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Review Article

Effectiveness and efficacy rates of progestin-only pills: A comprehensive literature review

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ABSTRACT

Objectives: To synthesize published literature on POP effectiveness and efficacy.
Study design: We searched PubMed Central, PubMed, and the Cochrane library through March 07, 2022. We included articles written in English reporting a Pearl Index or life table rate for pregnancy. We excluded articles only assessing formulations that: were never marketed globally, are only sold in combination with estrogen, are currently sold only for noncontraceptive purposes, or were not given to participants continuously. Four researchers independently extracted data and two analyzed data using Excel and R.
Results: We included 54 studies. Among studies at low or moderate risk of bias, the median Pearl Index rate (the failure rate during typical use) was 1.63 (range 0.00–14.20, IQR 4.03) and the median method failure Pearl Index rate (the failure rate during perfect use) was 0.97 (range 0.40–6.50, IQR 0.68). Excluding the newer formulations, Desogestrel and Drospirenone, which are closer to combined oral contraceptives in that they prevent pregnancy by inhibiting ovulation, the median Pearl Index rate is 2.00 (range 0.00–14.12, IQR 2.5) and the median method failure Pearl Index rate is 1.05 (range 0.00–10.90, IQR 1.38).
Conclusions: Among studies at low or moderate risk of bias, the median Pearl Index rate during typical POP use was much lower than currently estimated (7.00), while the median perfect use rate was similar to current estimates.
Implications: Future research should investigate the possibility that POPs may be much more effective during typical use than currently believed.

1. Introduction

Moving oral contraceptive pills—combined oral contraceptives (COCs) or progestin-only pills (POPs) —to over-the-counter (OTC) status in the United States (US) could increase accessibility for individuals encountering barriers to getting a prescription [1,2]. At the time of writing, the United States Food and Drug Administration (FDA) is currently reviewing the first-ever application for an OTC POP product which contains .075 mg Norgestrel [3]. A large coalition of prominent clinicians, researchers, and reproductive health, rights, and justice organizations has long focused on making POPs available OTC in the US because POPs have few contraindications and would therefore be appropriate for a wide range of people [4].

Although there is interest among US women in an OTC POP product [5], POP users constitute only 4% of contraceptive pill users [6], and this low user rate may be due to clinicians' hesitation to prescribe POPs based on their views of the pill's effectiveness. One study assessing how evidenced-based information influences clinicians' thoughts about an OTC oral contraceptive found that before receiving information, 69% of clinicians did not support an OTC POP, with 17% citing "less effective pill formulation" as a reason [7]. However, a 2013 systematic literature review of randomized controlled trials of progestin-only pills concluded there was insufficient evidence to compare POPs to COCs [8].

Efficacy rates refer to failure rates only when the pill is taken as directed (perfect use), whereas effectiveness refers to failure

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rates during typical use (which includes perfect use as well as incorrect and inconsistent use) [9]. Although pill effectiveness rates vary based on the population using the method [10], it is estimated that in the US 7% of individuals using oral contraceptives will have an unintended pregnancy during their first year of typical use [9]. However, this estimation does not distinguish between COCs and POPs and may be a better reflection of the failure rate of COCs because they are more commonly used in the US [9]. It is thought that this failure rate may be slightly higher for POPs because a common belief is that POPs lose effectiveness when not taken within a rigid timeframe of 24 hours after the previous pill with a strict 3-hour window [11,12], although little clinical data exist to support this belief [8,13].

In addition to a lack of evidence for the 3-hour window, there are many different POP formulations, including two newer formulations—Desogestrel and Drospirenone—that have been shown to inhibit ovulation even after long delays in pill intake (12-hour delays for Desogestrel and 24-hour delays for Drospirenone) [14,15] so the 3-hour window recommendation is likely not applicable to them. One study has also found that a 6-hour delay or a single missed POP containing Norgestrel 0.075 mg appears to not negatively impact contraceptive efficacy [16] Current estimates of the pregnancy rate for the first year of use among perfect users is based on the lowest reported pregnancy rate as well as pregnancy rates reported in recent studies—for COCs, the rate of pregnancy among perfect users is estimated to be 0.30% and although this rate is cited as the rate for all oral contraceptives, the pregnancy rate among perfect users of POPs is unknown [11]. As of 2018, the lowest reported pregnancy rate for POP use was 1.1% [11].

