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Original research article

Ulipristal acetate compared to levonorgestrel emergency contraception among current oral contraceptive users: a cost-effectiveness analysis☆,☆☆

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ABSTRACT

Objective: To estimate the cost-effectiveness of ulipristal acetate (UPA) and levonorgestrel (LNG) emergency contraception (EC) on pregnancy prevention among combined oral contraceptive (COC) pill users with an extended pill-free interval. We accounted for the potential interaction of COCs and obesity on EC efficacy.
Methods: We built a decision-analytic model using TreeAge software to evaluate the optimal oral EC strategy in a hypothetical cohort of 100,000 twenty-five-year-old women midcycle with a prolonged "missed" pill episode (8–14 days). We used a 5-year time horizon and 3% discount rate. From a healthcare perspective, we obtained probabilities, utilities and costs inflated to 2018 dollars from the literature. We set the threshold for cost-effectiveness at a standard $100,000 per quality-adjusted life-year. We included the following clinical outcomes: number of protected cycles, unintended pregnancies, abortions, deliveries and costs.
Results: We found that UPA was the optimal method of oral EC, as it resulted in 720 fewer unintended pregnancies, 736 fewer abortions and 80 fewer deliveries at a total cost savings of $50,323 and 79 additional adjusted life-years. UPA continued to be the optimal strategy even in the case of obesity or COCs impacting UPA efficacy, in which a COC interaction would have to change efficacy of UPA by 160% before LNG was the dominant strategy.
Conclusion: Our models found that UPA was the dominant choice of oral EC among COC users with a prolonged "missed" pill episode, regardless of body mass index or an adverse interaction of COCs on UPA.
Implications: Ulipristal acetate is the dominant choice of oral emergency contraception among combined oral contraceptive users.

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1. Introduction

Emergency contraception (EC) is an important strategy to reduce unintended pregnancy, though its public health potential has not yet been realized [1,2]. National Family Growth Statistics suggest that 5.8 million or 11% of sexually active reproductive-age women had ever used EC for pregnancy prevention after method failure or unprotected intercourse [3]. While oral EC use has increased annually since its initial Food & Drug Administration (FDA) approval in 1998, misconceptions among users and clinicians continue to adversely impact uptake [4–7]. In a recent national study, pharmacists mistakenly told one in five 17-year-olds that they would not be able to obtain EC under any circumstances when, in fact, no age restriction exists [7]. At a Title X clinic, 39% of women eligible for EC and seeking pregnancy tests were not routinely counseled on EC [5]. Since the efficacy of EC is time sensitive, factors that limit access to EC delay treatment and hinder or eliminate its utility.

Two oral formulations of EC exist, each with distinct advantages. Levonorgestrel (LNG) is available over-the-counter in retail outlets and is FDA approved for up to 72 h after unprotected intercourse, though its use may be extended to 120 h with reduced benefit [8–10]. Ulipristal acetate (UPA) was first approved in the United States in 2010 and is indicated for use up to 120 h after unprotected intercourse [11,12]. UPA's mechanism of action and longer window of duration may contribute to its superior efficacy [12,13]. However, people's access to UPA is impinged upon by the need for a prescription and limited provider familiarity [14]. Reduction in unintended pregnancy requires more than just improved access to EC but also clear clinical protocols regarding which oral EC formulation is more effective and for whom.

The cost-effectiveness of contraception for pregnancy prevention is well documented, and this extends to EC [15–18]. However, uncertainty of which contraceptive is most cost-effective arises when directly comparing methods in which each have unique advantages. A key population where uncertainty exists in EC management is among combined oral contraceptive (COC) users who miss pills. COCs continue to be one of the most commonly used methods in the United States, with

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25.3% of women ages 15–44 years currently using COCs in 2014 [19]. Typical-use rates demonstrate that no contraceptive method is perfect and that, even among contraceptive users, a role for EC exists [20]. Imperfect use of COCs can lead to unintended pregnancies, with a 7.2% probability of method failure within the first year of use [21]. COCs appear to interfere with UPA, a progesterone receptor modulator, and the reverse may be true [22,23]. A second population where the optimal management of EC is unknown is among overweight and obese women. Preliminary evidence suggests that LNG EC has decreased or no efficacy in overweight or obese women [10,22,24]. Despite a higher drug cost, previous studies determined that UPA was the cost-effective strategy when compared to LNG [18,25,26]. This is because the additional money spent to obtain UPA is still cheaper than the cost of additional unintended pregnancies incurred with LNG. It is unclear, however, if UPA would remain the dominant strategy in a population for which its effectiveness is potentially hindered.

