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Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel

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Abstract

Background: Emergency contraception (EC) does not always work. Clinicians should be aware of potential risk factors for EC failure.
Study Design: Data from a meta-analysis of two randomized controlled trials comparing the efficacy of ulipristal acetate (UPA) with levonorgestrel were analyzed to identify factors associated with EC failure.
Results: The risk of pregnancy was more than threefold greater for obese women compared with women with normal body mass index (odds ratio (OR), 3.60; 95% confidence interval (CI), 1.96–6.53; p<.0001), whichever EC was taken. However, for obese women, the risk was greater for those taking levonorgestrel (OR, 4.41; 95% CI, 2.05–9.44, p=.0002) than for UPA users (OR, 2.62; 95% CI, 0.89–7.00; *ns*). For both ECs, pregnancy risk was related to the cycle day of intercourse. Women who had intercourse the day before estimated day of ovulation had a fourfold increased risk of pregnancy (OR, 4.42; 95% CI, 2.33–8.20; p<.0001) compared with women having sex outside the fertile window. For both methods, women who had unprotected intercourse after using EC were more likely to get pregnant than those who did not (OR, 4.64; 95% CI, 2.22–8.96; p=.0002).
Conclusions: Women who have intercourse around ovulation should ideally be offered a copper intrauterine device. Women with body mass index >25 kg/m^2 should be offered an intrauterine device or UPA. All women should be advised to start effective contraception immediately after EC.

Keywords: Emergency contraception; Ulipristal acetate; Levonorgestrel; Risk factors

1. Introduction

Emergency contraception (EC) can prevent pregnancy after unprotected intercourse — but it does not always work. The most widely used emergency contraceptive, levonorgestrel 1.5 mg orally within 72 h of intercourse (LNG-EC), prevents at least 50% of pregnancies that would have occurred in the absence of EC [1]. Insertion of a copper intrauterine device (IUD) probably prevents more pregnancies [2,3] and is recommended as the EC of choice by some organizations [4], particularly for women who have intercourse midcycle when the risk of pregnancy is greatest [5]. However, this requires the ready availability of a health professional skilled to do the insertion. Moreover, many women, especially young women, find the idea of an IUD unacceptable [6,7]. Ulipristal acetate (UPA; ellaOne HRA Pharma, Paris, France), a selective progesterone receptor modulator, is more effective than LNG for EC and can be used up to 120 h after intercourse [8,9]. UPA has been marketed in Europe since 2009 and was approved by the Food and Drug Administration in 2010. As a new drug entity, UPA will only be available on prescription for several years before it can be considered for "over the counter" status.

The vast majority of women taking EC are not at risk of pregnancy. The chance of conception following a single random act of intercourse has been reported to be 4% to 6%

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[10,11], and even if sex occurs at the most fertile time of the cycle, only 30% at most [11,12]. The introduction of more effective methods of oral EC, such as UPA, raises the possibility of distinguishing between women at very low risk of pregnancy (and perhaps offering them the more easily available over-the-counter method) and those at high risk who may prefer to use a theoretically more effective method (UPA or an IUD) even if accessing it is more difficult. Assessing the risk of pregnancy based on the time in the cycle when intercourse occurred can be unreliable since many women are uncertain of the date of their last menstrual period [13] and because there is significant variation (even intraindividual) in cycle day of ovulation. However, there may be other factors that can be taken into account when estimating the risk of pregnancy and the risk of failure of a less effective method of EC.

In order to explore potential factors that could explain a higher risk of EC failures, we have used data from a meta-analysis of two randomized controlled trials comparing the efficacy of UPA with LNG for EC [9].

2. Materials and methods

Both trials combined in the meta-analysis had a similar design. One trial recruited 1672 women presenting for EC within 72 h of unprotected intercourse [8], whereas in the second trial, 2221 women could enroll up to 120 h after intercourse [9]. In both trials, LNG 1.5 mg orally was compared with UPA either 30 mg [9], the marketed formulation, or a 50 mg nonmicronized formulation [8], having a similar pharmacokinetic profile. Both trials enrolled women with regular menstrual cycles and not using hormonal contraception and excluded women relying on sterilization (themselves or their partner), using an IUD, breast-feeding, or aged under 16 years (17 in Northern Ireland and 18 in the United States and Ireland). Treatment was administered after a urinary pregnancy test was confirmed negative, and women were systematically tested for pregnancy at follow-up 1 week after the expected onset of next menses after treatment.

