

Emergency Contraception: Review and Update

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Abstract Unintended pregnancy continues to be a substantial public health problem. Emergency contraception (EC) provides a last chance at pregnancy prevention. Several safe and effective options for emergency contraception are currently available. The Yuzpe method, a combined hormonal regimen, was essentially replaced by other oral medications including levonorgestrel and the antiprogestin ulipristal. The antiprogestin mifepristone has been studied for use as emergency contraception. The most effective postcoital method of contraception is the copper intrauterine device (IUD). Obesity and the simultaneous initiation of progestin-containing contraception may decrease the effectiveness of some emergency contraception.

Keywords Emergency contraception · Contraception · Review

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Introduction

Unintended pregnancy continues to be a substantial public health problem. Emergency contraception (EC) provides a last chance at pregnancy prevention if another contraceptive method was not used or was underused, either by method failure or by misuse. As EC is the only contraceptive method that can prevent pregnancy after sex has taken place, it is especially important in the case of rape. Multiple EC methods are currently available in the USA and abroad. Overall, these methods have been shown to be safe and effective. This article reviews combined oral contraceptive pills (COCs), levonorgestrel (LNG), ulipristal acetate (UPA), the copper intrauterine device (IUD), and mifepristone, including mechanism of action and efficacy, with an emphasis on recent and landmark studies. This information is summarized in Table 1.

Efficacy of emergency contraception is generally described in the literature as absolute pregnancy rates or percentage of expected pregnancies prevented. The latter calculation necessitates a number of assumptions, which can vary across studies. Expected pregnancy rates without EC vary greatly depending on timing of intercourse within the menstrual cycle. In general, EC is recommended at any time during the menstrual cycle because of inaccuracies when estimating a woman's phase in the cycle due to variation in cycle length, day of ovulation, and recall. For consistency and accuracy, the absolute pregnancy rates in clinical studies are reported here. These are useful for comparison among methods. This article seeks to review the current evidence and recommendations regarding EC and discuss continuing challenges and future directions. It will explore the possible effect of obesity on efficacy as well as whether to quick start hormonal contraception after EC. It will also readdress remaining safety concerns as well as how to expand public health impact.

Table 1 Comparison of emergency contraception methods

Method	Dosage	Window of use after intercourse ^a (days)	Side effects	Pregnancy rate (%)	Access in USA
Combined oral contraceptive pills	Varies ^b	5	Nausea, vomiting, headache	2.0–3.5	Requires a prescription
Levonorgestrel	1.5 mg	3 ^c	Nausea, headache, earlier menses	1.5–2.6	Available over the counter
Ulipristal acetate	30 mg	5	Nausea, headache, delayed menses	0.9–2.1	Requires a prescription; expensive
Copper intrauterine device	Not applicable	5	Dysmenorrhea, heavier menses	0.1	Requires an office visit
Mifepristone	low dose (<25 mg) mid dose (25–50 mg) high dose (>50 mg)	5	Nausea, headache, delayed menses, vaginal bleeding	0.7–1.9 %	Not currently available for this indication ^d

^a The time interval affects the efficacy of levonorgestrel and COC, with greater efficacy associated with earlier administration

^b Dose is 100 µg ethinyl estradiol plus 0.50 mg levonorgestrel followed by a second dose of 100 µg ethinyl estradiol plus 0.50 mg levonorgestrel 12 h later. Actual number of pills depends on formulation of combined oral contraceptive pills

^c Approved for use within 3 days, but some efficacy up to 5 days after intercourse

^d Available for EC in China, Russia, Vietnam, Armenia, and Ukraine

Methods of Emergency Contraception

Combined Oral Contraceptive Pills

Oral estrogen and progestin have been used for emergency contraception since the introduction of the Yuzpe regimen (two doses of 0.1 mg ethinyl estradiol and 0.5 mg levonorgestrel 12 h apart) in the 1970s. Currently, this is achieved by taking multiple combined oral contraceptive pills, described in more detail at <http://ec.princeton.edu/questions/dose.html>. Given the affordability and wide availability of COC, this can be a convenient option in some settings. This regimen can be utilized within 72 h of unprotected intercourse. It works by inhibiting or delaying ovulation [1]. Clinical trials reveal pregnancy rates from 2.0 to 3.5 % per cycle [2–4]. In comparative trials, the Yuzpe method has been shown to be less efficacious than newer forms of emergency contraception and associated with more side effects, particularly nausea and vomiting [2, 3, 5•]. Therefore, COC for EC is infrequently used in settings where other methods are available.