Given these uncertainties, we sought to determine the cost-effectiveness of two clinical management strategies using a decision analytic model. Our primary objective was to estimate the cost-effectiveness of UPA and LNG among COC users with a prolonged "missed" pill episode. Our secondary objective was to assess the influence of the number of missed pills among COC users, and body mass index (BMI), on pregnancy outcomes and assess the number of pregnancies averted.

2. Materials and methods

We built a decision-analytic model to compare the cost-effectiveness of UPA and LNG among current COC users with a prolonged missed pill episode and unprotected intercourse (Fig. 1). Decision analysis is a tool to make stepwise quantitative comparisons of different probabilities in competing strategies [27]. Our primary outcomes of interest were costs, quality-adjusted life-years (QALYS) and the incremental cost-effectiveness ratio (ICER). Our secondary outcomes of interest included number of unintended pregnancies averted and the influence of a number of missed pills and BMI. Our model was built using TreeAge Pro Software (Fig. 1, TreeAge Software, Williamstown, MA, USA). This study was exempt from institutional review board approval at Oregon Health & Science University.

We assessed outcomes for a hypothetical cohort of 100,000 current COC users in the United States (US) who experienced an episode of unprotected intercourse after an extended pill-free period and sought EC. Individual variation exists in the risk of ovulation after missing days of COC pills; however, the greatest risk occurs when the pill-free interval is extended to 8–14 days [28]. We therefore adopted a conservative approach for our model and defined unprotected intercourse as occurring among women who had missed at least one pill immediately prior or after the pill-free interval in her COC pack (8 days). Our model began with women receiving UPA or LNG for EC within 72 or 120 h since unprotected intercourse. The model then branches based on the probability of EC being successful and women's pregnancy outcomes if it was not. Pregnancy outcomes in the model included unintended pregnancies, which could result in delivery, induced or spontaneous abortion, or ectopic pregnancy. We assumed for study purposes that women were age 25 and that pregnancies incurred despite COC and EC use were undesired. All pathways were followed to the same endpoints (Fig. 1). All model inputs were derived from the literature (Table1).

2.1. Probability and cost inputs

We used probabilities from the literature specific to UPA and LNG when available (Table 1), though some information required extrapolation. Contraception and vital statistics data do not reveal the prevalence of pregnancies after EC failure among women who had missed COCs, nor are those data differentiated based on the timing of EC. Therefore, we extrapolated ovulatory activity information contained in the COC literature to inform the risk of pregnancy to this population of EC users [28]. Probability of termination, miscarriage and ectopic pregnancy after EC failure was specific to UPA and LNG literature.

Cost data were derived from the literature and inflated to 2018 dollars using the medical component of the Consumer Price Index [29]. All hospital costs incurred were obtained from Healthcare Cost and Utilization Project diagnosis-related groups. Costs included in the model were the one-time costs of UPA, LNG, elective abortion, and hospital-based spontaneous abortion or ectopic pregnancy, and delivery. The cost of an elective abortion was based on a weighted national average of first- and second-trimester abortions, from which 91.5% occurred in the first trimester and 8.5% occurred at later gestations [30,31]. Similarly, we accounted for the proportion of vaginal compared to Cesarean deliveries using the National Vital Statistics Reports [32,33]. A healthcare perspective was assumed.

2.2. Utilities and QALY inputs

QALYs are a standard measure used in decision and cost-effectiveness analyses to inform the impact of a wide range of health outcomes on quality of life [27]. QALYs are calculated based on both estimated life expectancy and utilities of health states found in the literature. Utilities are a measure of happiness and quality of life regarding a particular outcome, reflecting patient preferences toward outcomes and procedures. We used utilities based on the standard gamble approach, in which adults are asked what probability of death they theoretically would be willing to accept to avoid a specific health outcome and live in perfect health [27].