Data from women meeting the protocol definition of the primary efficacy population of each trial (described in detail in Creinin et al. [8] and Glasier et al. [9]) were included in the meta-analysis. To be included, women had to receive EC, and their pregnancy status at follow-up had to be known. For both trials, pregnancies deemed to have occurred before EC was taken were excluded, and in the second trial [9], three pregnancies conceived long after EC was used were also excluded. In total, 3445 women were included in the meta-analysis (1546 women from the 72-h study [8] and 1899 from the 120-h study [9]; UPA n=1714, LNG n=1731). There were 60 pregnancies (UPA n=22, LNG n=38) [9].

A nominal logistic model was used to explain the occurrence of pregnancy. In addition to study and treatment factors included by constraint in the model, the effects of the following covariates were assessed in the model: age, body mass index (BMI) and weight, time (hours) from unprotected intercourse to treatment with EC, occurrence of further acts of unprotected intercourse (after use of EC) and history of pregnancy and conception probability defined according to the method of Trussell et al. [14]. Trussell et al. compiled data from two studies of conceptions by cycle day relative to the day of ovulation among women not using contraception to provide estimates of conception probabilities for each cycle day. In one study [15], the day of ovulation was estimated from daily measurements of basal body temperature, while in the other, daily early morning urine samples were assayed for metabolites of estrogen and progesterone [5]. Pooled data were used to estimate a risk of conception of 3.6% if intercourse occurred 5 days before ovulation; 13.6% and 15.5% at 4 and 3 days before ovulation, respectively; 27.7% and 29.8% at 2 and 1 days before ovulation, respectively; and 12.3% on the day of ovulation itself.

Likelihood ratio tests were used to select confounding factors with a significant marginal contribution and to test the treatment effect. Influence of the retained covariates and treatment on pregnancy risk was then expressed in terms of odds ratio (OR) and 95% confidence intervals (CI).

When deemed useful, a restricted spline cubic smoothing method was applied to the logistic model in order to better describe the relationship between a covariate and the risk of pregnancy [16].

3. Results

As already demonstrated [9], the risk of pregnancy was reduced by almost 50% among women using UPA compared with those using LNG (OR, 0.55; 95% CI, 0.32–0.93; p=.025).

Three of the six covariates tested were found to have a statistically significant effect on the risk of pregnancy: BMI, conception probability and further intercourse.

The variable with the most highly significant impact on the risk of pregnancy was BMI. Compared with women with a BMI under 25 kg/m^2 [normal weight or underweight according to the World Health Organization (WHO) [17]], the risk of pregnancy was more than three times greater (OR, 3.60; 95% CI, 1.96–6.53; p<.0001) for obese women (BMI of 30 kg/m^2 and above according to WHO) and 1.5 times greater (OR, 1.53; 95% CI, 0.75–2.95) for overweight women (BMI between 25 and 30 kg/m^2), whichever EC drug was taken (Table 1). When the pregnancy rates were compared within the two treatment groups, the effect of BMI was more pronounced in women treated with LNG than with UPA. The relative risk of becoming pregnant was doubled when overweight women taking LNG were compared with normal-weight or underweight women (OR, 2.09; 95% CI, 0.86–4.87; *ns*) using LNG, whereas the risk was not different when women taking UPA were compared (OR, 0.97; 95% CI, 0.27–2.83). Moreover, obese women

Table 1
Pregnancy risk according to BMI, conception probability and further intercourse

Confounding factors	Subgroups	Pregnancy, *n*/*N* (%) [95% CI]		
		Overall	UPA	LNG
BMI (kg/m^2)	Normal or underweight (< 25 kg/m^2)	27/2232 (1.2) [0.8–1.8]	12/1110 (1.1) [0.6–1.9]	15/1122 (1.3) [0.8–2.2]
	Overweight (25–29.9 kg/m^2)	13/744 (1.7) [1.0–3.0]	4/377 (1.1) [0.4–2.7]	9/367 (2.5) [1.3–4.6]
	Obese (≥30 kg/m^2)	20/469 (4.3) [2.8–6.5]	6/227 (2.6) [1.2–5.6]	14/242 (5.8) [3.5–9.5]
Conception probability[a]	Outside fertile window (0)	25/2227 (1.1) [0.8–1.7]	9/1101 (0.8) [0.4–1.5]	16/1126 (1.4) [0.9–2.3]
	Inside fertile window (>0)	35/1218 (2.9) [2.1–4.0]	13/613 (2.1) [1.2–3.6]	22/605 (3.6) [2.4–5.4]
Further intercourse	No	49/3274 (1.5) [1.1–2.0]	17/1625 (1.0) [0.7–1.7]	32/1649 (1.9) [1.4–2.7]
	Yes	11/171 (6.4) [3.6–1.1]	5/89 (5.6) [2.4–12.5]	6/82 (7.3) [3.4–15.1]