Contraceptive effectiveness and efficacy rates can both be measured by the Pearl Index and the life table. The Pearl Index calculates an effectiveness rate by dividing the number of total pregnancies (contraceptive failures) by 100 person-years of exposure to the contraceptive method [17]. A Pearl Index that measures efficacy (often referred to as a method failure Pearl Index) only includes pregnancies resulting from a method failure among perfect users. Due to its ease of calculation, the Pearl Index has been reported more frequently in the literature than life table rates, but a significant limitation is that estimates can vary with study length. For longer durations of pill use, the Pearl Index tends to underestimate failure rates since pregnancies are more common at the beginning of pill use and study participants more likely to conceive become pregnant early and withdraw from the study, leaving a group of participants less likely to conceive [18]. This limitation is eliminated by a life table analysis, which estimates monthly probabilities of failure and cumulative probabilities over time.

Previous reviews of the effectiveness and efficacy of POPs have focused on few formulations [19,20] and there is insufficient information among randomized trials to make comparisons between different POPs [8]. This review aims to expand upon previous reviews by including a range of study types reporting effectiveness and efficacy rates of various POP formulations, while recognizing the limitations of nonrandomized trials. Our findings can help ensure that policymakers, reproductive health advocates, and the general public have the necessary information, backed by clinical evidence, to make decisions about an OTC POP product.

2. Material and methods

2.1. Literature search and study selection

We searched PubMed Central, PubMed, and the Cochrane library for articles and reports written in English on the effectiveness or efficacy of POPs through March 07, 2022. The search did not include limits by study publication type, date, or study design. We did not include overall findings from literature reviews but searched the references of reviews and included articles with original or primary research. Four researchers screened the titles and abstracts of articles for eligibility. We included randomized and nonrandomized studies (with or without a control group) with data on pregnancy rates among users of at least one POP formulation currently or previously sold in any country. We excluded articles assessing formulations that: were never marketed globally, are only sold in combination with estrogen, are currently sold only for noncontraceptive purposes, or were not given to participants continuously (except for the newer Drospirenone-only pills which is the only POP product sold with placebo pills in a pack). We also excluded articles if they did not report information on the duration of person-time used for estimations of effectiveness. See Appendix A for details of our search process and Appendix B for search terms.

2.2. Data extraction and calculations

We extracted the following data from each study: first author, title, year of publication, study location, participant characteristics, study design features (n, duration, randomization), POP formulation and dosage, loss-to-follow-up, number of total pregnancies, number of pregnancies attributed to user error and method failure, Pearl Index, method failure Pearl Index, Pearl Index rates adjusted for patient characteristics or behaviors, and life table data. We converted dosage units to milligrams and summed up dosages taken more than once a day as a single daily dosage. We also calculated Pearl Index rates if sufficient data were available and compared them to reported rates. In our analyses, we used Pearl Index rates reported by studies and only used calculated rates if no single Pearl Index rate was reported. We included aggregated Pearl Index rates that combined rates from multiple formulations or studies.

As failure rates tend to be high at the start of studies and decrease over time [18], we also extracted data on study duration to analyze effectiveness and efficacy rates by study length. Studies reported study duration in different units (cycles, months, years), which we converted into months. (since 12 months is equivalent to 13 cycles, we calculated that there are .92 months in a cycle). If study length was not reported, we estimated study duration based on the longest reported cycle or month of treatment completed. If we could not estimate study length, we used average length of participation in the study, if available. In our analysis of study duration and Pearl Index rates, we excluded one Pearl Index rate that was pooled from two studies of different durations [21].