In this setting, utilities were applied to measure women's experiences of their pregnancy outcomes over a 5-year time horizon and discounted at a rate of 3%. The maternal utility for pregnancy averted was set to 1 (perfect health) and applied over a 5-year time horizon, whereas the utility for undesired delivery was set to 0.991 and also

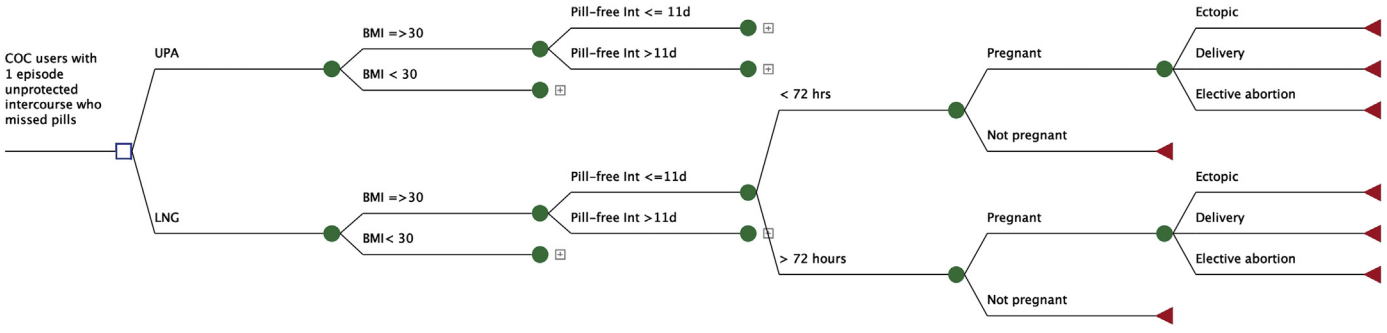

Fig. 1. Truncated tree schematic for comparing UPA and LNG EC in current oral contraceptive users. Decision analytic model. [+] Indicates that further branches are hidden; they lead to the same subsequent branches as what is displayed. Int, interval.

Table 1
Model input parameters for the cost-effectiveness of UPA compared to LNG EC in current oral contraceptive users

Variable	Value	Range considered in sensitivity analysis	Source
Probabilities			
BMI ≥30	0.3567	0.20–0.60	[40]
EC <72 h since unprotected intercourse	0.8995	0.60–0.99	[46]
Pregnant after taking UPA <72 h	0.0136	0.001–0.20	[47]
Pregnant after taking UPA 72–120 h	0.0182	0.001–0.20	[48]
Pregnant after taking LNG <72 h	0.0215	0.001–0.20	[47]
Pregnant after taking LNG 72–120 h	0.0283	0.001–0.20	[47]
Proportion ≥3 days' missed pills	0.3833	0.050–0.800	[49]
SAB or ectopic after UPA	0.1751	0.010–0.300	[11]
SAB or ectopic after LNG	0.0619	0.010–0.300	-
[a]*b[a]Induced abortion after UPA	0.7134	-	-
[a]Induced abortion after LNG	0.8266	-	[50]
Delivery after failed EC	0.1115	0.050–0.300	[11,50]
Reduced risk of ovulation from COC	0.5000	0.100–0.900	
Costs (2018 $)			
UPA	$57	$10–100	[45]
LNG	$51	$10–100	[45]
Delivery	$5051	$500–10,000	[33,51]
SAB or ectopic	$2374	$100–10,000	[33,52]
Abortion	$629	$200–1600	[31]
Utilities (maternal, duration)			
Undesired live birth (5.0 years)	0.991	0.970–0.999	[34]
Elective termination (2.0 years)	0.91	0.65–0.95	[35,36]
Spontaneous abortion or ectopic (4.4)	0.87	0.51–0.99	[53]
Indicator variables			
BMI	1.0	0.25–1.25	See text
[b]Ovulation risk ≥11 days vs. <11 days pill-free interval	3.02	1.00–5.00	[28][b]
Pregnancy risk reduction from COC	0.50	0.01–2.00	See text

SAB, spontaneous abortion.
[a] Range of probabilities for induced abortion after UPA or LNG considered in sensitivity analyses is reflected in ranges of complementary variables within the same chance node (SAB or ectopic and delivery after failed EC).
[b] Based on data studying follicle change and ovarian function with deliberate extension of the pill-free intervals 8–10 versus 11–14 days.

applied over a 5-year time horizon [34]. The maternal utility for termination of pregnancy was set to 0.91 and applied for 2 years, after which a woman resumed her perfect state of health [35,36]. The estimated utility for an ectopic pregnancy is traditionally applied across a woman's remaining reproductive health years, but because we collapsed spontaneous abortion and ectopic pregnancy into one variable, a weighted average of 2 and 25 years (4.4 years) was utilized.