[a] Fertile window: day of ovulation minus 5 to plus 1.

who took LNG were at more than four times greater risk to get pregnant (OR, 4.41; 95% CI, 2.05–9.44; p=.0002) in comparison with normal-weight or underweight women. For women treated with UPA, the same OR comparing obese women to normal or underweight women was estimated to be 2.62 (95% CI, 0.89–7.00). Based on the spline cubic smoothing method applied to the logistic model, LNG showed a rapid decrease of efficacy with increasing BMI, reaching the point where it appeared no different from pregnancy rates expected among women not using EC at a BMI of 26 kg/m^2 compared with 35 kg/m^2 for UPA.

Following these results, the same series of analyses was performed with weight as a covariate instead of BMI. Weight was found to be a highly statistically significant risk factor (p<.0001) with marked differences between the two treatments: according to a spline cubic model, the limit of efficacy was reached at a weight of 70 kg for LNG compared with 88 kg in women having taken UPA.

For both methods of EC, the risk of pregnancy was also significantly related to the cycle day of intercourse. According to the logistic model, the risk of pregnancy was increased more than fourfold (OR, 4.42; 95% CI, 2.33–8.20; p<.0001) among women with the highest probability of conception (who had intercourse on the day before ovulation when conception probability is 30%, *n*=195) compared with women who reported having intercourse when the risk of conception was theoretically nil (outside the fertile window ranging from 5 days before ovulation to the first day after ovulation, *n*=2227). No significant difference between treatment groups in the effect of conception probability on the pregnancy rate was observed (p=.535; Table 1).

The third most significant variable in terms of the effect on pregnancy risk was the occurrence of further unprotected intercourse. Regardless of which method of EC was used, women who had further unprotected intercourse after using EC (*n*=171, pregnancy rate of 6.4%) were more than four times as likely to get pregnant than those who did not report further intercourse (*n*=3274, pregnancy rate of 1.5%) (OR, 4.64; 95% CI, 2.22–8.96; p=.0002). There was no difference between treatment groups in the effect of further intercourse on pregnancy rate (p=.489).

In the multivariate analysis, none of the other variables studied (age, time from unprotected intercourse to treatment or pregnancy history) had any significant contribution to the occurrence of pregnancy.

4. Discussion

Data used for this research came from two clinical trials, neither of which was designed to explore the effect of weight or other risk factors on the effectiveness of EC. Moreover, the number of women in the studies with a BMI of 35 kg/m^2 or greater was small, and the number of pregnancies among this group was extremely small. Nonetheless, the results are clinically important as they suggest that women with BMI of 25 kg/m^2 and over, as well as confirming that those who have intercourse at the most fertile time of the cycle and those who have further acts of intercourse in the same cycle, are all at increased risk failure of EC. Indeed, among obese women treated with LNG, the observed pregnancy rate was 5.8%, which is slightly above the overall pregnancy rate expected in the absence of use of EC based on the conception probabilities of Trussell et al. [14] (5.6%), suggesting that for this group of women, LNG-EC may be ineffective. To our knowledge, this is the first time that an association between BMI and EC failure has been reported.

It is not surprising that the timing of intercourse before using EC and further acts of intercourse after treatment are related to the risk of pregnancy, and in this respect, our findings support those of others [18]. The egg is only capable of being fertilized for 24 h after ovulation, and sperm are only capable of fertilizing the egg for 5 to 6 days. The probability of conception increases from the first 3 days of the cycle (when it is negligible) to a peak of 30%, at most, on the day before ovulation [5]. The probability of conception falls rapidly and is again negligible after 24 h following ovulation, so if intercourse occurs early or late in the cycle, pregnancy is highly unlikely and it is *most likely* in the 48 h before ovulation. Clinicians are aware of this — and so are many women. Indeed, some women make a judgement as to whether or not to use EC at all based on the timing of intercourse; and if it occurred at a time in the cycle when they think they are at low risk, they do not bother to use EC [19,20]. For clinicians, the standard consultation for EC involves asking the woman the date of her last menstrual

period, not only to exclude an existing pregnancy but to gauge the likely risk of conception. Some clinicians do offer women an IUD if sex has occurred around midcycle arguing that an IUD is more likely to prevent pregnancy than EHC even if an IUD is more difficult to provide. It is likely that in the same woman, the day of ovulation varies from one cycle to another, even in women with regular cycles and in both trials [8,9], a small number of women conceived outside the theoretical fertile window. Of course, some women have no idea when their last menstrual period was, not many keep a diary, some get it wrong [13] and still others do not have regular cycles, and so from time to time, pregnancies do occur following intercourse at times in the cycle when the risk is theoretically low [12].