Levonorgestrel

Levonorgestrel (LNG) emergency contraception was first approved by the US Food and Drug Administration (FDA) in 1999 as a two-dose regimen of 0.75 mg taken 12 h apart. A single dose of 1.5 mg became available in 2009. This single-dose regimen has generally replaced the original two-dose regimen given comparable efficacy and improved adherence [5•, 6]. After years of political controversy, it became available over the counter without age restriction in June 2013 in the form of Plan B One-Step® (Teva Women's Health, North Wales, PA), a ruling which was expanded to generic

formulations in February 2014. In contrast, France was the first country to allow the sale of LNG EC without prescription or parental consent in 1999. The single-dose regimen is approved for use within 72 h of unprotected intercourse, though data support some continued efficacy up to 120 h [6]. Levonorgestrel works by inhibiting the luteinizing hormone (LH) surge if taken before the surge has started [7, 8]. In other words, it works to delay or prevent ovulation but is ineffective if ovulation, fertilization, or implantation has already occurred. Clinical trials reveal pregnancy rates from 1.5 to 2.6 % of women per cycle when using LNG EC [6, 9, 10]. This includes trials in which LNG EC was taken within 72 h as well as within 120 h.

Ulipristal Acetate

Ulipristal acetate (UPA) is a second-generation progesterone receptor modulator that has been marketed in Europe since May 2009. A 30-mg tablet was approved by the FDA in June 2010 as an emergency contraceptive method. It is only available by prescription in the USA. The European Medicines Agency (EMA) recommended UPA for non-prescription use in November 2014 and its status was changed accordingly in January 2015. It is effective within 120 h of unprotected intercourse. The mechanism of action is to inhibit or delay follicular rupture by postponing the LH peak, even when it has already started to rise [11•]. It also directly inhibits follicular rupture [12]. This creates a wider window of action than LNG. Like LNG, this medication does not prevent fertilization or implantation [12]. Pregnancy rates after UPA use are 0.9–2.1 % [9, 10, 13]. Furthermore, unlike with LNG, efficacy of UPA does not appear to decrease over time [13]. A meta-analysis of two randomized controlled trials to compare UPA

and LNG showed that UPA is more efficacious with lower odds of pregnancy (odds ratio (OR) 0.58, 95 % confidence interval (CI) 0.33–0.99) when taken within 72 h of unprotected intercourse [10].

Copper Intrauterine Device

The copper IUD has been studied and used as EC since the 1970s. Insertion is recommended within 120 h of unprotected intercourse. However, recent research suggests that it is highly effective at any time during the menstrual cycle in women with regular cycles and a known last menstrual period (LMP), as long as a urine pregnancy test is negative at time of insertion [14]. The mechanism of action is not fully understood but is thought to be a combination of copper ions inhibiting sperm function, the main effect, and the IUD creating an inflammatory environment that could prevent implantation [12]. This is the most efficacious method of EC and remains the only method to provide ongoing, long-acting, effective contraception. A review of 42 studies on IUD use as EC demonstrated that only 0.09 % of 7034 women became pregnant [15]. Furthermore, another study showed that for women who chose the IUD for EC, the rate of pregnancy one year after EC was half of that compared to women who used LNG, at 6.5 vs. 12.2 % (hazard ratio (HR) 0.53, 95 % CI 0.29–0.97) [16]. Analysis according to type of EC method received showed pregnancy rates were 5.2 vs. 12.3 % (HR 0.42, 95 % CI 0.20–0.85) [16].