We calculated the ICER to compare UPA and LNG interventions. The ICER was estimated by dividing the difference in cost between the two interventions by the difference in QALYs. The threshold for cost-effectiveness was set at a standard of $100,000 per QALY, meaning that a cost of less than $100,000 per each additional QALY would be considered cost-effective [37,38].

2.3. Sensitivity analysis

Sensitivity analysis is used to determine how changes in model inputs might impact results. We performed sensitivity analyses on all probabilities, costs, and utilities and utilized indicator variables to proportionately vary multiple probabilities simultaneously. A tornado diagram was then made to identify which variables appeared to have the greatest influence on our model [39]. We expanded the ranges of such variables to examine threshold values.

Monte Carlo simulation was performed to test the robustness of our model and address the uncertainty contained in model inputs. Monte Carlo simulation is a multivariable sensitivity analysis in which multiple probabilities and costs can be varied simultaneously by sampling their distributions around their baseline estimates [27]. Because neither probabilities nor costs can be normally distributed, beta distributions were utilized for probabilities and gamma distributions for costs. We ran the simulation with 10,000 iterations.

Table 2
Outcomes, costs, and incremental cost-effectiveness ratio over 5 years in a hypothetical cohort of 100,000 COC users with missed pills using of EC

n=100,000	UPA	LNG	Difference
No pregnancy event	98,753	98,033	720
Unintended pregnancy	1247	1967	−720
Abortions	889	1625	−736
Deliveries	139	219	−80
Cost	$7,462,365	$7,512,688	−$50,323
QALY	457,696	457,617	79
ICER	Dominant		

Time horizon of 5 years.
The incremental differences between UPA and LNG were used to calculate the ICER. The ICER was then assessed with cost-effectiveness threshold set to $100,000 per QALY to understand if UPA was cost-effective.

3. Results

In a hypothetical model among 100,000 COC users requiring EC due to missed pills and unprotected intercourse, UPA was found to be the dominant strategy: it improved health outcomes and cost less, with an ICER of -638.58. As compared to LNG, women's use of UPA prevented an additional 720 unintended pregnancies (Table 2). Among 100,000 women, UPA resulted in 80 fewer unintended deliveries and 736 fewer terminations. Compared to LNG, selection of UPA resulted in a $50,323 reduction in healthcare costs and addition of 79 QALYs.

Based on the tornado diagram (Fig. S1), the risk of pregnancy based on the influence of COCs on fecundity and the costs of UPA, LNG and abortion had the largest impact on the ICER (Fig. S1). As a simple decision analysis, the model was most sensitive to changes in the risk of pregnancy based on the influence of COCs on fecundity, the probability of delivery, risk of ovulation after missing ≥3 days' pills and effect of obesity (Fig. S2).

We then further examined these variables using multivariable sensitivity analysis. COCs' influence was assessed in sensitivity analysis by the creation of an indicator variable to vary the effect of COC on risk of pregnancy with LNG and UPA. We sought to determine by how much