It is always difficult to tell if pregnancy has occurred as 'true' failure of EC; that is, the method is used perfectly, but nevertheless, it fails. Many perceived EC failures are likely to be "user failures." Some women are already pregnant when they take EC and others conceive after EC has been used. Outside clinical trials pregnancy testing before giving EC is not routine but reserved for women in whom there is some suspicion of a pre-existing pregnancy. Even in clinical trials when pregnancy testing is routinely done, some women may have conceived within only a couple of days before treatment, too recently for even the most sensitive pregnancy test to detect. Clinical trials in which women are either asked to abstain from sex after taking EC or to use a barrier method until the onset of menses, provide evidence that repeated acts of intercourse are common, and many of them are unprotected [18,19]. From the meta-analysis reported here, it is clear that repeated acts of intercourse after taking EC put women at higher risk of pregnancy — a pregnancy that is often regarded as a failure of EC. In a trial comparing LNG with mifepristone, 30% of the 4071 women participating admitted to at least one act of intercourse after taking EC [18]. The pregnancy rate was more than doubled among women having sex after treatment (2.7% vs. 1.1%). While in the WHO study, pregnancy was more likely among women having intercourse after treatment with mifepristone than after treatment with LNG [18], there was no such difference between UPA and LNG observed in the present study.

The observation that BMI is associated with failure of EC is also not a surprise, although this is the first time that it has been reported. An association between weight and contraceptive failure has been reported for all but the very high-dose hormonal contraceptives [21–23]. Although it is not possible to compare different contraceptive methods given by different routes of administration at different doses, it is possible to draw some parallels particularly in respect of the robustness of the evidence. Doubt has been cast on the observation in relation to oral contraceptives [24], as it is hard to distinguish between method failure and user failure, and so the effect of weight on failure rates may reflect issues of compliance [25]. However, the finding that increasing BMI (or weight) is associated with increased failure rates of the LNG-only implant Norplant [26,27] — a method that is independent of compliance for its effectiveness — suggests that there may be a real effect. Indeed, obese women are at demonstrably higher risk of failure of Norplant if use is extended to 6 and 7 years when the dose of LNG in the implants has decreased significantly [28]. A recent pharmacokinetic study in which normal-weight or obese women were treated with a low-dose combined oral contraceptive pill containing LNG demonstrated an increase in the time taken to achieve a steady state of LNG concentrations in relation to obesity [29]. The authors of this small study suggested this as a possible mechanism for increasing failure rates of hormonal contraception in obese women. Whatever the underlying mechanism, the observation that the risk of pregnancy following EC use is higher among overweight women is important, not least because the risks of pregnancy per se are increased among obese women [30].

How should those of us who are advising women about EC interpret these findings? It is easy to identify women who are overweight, and we can advise them that they may be more at risk of EC failure and may suggest they use UPA or an IUD rather then LNG. In this study, in addition to exploring the effect of BMI on the risk of pregnancy after EC use, we have presented the results for weight since most women know their weight, while few would be able to tell a health provider their BMI. Moreover, a woman who weighs over 70 kg may have a low BMI if she is tall, but she would, nonetheless, be advised that she may be at greater risk of EC failure. It might be tempting to suggest doubling the dose of EC for women over 70 kg (as is advised for women on enzyme-inducing anticonvulsant drugs [4]), but data are necessary to support such practice.

It is much more difficult to be confident in assessing pregnancy risk in relation to the time in the cycle of intercourse, but while we might be reluctant to advise a woman that her risk is low or negligible, we lose nothing by telling someone that the risk of pregnancy might be rather high and that she might be advised to have an IUD (if acceptable and accessible).

We can strongly advise women not to have *unprotected* sex after using EC, and we can strongly recommend that all women immediately start ongoing contraception. In the UK, it has long been routine clinical practice to offer women the choice between waiting for the onset of menses or starting hormonal contraception immediately after using EC. Indeed, the fact that easy access to EC from pharmacies risks missing the opportunity for EC users to "bridge" immediately to ongoing contraception is of growing concern [31,32]. Since the motivation to do something about an act of risky sex probably declines with time, we should continue to advise women to use EC as soon as possible. In order for women to do this, we have to continue to make EC easily available. However, it is reassuring for providers and for women who delay seeking EC to know that with the availability of UPA (up to 120 h after sex) as an alternative to the IUD, all may not be lost.

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