Since person-time depends on both duration of use and number of participants, we also looked at Pearl Index rates by study size. We recorded the number of participants who started treatment in each study arm. For retrospective studies, we extracted the number of participants included in the analysis, if available.

Four researchers independently extracted data and placed data in an Excel spreadsheet.. Two researchers used Excel and R for data analysis and visualizations [22].

2.3. Assessing risk of bias

We assessed risk of bias for included studies using the Cochrane risk-of-bias tool for randomized trials (RoB 2) [23], the Cochrane Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool [24] for nonrandomized studies with a comparator, and a newly developed tool for assessing bias in estimation of contraceptive failure rates in studies lacking a comparator. We included data from a single arm of a study when a POP was compared with a non-POP method or compared with a POP formulation not given continuously to participants. We only extracted pooled data when studies compared the impact of the same formulation on different

groups of participants (as opposed to comparing two or more different formulations). To assess risk of bias for these single arm estimates of contraceptive failure, we created a tool adapted from existing Cochrane tools that included domains for assessing bias relevant to valid estimation of contraceptive failure rates [25]. We assessed all studies using the appropriate risk of bias tool by two researchers, who judged all studies to be in one of three categories: low risk, moderate risk, or high risk of bias. Across all tools, we judged studies based on the most severely rated domain. If we assessed three or more domains to be at moderate risk of bias, then we judged the study's overall risk of bias to be high. If a domain did not have enough information for us to make an assessment, we assessed the domain as moderate. If more than one domain did not have sufficient information to make an assessment, we excluded the study from our analysis. See Appendix C for our tool to assess risk of bias in noncomparative studies and Appendix D for tables summarizing our risk of bias judgments for all studies.

2.4. Data synthesis and analysis approach

Our main outcome was median effectiveness and efficacy rates reported by studies assessed to be at low or moderate risk of bias, although we also conducted a sensitivity analysis by calculating the median effectiveness and efficacy rates across all studies. We also analyzed effectiveness and efficacy rates by study duration, size, and formulation. We conducted additional sensitivity analysis by removing rates for Desogestrel and Drospirenone, as these newer formulations are different from other POP because they reliably inhibit ovulation after delayed pill intake [14,15]. In addition, given the FDA's current review of an application for an OTC product containing Norgestrel 0.075 mg, we also looked at Pearl Index rates reported by studies analyzing that particular dosage and formulation. As most Pearl Index rates were not accompanied by confidence intervals, we report ranges and interquartile ranges to provide information on the spread of data. If a study was aiming to compare different groups of participants (e.g., lactating versus nonlactating) and reported separate Pearl Index rates, these rates are included in our main findings. However, if studies reported rates that took into account participant behaviors or characteristics (e.g., taking into account that their sample included some lactating participants and reporting analyses with this group excluded from calculations) in addition to overall Pearl Index rates, we did not include these adjusted or stratified rates in our overall calculations but report these separately.

3. Results

3.1. Included studies

Fifty-four studies met our eligibility criteria [21,26–78]. Table 1 displays descriptive information for each article. Included studies were published between 1966 and 2019, with almost half published in the 1970s [26,31,32,34–36,39–42,45,47,48,52,55–61,64,66,68,71,72,75,76]. Forty-four studies were conducted primarily in either Europe or North America [21,27–29,31–40,42,43,45–52,57–61,63,67,68,70,72,74–78], and all were prospective studies with the exception of three that were retrospective [70,74,79]. Seven were randomized trials [21,43,44,49,57,62,66], 15 were nonrandomized comparative studies [34,39,48,50–54,64,65,67,69–71,74], and 32 were noncomparative studies [26–33,35–38,40–42,45–47,55,56,58–61,63,68,72,73,75–78]. All studies were peer-reviewed except two—one was described in a letter published in the correspondence section of a peer-reviewed journal [29] and one was an abstract published in a conference proceeding [52].