Mifepristone

Mifepristone was approved for use as EC in China in 2002. It is not available for emergency contraception in most other countries with the exception of Russia, Vietnam, Armenia, and Ukraine. However, it is included in this review given the growing evidence of its safety and efficacy for this purpose. Several doses have been studied, divided into low- (<25 mg), mid- (25–50 mg), and high- (>50 mg) dose categories. Mifepristone can be used up to 120 h after unprotected intercourse. It is a first-generation progesterone receptor modulator. The mechanism of action is to delay or prevent ovulation in a dose-dependent fashion [12]. This medication has also been shown to affect the endometrium and may prevent implantation [12]. Pregnancy rates for mifepristone are 0.7 to 1.9 % [5, 6, 17].

A Cochrane review showed that low- and mid-dose mifepristone were both significantly more efficacious than LNG at preventing pregnancy [5•]. When combining nine Chinese, one UK, and one multinational trial, low-dose mifepristone was associated with a lower risk of pregnancy than LNG (relative risk (RR) 0.70; 95 % CI 0.50–0.97). When combining 20 trials conducted in China, mid-dose mifepristone was also more efficacious than LNG (RR 0.64; 95 % CI 0.45–0.92).

Side effects were also more tolerable for mifepristone than LNG (RR 0.58; 95 % CI 0.41–0.82). There were no trials that compared high-dose mifepristone with LNG or mifepristone with UPA. Overall, there was no significant difference in the efficacy of the various dose options for mifepristone when combining high-quality studies, although there were some differences in side effect rates, with menstrual delay more common with higher doses. A recent study comparing 5 to 10 mg suggested a higher failure rate of the lower dose and thus advised against using a 5-mg dose [17].

Special Considerations and Controversy

Obesity

The efficacy of certain EC methods may be reduced in overweight and obese women. This issue was first reported in 2011 when a meta-analysis of two randomized controlled trials revealed that risk of pregnancy was more than three times greater for obese (body mass index (BMI) ≥ 30 kg/m²) compared to normal weight (BMI <25 kg/m²) women after taking UPA or LNG (OR 3.60; 95 % CI 1.96–6.53) [18]. In this analysis, the effect of obesity on pregnancy rates with LNG (OR 4.41; 95 % CI 2.05–9.44) was greater than with UPA (OR 2.62; 95 % CI 0.89–7.00). The analysis was performed with two models, using BMI and then weight as a covariate, which each had a significant effect on pregnancy risk. The limit of efficacy was reached at approximately 70 or 26 kg/m² for LNG and 88 or 35 kg/m² for UPA. Another study performing further statistical analysis of the same data confirmed these findings [19].

However, these trials were not designed to evaluate the association between weight and BMI and pregnancy risk, and as such, the number of women who were overweight or obese was small. In fact, the weight and height data for one of the two trials included in these analyses were self-reported instead of measured, introducing potential error [19]. Nevertheless, these findings spurred regulatory bodies in Europe and Canada to mandate warnings on LNG EC packaging in November 2013 and March 2014, respectively [20]. Labels warned that LNG EC might be less effective for women with higher body weights. After further review, in July 2014, the EMA removed the warnings from labels due to the limited data [21]. The FDA has not changed its labeling. More recently, a pooled analysis of three multinational randomized controlled trials failed to demonstrate a correlation between increasing weight and greater risk of pregnancy [22•]. Again, these studies were not designed for this purpose and were limited by small numbers of women in the high BMI group with under 10 % with a BMI over 30 kg/m² or weight over 75 kg [22•].

Studies designed to determine whether there is a decrease in efficacy with increasing body weight and/or BMI are

lacking. Given the limited evidence to the contrary, the World Health Organization Medical Eligibility Criteria advises that obese women can use COC, LNG, or UPA for EC without restriction [23]. Furthermore, the aforementioned secondary analysis studies only pertain to LNG and UPA. Apart from the lowest 5-mg dose, mifepristone effect does not seem to vary by weight, although there are no studies to directly measure this either [17]. The efficacy of the copper IUD does not appear to be affected by body mass index or weight, and thus can be used as a first-line option for obese women when available [15].

