hormonal contraception, continue to use it as usual after taking ellaOne, but be sure to use condoms every time you have sex until your next period' (HRA Pharma, 2015). Ironically, the EMA seems content to allow the PIL to suggest that UPA may jeopardize the efficacy of the quick-started OC (which the data suggest may not be the case) but remain silent about the possible adverse effect on the efficacy of the emergency contraceptive. In contrast, presented with exactly the same data, the FDA has specifically advised against quick-starting, recommending in the labelling 'Subsequent acts of intercourse should be protected by a reliable barrier method until next menstrual period. If a woman wishes to use hormonal contraception, she should do so no sooner than 5 days after intake of ella® (UPA)' (USFDA, 2015).

Where does this leave clinicians? The results seem sufficiently concerning to advise women not to quick-start an OC pill immediately. Why take the risk of jeopardizing the effectiveness of the emergency contraceptive? Best practice may rather be to give women a supply of pills with explicit instructions to delay starting until at least 5 days after taking UPA. Importantly, it should be made clear to women (and to clinicians who may be confused) that the concern is not about acts of intercourse which may or may not occur in the next few days (and for which a condom can be used), but for the risk of pregnancy arising from the unprotected act of sexual intercourse that definitely happened and for which EC was taken.

It would be a pity if these findings deterred us from developing strategies to improve the timely uptake of ongoing contraception after EC use. Interventions of the sort described by Michie *et al.* (2014) should be explored further but with women given firm advice about exactly when to start their pills (and why). It would be a pity too if these findings deterred clinicians from prescribing UPA for EC or pharmacists from recommending it (ellaOne® is now approved for over-the-counter provision in much of Europe) since UPA is more likely to prevent pregnancy than levonorgestrel EC (Glasier *et al.*, 2010), especially if women are obese (Glasier *et al.*, 2011)—although this is another issue about which the regulatory authorities are unable to agree (ESHRE Capri Workshop, 2015).

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