Data on study participant characteristics varied widely: age (reported by 44 studies) [21,26,27,30–37,39–41,43–48,50–60,62–64,66–69,71–74,77,78] and fertility (reported by 40 studies) [21,26,27,29–34,36–43,45–47,49,51–55,60,63,64,66,68,69,71–76,78] were most frequently reported. Although studies reported ages differently (range, average age, maximum age, or a mix of these measures), ages ranged from 13 to 54 years. Studies also measured fertility in various ways, including number of previous pregnancies, number of living children, and number of live births. Twenty-seven studies noted that all or most participants (between 75% and 99%) had proven to be fertile [26,27,31–34,36,39,41,45,46,49,51–54,60,63,64,66,68,69,72,73,75,76,78]. We included other commonly reported participant characteristics in Table 1.

Thirty-six studies [21,26–31,34–38,41–43,45–48,50,52,53,55,56,58–61,66,67,70,74–78] reported effectiveness rates using the Pearl Index method and 12 studies that did not report a Pearl Index contained enough data to calculate one [32,33,39,40,44,51,57,58,65,68,69,72]. Twenty-four studies [21,28,31,33,36,41,42,45–47,50,52,55,56,58,59,63,70,71,75,76,78] reported method failure Pearl Index rates. Four studies reported effectiveness rates solely by life table calculations [54,62,64,73]. Nine studies [21,27,30,31,34,40,56,59,66] reported both Pearl Index and life table data and one study reported both a method failure Pearl Index and a life table rate [63].

3.2. Discrepancies between reported and calculated Pearl Index rates

Although we used reported Pearl Index rates for our analysis when available, we calculated Pearl Index rates for all studies that provided sufficient information. Among 40 Pearl Index rates, we found discrepancies between our Pearl Index calculations and 15 of the rates (35%) reported in 14 studies [34,35,39,41,42,45–48,52,53,55,56,78]. See Appendix E for details on Pearl Index discrepancies.

3.3. Effectiveness rates

Among studies reporting a Pearl Index, we assessed 34 to be at high risk of bias, 11 at moderate risk of bias, and two at low risk of bias. Only five studies [21,37,43,44,74], published between 1998 and 2019, reported confidence intervals for Pearl Index rates. Table 2 shows average and median Pearl Index rates by study risk of bias and Figure 1 displays box plots of Pearl Index rates grouped by study risk of bias (high risk and not high risk).

Among studies assessed to be at low or moderate risk of bias, 26 Pearl Index rates ranged from 0.00 to 14.12, with a median of 1.63 (IQR 4.03). Without rates for Desogestrel and Drospirenone, the median Pearl Index rate increased slightly to 2 (range 0.00–14.12, IQR 7.00). Among the two studies assessed to be at low risk of bias [21,43], five Pearl Index rates ranged from 0.41 to 1.55 with a median of 0.73 (IQR 0.45). Of the five rates reported, four were rates for Desogestrel or Drospirenone. Including studies assessed to be at high risk of bias, 66 Pearl Index rates ranged from 0.00 to 14.12, with a median of 1.76 (IQR 2.47). The rest of our analysis on effectiveness rates focuses on results reported by studies not at high risk of bias.

3.3.1. Pearl Index rates by study duration

All but one of the 12 studies with Pearl Index data reported intended study duration or average duration of use, or allowed us to estimate one [74]. Three studies [21,36,44] lasted less than a year with the shortest study lasting for 6 months and reporting the highest Pearl Index rate (14.12) in our review [44]. The other studies lasted an average of 34 months and a median of 12 months. Figure 2 shows Pearl Index rates by study duration.