Quick Start of Contraception After Use of Oral EC

The most recent published recommendations advise immediately starting any regular contraception after use of UPA, LNG, or COC as EC to enhance contraceptive continuation and reduce the risk of unintended pregnancy with subsequent acts of intercourse [24, 25]. Abstinence for 7 days after LNG or COC and for 14 days after UPA is recommended based on expert opinion [24]. However, there is theoretical concern that because UPA is a progesterone receptor modulator, it could make hormonal contraception, particularly progestin-containing methods, less effective or vice versa. Recent pharmacodynamic studies have explored this issue further.

A randomized controlled trial by Cameron et al. was designed to determine the effect on ovarian activity of UPA followed by immediate COC use [26]. It demonstrated that UPA does not alter the ability of COC to achieve ovarian quiescence, supporting the safety of a quick start approach. On the other hand, a study by Brache et al. was designed to test whether there is an interaction between UPA and immediate initiation of a desogestrel progestin-only pill [27]. Although UPA did not affect the contraceptive effect of desogestrel, desogestrel significantly decreased ovulation delay and inhibition ($p=0.0054$) and thus could impair the efficacy of UPA. During the five days after UPA administration, ovulation was noted in one of the 29 UPA-only cycles (3 %), whereas it occurred in 13 of the 29 cycles of UPA followed by desogestrel (45 %). Given these findings, in March 2015, the FDA updated UPA packaging to include a warning that a woman should wait five days after ingestion of UPA before starting hormonal contraception, as co-administration may reduce the efficacy of UPA [28]. In Europe, the EMA has not changed its recommendations based on the limited nature of the data.

This new finding is concerning and brings important unanswered questions to the forefront. It has yet to be demonstrated that quick starting hormonal contraception after UPA actually increases pregnancy rates. Furthermore, studies are needed regarding the impact on UPA efficacy of COC, other progestin-only oral contraceptive pills, and progestin contraceptives such as the implant or shot. In the meantime, it seems

reasonable to dispense hormonal contraception at the time of EC administration and advise waiting five days before initiating due to the potential interaction.

Safety

Given extensive safety data, the benefits of levonorgestrel and COC for EC always outweigh the risks according to the Center for Disease Control's Medical Eligibility Criteria for Contraceptive Use [29]. Ulipristal was not available at the time of the CDC review, though no particular safety concerns exist for this method of EC. However, concern lingers surrounding risk for ectopic pregnancy and exposure to EC during pregnancy, which will be reviewed here in more detail, including the most recent data.

A systematic review of 136 studies of LNG or mifepristone EC showed that 3 of 494 (0.6 %) pregnancies in those who used mifepristone were ectopic, and 3 of 307 (1 %) of those who used LNG were ectopic [30]. Overall, these rates did not surpass the rate in the general population of approximately 2 % [31]. Like other forms of contraception, by reducing the risk of pregnancy, emergency contraception decreases the absolute risk of ectopic pregnancy. A large retrospective case-control study also demonstrated that use of LNG EC does not correlate with risk of ectopic pregnancy [32]. However, in the case of EC failure, there was a higher risk of ectopic pregnancy compared to women not using contraception (OR 2.79; 95 % CI 2.27–3.43; adjusted OR 5.29; 95 % CI 4.07–6.87) [31]. It is hypothesized that this is due to the adverse effect of progesterone on tubal motility and ciliary activity [33, 34]. Although this is clearly not a reason to avoid EC, it is useful to keep in mind in the case of EC failure.

