European Journal of Obstetrics and Gynecology 300 (2024) 345–346

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Brief Communication

Comparative efficacy of combined oral contraceptives and the levonorgestrel 52 mg IUD

ARTICLE INFO

Keywords:
Contraception
Intrauterine device
Levonorgestrel
Combined oral contraceptives
Efficacy
Adherence

SHORT CONDENSATION

The relative risk of pregnancy with the levonorgestrel 52 mg IUD is 3 times lower than with optimal combined oral contraceptive use.

Dear Editors,

Frequently referenced contraceptive effectiveness tables include outcomes commonly based on older studies, especially for methods available for decades like oral contraceptives [1,2]. These tables report failure rates as typical use (including outcomes with inconsistent and imperfect use) and perfect use (following the package directions), in which typical use rates are derived from national surveys and updated periodically [3]. For oral contraceptives, the most commonly used reversible contraceptive method [4], perfect use implies taking all hormone pills in the package, providing correct replacement ("doubling up") when pills are not taken on a specific day, and using a back-up method for one week if ≥two pills are missed. For long-acting methods like intrauterine and implantable contraceptives, patient adherence is eliminated, so typical and perfect use will almost always be the same. We aimed to better understand the relative differences in optimal efficacy of combined oral contraceptives (use of all hormonal pills in a cycle on the day scheduled) and a hormonal intrauterine device (IUD) using contemporary data based solely on adherence.

We used published outcomes to compare per cycle pregnancy rates with optimal use of a combined oral contraceptive (COC) and a levonorgestrel 52 mg IUD and to determine the relative difference in efficacy between the two methods with best possible use. For the COC, we used published data with an estetrol/drospirenone 24/4 COC that evaluated per cycle pregnancy rates based on adherence over 13 cycles (1 year) of use [5]. The study included 3027 global participants aged 16–35 years as the primary efficacy population with an average age of 25.4 ± 4.6 years with 65.6% nulligravid [6]. For the IUD, we calculated the pregnancy rates per cycle each year for 8 years with optimal use, defined as knowing or assuming the IUD was in the uterus, using data from the ACCESS IUD levonorgestrel 52 mg IUD phase 3 study [7]. This study was performed in the U.S. in a mostly nulliparous population (61.8%) and enrolled 1600 participants aged 16–35 years as the primary efficacy population with an average age of 26.2 ± 4.4 years [8]. We calculated

Table 1
Annual pregnancies per 28-day cycles of optimal use of a combined oral contraceptive and a levonorgestrel 52 mg intrauterine device.

Year	Estetrol/drospirenone COC*			Levonorgestrel 52 mg IUD†			Relative Risk of pregnancy (Year 1 COC compared to IUD [95 % CI])
	28-Day Cycles	Pregnancies	Pregnancies per cycle	28-Day Cycles	Pregnancies	Pregnancies per cycle	
1	23,360	21	0.0899%	17,175	2	0.0116%	7.72 (1.81–32.92)
2				14,205	4	0.0282%	3.19 (1.10–9.30)
3				11,760	1	0.0085%	10.57 (1.42–78.59)
4				9891	1	0.0101%	8.89 (1.20–66.10)
5				8337	1	0.0120%	7.49 (1.01–55.71)
6				6916	0	0.0000%	12.73 (0.77–210.16)
7				5646	1‡	0.0177%	5.08 (0.68–37.73)
8				4299	0	0.0000%	7.91 (0.48–130.64)

COC: combined oral contraceptive; IUD: intrauterine device.
* Optimal use is taking one hormone pill daily for the 24 hormone use days per 28-day cycle, from [5].
† Adapted from [1]; optimal use is knowing or believing the intrauterine device was in the uterus.
‡ 1 pregnancy occurred 4 days after removal and is not included in the calculations.

https://doi.org/10.1016/j.ejogrb.2024.07.044
Received 10 June 2024; Received in revised form 18 July 2024; Accepted 21 July 2024
Available online 22 July 2024

the relative risk and 95% confidence intervals of pregnancy between the established optimal COC and the calculated optimal IUD use per cycle pregnancy rates.

The pregnancy risk with daily use of all scheduled hormonal pills was 0.0899% per 28-day cycle (Table 1) [5]. The IUD annual pregnancy rate per cycle (Table) ranged from a low of 0% (years 6 and 8) to a high of 0.0282% (year 2). In the first year (13 cycles) of IUD or COC use, the relative risk of pregnancy is 7.72 (95% CI 1.81–32.92) times higher with COC use. When considering the highest annual pregnancy rate for the IUD (0.0282%, year 2), the relative risk of pregnancy is 3.19 (95% CI 1.10–9.30) times higher with COC use. The relative risk confidence intervals are wide, as expected, due to the infrequency of the outcome.

Commonly cited reference tables commonly cite perfect use pregnancy rates of 0.3 per 100 women-years for COCs and 0.15 per 100 women-years for the levonorgestrel 52 mg IUD, suggesting only a 2 times lower rate of efficacy of a COC compared to the IUD when both are used perfectly. The COC rate from our current study calculates to 1.17% of optimally adherent users becoming pregnant over 13 cycles. When the COC adherence outcomes include those participants who missed pills but used appropriate replacement ("doubling up"), the pregnancy risk is 0.0859%, which calculates to 1.12% over 13 cycles [5]. These COC efficacy rates are much higher than those in the reference tables and may underscore an outdated understanding of product efficacy [1,2]. The pregnancy risk in the first year for the levonorgestrel 52 mg IUD of 0.116% per cycle calculates to 0.15% over 13 cycles, the same as the reference tables [1,2].

Although both methods, when used optimally, have low pregnancy rates, the differences are large when considered at a population level. It is possible that optimal or perfect use efficacy of COCs that do not contain estetrol/drospirenone may be different, based on factors that can influence oral hormone absorption, including body mass index [9]. Typical use pregnancy rates of COC users will differ more broadly because of the higher adherence required for perfect use. These outcomes, which compare phase 3 data from similar population characteristics, provides a contemporary understanding of the relative efficacies of COCs and the levonorgestrel 52 mg IUD and should be considered in contemporary discussions of these commonly used contraceptives.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Creinin has received speaking honoraria from Gedeon Richter, Mayne, and Organon, has stock options with Femasys, and has consulted for Curai, Estetra SRL, Medicines360, and Organon. All other authors have no personal disclosures. The Department of Obstetrics and Gynecology, University of California, Davis, has received contraceptive research funding from Chemo Research SL, HRA Pharma, Medicines 360, Merck, and Sebela.

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