Table 1
Description of studies reporting effectiveness and/or efficacy rates of progestin-only pills

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Apelo [26]	1973	The Philippines	Levonorgestrel	Noncomparative study	High	Age Range: 17–37 years Mean: 26 years Fertility All participants had at least one pregnancy Mean 3.5 Mean interval between last delivery and start of medication was 8 months with a range of 1–55 months Weight Range: 75–149 lbs Mean 101.6 lbs
Archer [37]	2015	Czech Republic, Germany, Hungary, Poland, and Romania	Drospirenone	Noncomparative study	Moderate	Age Range: 18–46 years Mean: 28.7 years Age group: 79.8% were 35 years old or younger Fertility 42.8% had a previous delivery Previous Contraceptive Use 63.8% had "prior treatment with sex hormones and modulators of the genital system" Race 99.6% Caucasian Weight BMI range: 16–38 Mean BMI: 23
Aznar-Ramos [48]	1971	Mexico	Chlormadinone acetate	Nonrandomized comparative study (comparing two different divided dosages)	Moderate	Age Range: 19–35 years
Bernstein [59]	1972	United States	Chlormadinone acetate	Noncomparative study	High	Age Maximum: All participants were under 40 years
Bisset [70]	1990	United Kingdom	Ethynodiol diacetate Levonorgestrel Norethisterone Norgestrel	Nonrandomized comparative restrospective study	High	Lactating or postpartum 6% of participants on ethynoldiol diacetate lactating 26% of participants on levonorgestrel lactating 2% of participants on norethisterone lactating 23% of participants on norgestrel lactating
Board [75]	1971	United States	Norethindrone	Noncomparative study	High	Fertilitiy Each participant of proved fertility Marital Status All participants were living with their husbands Previous Contraceptive Use All had taken either combination or sequential oral contraceptives 31.8% of participants had not been using OCs for at least 2 months prior to the study Most participants started norethindrone immediately after discontinuing their previous oral contraceptive
Board [76]	1976	United States	Norethindrone	Noncomparative study	High	Fertility Each participant of proved fertility Marital Status All participants were living with their husbands Previous Contraceptive Use Most had taken either combination or sequential oral contraceptives 29% of participants did not take an oral contraceptive for 2 months prior to beginning the study

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Broome [77]	1990	United Kingdom	Ethynodial diacetate Norethisterone Levonorgestrel	Noncomparative restrospective study	High	Age Majority: 59% of 358 women were 31–40 years old Lactating or postpartum Excluded from analysis (not included in the 358)
Butler [78]	1969	United Kingdom*	Chlormadinone acetate	Noncomparative study	Moderate	Age Maximum: 34 years Fertility Each participant had at least one living child Marital Status All participants were married Previous Contraceptive Use No OCs used in the 2 months before the study
Canto [27]	1989	Mexico	Norgestrel	Noncomparative study	High	Age Minimum: 18 years Majority: 56% were 20–29 years Mean: 26.1 years Fertility All participants had given at least one live birth Mean: 3.5 births Lactating or postpartum All were breast feeding on admission 43.5% were <6 weeks postpartum 56.5% were 6–26 weeks postpartum 83% were still breastfeeding at end of study Previous Contraceptive Use (month before the study) 38.5% participants were not using any method 26.5% used oral contraceptives 17% used injectables 11.5% used an IUD 5% used withdrawal/rhythm 1.5% used a condom
Cerais [73]	1991	Sudan	Norgestrel	Noncomparative study	High	Age Mean: 26.3 years Fertility All participants had at least one live birth Mean: 2.3 live births Lactating or postpartum All were breastfeeding on admission 177 women were between 42 day and 26 weeks postpartum 23 women were less than 42 days postpartum Previous Contraceptive Use (month before the study) 61% of participants not using any contraception immediately prior to admission or conception 32% of those using a method were using an oral contraceptive 34.5% reported ever having used an oral contraceptive prior to the study
Christie [28]	1969	Jamaica Mexico United Kingdom United States	Chlormadinone acetate	Noncomparative study	High	–