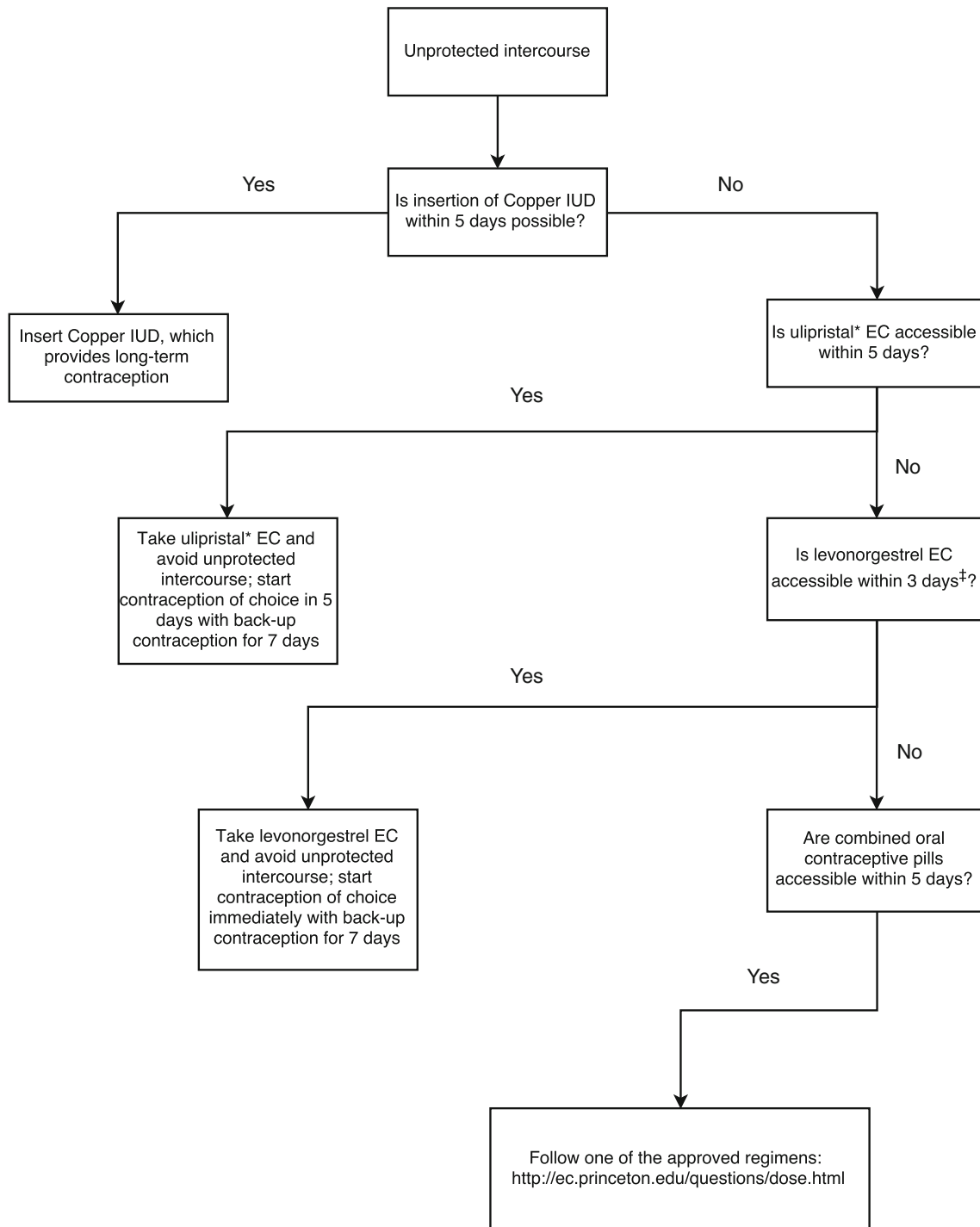
Although evidence is limited, in utero exposure to EC does not seem to increase the incidence of fetal malformation. Multiple prospective studies have failed to find a statistically significant association between oral contraceptive use in early pregnancy and fetal anomalies [35]. A recent case-control study showed no difference in the mental development, physical growth, or rate of birth defects between children exposed to LNG EC and those who were not [36]. With regard to UPA, prospective studies and post marketing safety data, accounting for over 1.4 million UPA exposures, show no adverse effects on pregnancy [37]. A total of 376 exposed pregnancies have been reported with no anomalies or adverse outcomes attributed to UPA.

If pregnancy occurs with an IUD in place, including after placement of a copper IUD for EC, removal is recommended due to increased risk of complications such as spontaneous abortion, chorioamnionitis, and preterm delivery [38]. After early IUD removal, although there is no evidence of teratogenic effects, women who conceive with a copper IUD in place remain at higher risk for preterm delivery [38].