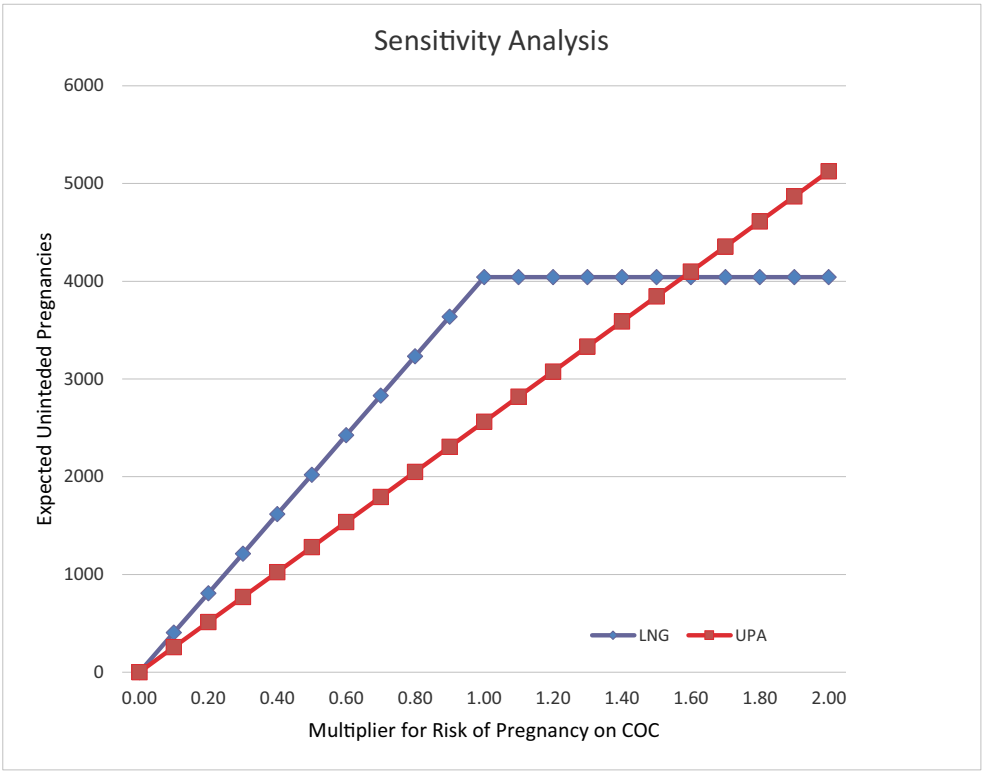

Fig. 2. Sensitivity analysis of COCs' influence on fecundity at time of EC use. Univariate sensitivity analysis. The vertical axis displays the expected total of unintended pregnancies among 100,000 women. The horizontal axis shows the factor by which COC would impair UPA and LNG efficacy and change the risk of pregnancy. Risk of pregnancy with UPA would need to increase by 160% before LNG results in fewer pregnancies and becomes the preferred strategy.

COCs would have to impair EC efficacy to alter the strategy selection. Multiplier values >1.0 account for this increased risk from EC impairment, whereas values <1.0 account for a reduction due to ovulatory changes from regular COC use. While there is clinical interest and uncertainty as to the potential interaction between COC and UPA, COC is not thought to impinge LNG efficacy but only UPA efficacy. As such, LNG values were arrested at a risk of up to baseline value of 1.0. Fig. 2 indicates that UPA remained the superior strategy compared to LNG until a COC interaction changed the efficacy of UPA and increased pregnancy risk by 160%.

Similarly, we sought to identify the best strategy to meet the EC needs of obese women. Nearly 36% of reproductive-age women are considered obese [40]. We performed a sensitivity analysis to account for the interaction between obesity, risk of pregnancy and the efficacy of

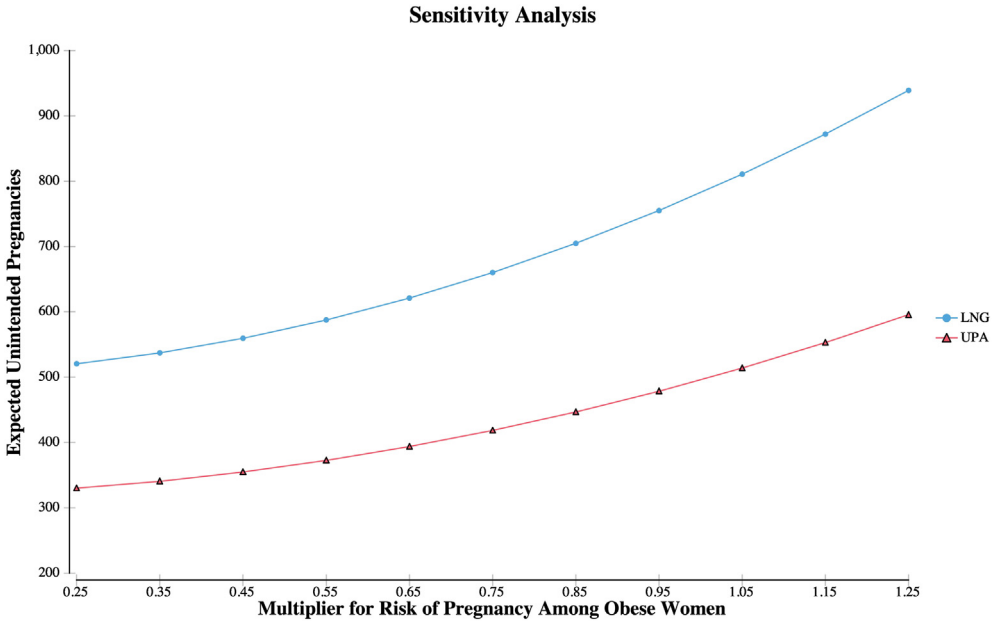

Fig. 3. Sensitivity analysis of BMI influence on fecundity at time of EC use. Univariate sensitivity analysis. The vertical axis displays the expected total of unintended pregnancies among 35,670 obese women in the theoretical cohort. The horizontal axis shows the factor by which risk of pregnancy was multiplied. This figure demonstrates that no matter how pregnancy risk changes, LNG never becomes the preferred strategy among obese women.