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Cox [29]	1969	United Kingdom*	Norgestrel	Noncomparative study	High	Fertility Mean parity: over 2
Dunson [30]	1993	22 medical facilities in Africa, Latin America and the Caribbean	Norgestrel	Noncomparative study	High	Age Mean: 25.7 (±4.9) Fertility Mean number of live births: 2.5 (±1.7) Lactating or postpartum 74% entered the study when they were between 1 and 2 months postpartum 56.6% breastfeeding at admission with no supplementation: 43.4% breastfeeding at admission with supplementation Previous Contraceptive Use 62% of participants had not used any contraception in the month before the study began Of women who had used a method, oral contraception was the most common (23.5%)
Eckstein [31]	1972	United Kingdom	Norgestrel	Noncomparative study	High	Age Maximum: All participants were under 40 years Majority: 24–35 years Fertility All participants had at least one living child of the present marriage
Foss [32]	1975	United Kingdom	Norgestrel	Noncomparative study	Moderate	Age Range: 19–41 years Fertility All participants had more than one child Previous Contraceptive Use This study included participants who wished to continue using Norgestrel from Foss study, so all had previously used this pill.
Foss [33]	1968	United Kingdom	Norgestrel	Noncomparative study	High	Age: Age group: 92% of participants were between 17 and 40 years old; 8% were between 41 and 18 years old Fertility 88% of participants were of proven fertility Range of number of children: 0–9
Hawkins [34]	1977	United Kingdom	Chlormadinone acetate Norethisterone	Nonrandomized comparative study	Moderate	Age Mean age for chlormadinone acetate: 26.1 (±6.1) Mean age for norethisterone: 24.7 (±5.1) Fertility 95% of participants parous Average parity: 1.9 (±1.5) Lactating or postpartum 71% of patients were within 3 months postpartum at start of study and a higher proportion of patients given norethisterone were more than 6 months postpartum on admission Race 76% White 16% Black 8% Asian, Latin American, mixed race
Heinen [35]	1970	Germany*	Chlormadinone acetate	Noncomparative study	High	Age Average: 30 years Majority: 60% of study participants were 26 –35 years old

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Hernandez-Torres [36]	1970	Puerto Rico	Norgestrel	Noncomparative study	Moderate	Age Maximum: No one was older than 36 years Fertility All had one or more previous pregnancies or abortions Lactating or postpartum All were nonlactating Previous Contraceptive Use No participants received oral contraceptive treatment for 90 days prior to the study
Howard [38]	1969	United Kingdom	Chlormadinone acetate	Noncomparative study	High	Fertility Participants not necessarily of proven fertility Lactating or postpartum 26% of patients were lactating and amenorrhoeic at the start of the study
Jeppsson [39]	1970	Sweden	Chlormadinone acetate	Nonrandomized comparative study	High	Age Majority: 83.5% were between the ages of 20–39 years Fertility 32% had never been pregnant Previous Contraceptive Use The sample included both women who had and hadn't use oral contraceptives before Other 48% of patients were upper-middle class and sought contraceptive advice at an outpatient department for private patients; 52% sought free advice on contraceptives at a public family planning facility
Jick [74]	2009	United Kingdom	Levonorgestrel Norethisterone Desogestrel	Nonrandomized comparative retrospective study	Moderate	Age Range: Minimum 13 years Fertility 71% had no prior deliveries Lactating or postpartum Evaluated the recency of delivery in users of the progestin-only pills compared to the COCs (to evaluate whether POP users were more likely to be breastfeeding) Weight BMI: (<20, 20–23, 24–27, 28+, Unknown)
Jubhari [40]	1974	United States	Quingestanol acetate	Noncomparative study	High	Age Mean: 23.1 years Fertility Most had never had a child Marital Status Most were single Race Most were White
Kesserü [41]	1972	Peru	Levonorgestrel	Noncomparative study	High	Age Range: 16–43 years Mean: 26.5 years Fertility Range number of pregnancies: 1–19 Mean number of pregnancies: 4.9
Korba [42]	1974	Puerto Rico Unites States	Norgestrel	Noncomparative study	High	–