Lastly, the data on fetal anomalies among women with failed medical abortion using mifepristone can be extrapolated to exposure to mifepristone used for EC. Findings are overall reassuring, although limited to adverse event reporting so data quality is poor [39].

Public Health Impact

Although emergency contraception effectively prevents pregnancy at an individual level, several studies have demonstrated that this does not necessarily translate to the population



* or mifepristone in limited countries where it is available

‡ or within 5 days with decreased efficacy

Fig. 1 Clinical algorithm for emergency contraception

level [40, 41]. Increasing access to EC, whether by making EC pills available over the counter, supplying them to women in advance of need, or prescribing them over the phone, does not seem to decrease pregnancy rates. In a systematic review, only one of 15 studies designed to increase access to EC showed a reduction in unintended pregnancy or abortion rates [40, 42]. This study took place in Egypt and included an educational component focused on when and how to use EC in addition to increasing access with advance provision [42].

Several potential explanations for the overall null effect on unintended pregnancy are possible. Although access to EC has expanded worldwide as more methods have become available and over the counter access has increased, a lack of comprehensive sexual education in many settings may lead to an under-informed public regarding this method of contraception. Numerous studies demonstrate that women have limited knowledge about the existence or proper use of emergency contraception [43]. A systematic review reported that even when women have EC available, they often do not take it when indicated, showing that access is not the only issue [40]. Studies have demonstrated that women fail to use EC due to lack of knowledge about the method and not recognizing they are at risk of pregnancy [44, 45]. Furthermore, provision is obstructed by suboptimal knowledge and principled objections from providers, including doctors and pharmacists [41]. In other words, education likely needs to accompany access for a successful public health intervention.

Furthermore, access to many EC methods is still limited. Most women in low-income countries do not have access to EC [46]. In countries where EC is available, even over the counter, access can still be an issue. For example, LNG is the most widely available EC method in the USA due to over-the-counter availability. However, the cost may be prohibitive to many women, at an average of US\$41 for the generic form [47]. According to a recent nationwide US survey, many pharmacies do not stock generic LNG EC, and 95 % of pharmacies called did not stock UPA [47]. Additionally, the most effective methods may be the most challenging to obtain. The copper IUD requires a prompt visit to see a clinician who must be able to provide same-day placement. Mifepristone is not available for EC in most countries, and UPA is only available with a prescription except in Europe. There is still an opportunity to increase access to the most effective methods of EC in the USA and abroad.

Future Directions

More research is needed on the effect of body weight and BMI on the efficacy of EC as well as any interaction between other contraceptive methods and EC. Furthermore, there is still the possibility for development and study of alternative methods of EC. For example, studies are

underway to evaluate the efficacy of the levonorgestrel intrauterine system for this purpose.

In addition, there is work to be done in making the most effective methods of EC more accessible. A push to expand access should be combined with an effort to improve public and professional education concerning EC methods and relative efficacy. One proposed way of achieving this is to train providers in a tiered approach to EC counseling to highlight which EC methods are most effective and increase their uptake [48]. Figure 1 provides an algorithm for clinical use with a focus on efficacy.

Conclusions

Several safe and effective options for emergency contraception are currently available. The most efficacious methods of EC are the copper IUD, mifepristone, and ulipristal acetate followed by levonorgestrel EC. Combined oral contraception is the least effective option with the greatest side effects. The EC methods that are most accessible are often not the most efficacious and vice versa. Increasing access to and education regarding the most efficacious methods may help improve the public health impact of EC. Data regarding medical safety and mechanism of action of EC methods are plentiful. However, studies are needed that are designed to evaluate the relationship between weight and BMI on EC efficacy. These should measure height and weight accurately and include an adequate number of overweight and obese women. Further studies are also needed to assess the effect of progestin-containing contraceptive options on the efficacy of EC.

Compliance with Ethical Standards

Conflict of Interest Katharine Sznajder and Roxanne Jamshidi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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