oral EC. Regardless of how obesity impacts fertility (ranged from 0 to 1.25 increased risk), UPA remained the preferred strategy for reducing unintended pregnancy, in which fewer unintended pregnancies resulted with UPA at all risk levels than with LNG (Fig. 3).

Finally, of the 10,000 iterations completed during the Monte Carlo simulation, UPA was the dominant strategy in 8165 iterations (82%) and was dominated by LNG in 1835 iterations (18%).

4. Discussion

Among a population of COC users who missed pills and had unprotected sex, the selection of UPA for EC increased quality of life for women and substantially reduced health costs, regardless of whether BMI or COC use impacts EC efficacy.

Our findings have important policy implications. Current clinical algorithms may steer women utilizing COC away from UPA for EC use due to concerns of a theoretical interaction.However, this interaction would have to hinder UPA efficacy by 160% before LNG became superior, and it is highly unlikely that any interaction would reach this threshold value. Our findings suggest that using LNG EC instead of UPA for this scenario may result in women using a less effective form of EC and subsequently increasing their risk of unintended pregnancy. We believe this is a common clinical scenario given the 15.6 million COC users in the United States [19].

Despite taking UPA, we found that 1247 women would still experience an unintended pregnancy, resulting in 889 terminations and 139 deliveries. The potential for unintended pregnancies with either method highlights the role for proper counseling and strategies for optimizing adherence to a woman's routine method of contraception. Nonetheless, the majority of women would not get pregnant with either EC strategy. In addition to the efficacy of EC, COC users with or without missed pills may be at variable risk for breakthrough ovulation. It is thought that women who are otherwise using COCs consistently may have residual suppression of ovulatory function [41–43]. We have no literature on the risk of pregnancy after EC use among nonadherent COC users, so we assumed a 50% risk reduction. Aside from sensitivity analyses comparing LNG and UPA, we are unable to account for the possibility that women with ovulatory suppression did not actually need to take anything. Future studies should further delineate actual risk of pregnancy in this setting.

As with all decision analyses, the reliability of this model depends on a set of assumptions made and estimates found in the literature. Data around number of missed pills are likely affected by underreporting and social desirability bias. However, our sensitivity analysis suggested that regardless of the proportion of women who had missed ≥3 pills past the placebo week, fewer unintended pregnancies were expected with UPA. Our model is also limited by our assumption that women only had one episode of unprotected intercourse occurred. Previous studies suggest that 5% of women will have more than one episode of unprotected intercourse during the month they obtain EC [10]. However, we did increase the risk of pregnancy through a sensitivity analysis, and UPA continued to be the dominant strategy, which suggests that a similar conclusion would be drawn among women who have multiple episodes of unprotected intercourse. Our study is additionally limited by our narrow perspective on cost. With a healthcare perspective, we did not include societal costs that challenge a person's access to effective pregnancy prevention: the patient time needed for phone and in-person visits to acquire prescriptions for UPA. Furthermore, limiting UPA access to a healthcare system requires women have a baseline knowledge to know she is entitled to this service and excludes those who are uninsured or otherwise unable to engage.

There is a need for further research on the utility of unintended pregnancy among diverse populations. Currently, only scant data exist. It is believed that the utility of unintended pregnancy may vary both by individual characteristics as well as whether the pregnancy is mistimed or undesired. Further research is needed to inform this area. This model only accounts for women able to obtain UPA or LNG, and does not factor in women's ability to achieve access. Because there is variability in formulation availability, price and clinical distribution, many women may not be able to obtain this mode of EC regardless of its improved efficacy [14,44,45]. Clinical algorithms should be updated to reflect a preference toward the method that achieves superior effectiveness: UPA. However, algorithms only hold weight if the supported mode of EC is accessible and streamlined. Current regulatory standards must be revised so that UPA is set to the same specifications as LNG and be made over-the-counter.

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