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Korver [43]***	1998	Finland Germany The Netherlands Norway Sweden United Kingdom	Desogestrel Levonorgestrel	Randomized control trial	Low	Age Range: 18–45 years Mean age: 29.6 Fertility Mean number of pregnancies: 1.6 Lactating or postpartum Desogestrel users: 30.7% breastfeeding Levonorgestrel users: 30.9% breastfeeding Previous Contraceptive Use in Previous 2 months Desogestrel users: 36.5% switched directly from another pill Levonorgestrel users: 37.9% switched directly from another pill Weight Range: All were between 80% and 130% of the ideal body weight Mean BMI: 22.8 kg/m2
Lakha [44]	2007	China Nigeria South Africa United Kingdom	Levonorgestrel	Randomized control trial	Moderate	Age Mean age: 30.4 years Previous Contraceptive Use The majority 21 (of 23) did not use contraceptives in the previous few months Weight Mean: 58.4 kg Mean BMI: 22.4 kg/m2
Laurie [45]	1972	Puerto Rico Unites States	Norgestrel	Noncomparative study	High	Age Mean: 23 years Fertility 87.4% of participants multigravidae Race 52.7% White
Lawson [46]	1972	Jamaica New Zealand United Kingdom	Norethisterone	Noncomparative study	High	Age Range: 16–54 years Median: 27 years Fertility 78% of participants had a previous pregnancy Lactating or postpartum 9% of participants were breastfeeding Previous Contraceptive Use 53% of participants switched directly from another oral contraceptive
Maqueo [47]	1972	Mexico	Quingestanol acetate	Noncomparative study	High	Age Mean: 29 years Fertility Mean number of previous pregnancies: 4.5 Previous Contraceptive Use 36% of participants had previously received varying doses of quingestanol acetate for other studies 61% patients had no previous oral contraceptive therapy
Martinez-Manatou [49]	1967	Mexico*	Chlormadinone acetate	Randomized comparative study (comparing different doses)	High	Fertility Women of proven fertility with no more than two children Lactating or postpartum No participants were lactating
Martinez-Manatou [50]	1967	Mexico*	Chlormadinone acetate	Nonrandomized comparative study (comparing lactating to nonlactating group)	High	Age Maximum: Less than 36 (at least among the nonlactating group) Lactating or postpartum In one group, all women (100) were lactating and were between 1 and 15 months postpartum; the other group consisted of nonlactating participants

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Martinez-Manatou [51]	1966	Mexico*	Chlormadinone acetate	Nonrandomized comparative study (comparing cyclical to continuous pill taking regimen)	High	Age Maximum: Less than 36 Fertility All participants of proven fertility Lactating or postpartum No participants were lactating
McQuarrie [52]	1972	United States*	Norethindrone	Nonrandomized comparative study	High	Age Range: 16–42 years Mean: 26.4 years Fertility Parity range: 1–9 Mean: 2.5 children delivered
Mears [53]	1969	Yugoslavia	Chlormadinone Norethisterone acetate Norgestrel	Nonrandomized comparative study	Moderate	Age Range: 18–40 years Fertility All participants of proven fertility Previous Contraceptive Use All participants took no hormones or oral contraceptives during the previous 2 months
Moggia [54]	1991	Argentina	Norgestrel	Nonrandomized comparative study	Moderate	Age Range: 18–35 years Fertility All participants had given birth 2–6 times Lactating or postpartum All participants were lactating at beginning of study
Moggia [55]	1972	Argentina	Quingestanol acetate	Noncomparative study	High	Age Range: 15–44 years Mean: 26.1 (±0.2) Fertility Mean number of prior pregnancies: 2.7 (±0.1) Lactating or postpartum 80% of participants were postpartum Weight Range: 40–100 kg Mean: 60.0 kg (±0.4)
Moggia [56]	1973	Argentina	Quingestanol acetate	Noncomparative study	High	Age Range: 15–44 years Mean: 26.1 years (±0.2) Fertility Range number of prior pregnancies: 0–9 Mean number of prior pregnancies: 2.7 (±0.1) Lactating or postpartum 53.65% of patients lactating 76% postpartum Weight Range: 40–100 kg Mean 60.1 (±0.3)

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Palacios [21]^	2019	Austria, Czech Republic, Germany, Hungary, Poland, Romania, Slovakia and Spain	Drospirenone Desogestrel	Randomized control trial	Low	Age Drospirenone: Range: 18–45 years; Mean: 28.9 years; Age group: 79.5% were 35 years old or younger Desogestrel: Range: 18–45 years; Mean: 28.9 years; Age group: 78% were 35 years old or younger Fertility Drospirenone:46 % had a previous delivery Desogestrel: 45 % had a previous delivery Previous Contraceptive Use 54.7% of Drospirenone users and 58.7% of Desogestrel users had "prior treatment with sex hormones and modulators of the genital system" Race 99.8% of Drospirenone users and 99.7% of Desogestrel users were Caucasian Weight Drospirenone: BMI range: 16.6–41; Mean BMI: 22.96 Desogestrel: BMI range: 15.9–38; Mean BMI: 22.82
Paulsen [57]	1974	United States	Ethynodiol diacetate	Randomized control trial	High	Age Range: 18–39 years Mean: 20.5 years (±2.7) Fertility 5% had a previous pregnancy: 2.5% had a previous live birth Previous Contraceptive Use Majority of patients did not have prior experience with oral contraceptives
Postlethwaite [58]	1979	United Kingdom*	Ethynodiol diacetate	Noncomparative study	High	Age Range: 17–48 years
Rice-Wray [60]	1972	Mexico	Levonorgestrel	Noncomparative study	High	Age Range: 18–40 years Fertility All participants of proven fertility Previous Contraceptive Use None had any steroid therapy for at least 60 days prior to initiating study.
Scharff [61]	1971	Germany	Levonorgestrel	Noncomparative study	High	–
Sheth [62]	1982	India Yugoslavia	Levonorgestrel Norethisterone	Randomized control trial	Moderate	Age Range: 18–38 Levonorgestrel users mean age: 25.7 years (±4.57) Norethisterone users mean age: 25.6 (±4.68) Previous Contraceptive Use No participants had used oral contraceptives within 28 days or long acting injectable hormonal contraceptives within 90 days of starting treatment 27.4 % of levonorgestrel users had ever used oral contraceptives 26.8% of Norethisterone users had ever used oral contraceptives

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Shroff [63]	1987	United Kingdom	Ethynodiol diacetate	Noncomparative study	High	Age Range: 16–45 years Age group: 72% were 16–34 years old 28% were 35–47 years old Median: 30 years Fertility 75% experienced at least one previous pregnancy Previous contraceptive use None: 8% COCs: 48% POPs: 9% OCs: (unknown) 1% IUCD: 15% Other 19%
Statzer [72]	1972	United States	Norgestrel	Noncomparative study	High	Age Range: 15–44 years Fertility All participants demonstrated fertility. Previous pregnancies ranged from 1 to 9 Previous contraceptive use Subjects have taken no oral or injectable contraceptive for 90 days or more In some cases, subjects switched directly from Oral (norgestrel 0.5 mg and ethinyl estradiol 0.05 mg) to microdose norgestrel Race 14% White 86% Black
Tejuja [64]	1974	India	Norgestrel	Nonrandomized comparative study (comparing two doses)	Moderate	Age 50 μg Norgestrel users: 79.2% between 20 and 29 years old 75 μg Norgestrel users: 80.1% between 20 and 29 years old Fertility 50 μg Norgestrel users: >99% of participants had had at least one pregnancy 75 μg Norgestrel users: >99% of participants had had at least one pregnancy Lactating or postpartum 50 μg Norgestrel users: 27.2% had lactational amenorrhea prior to commencement of the study 75 μg Norgestrel users: 29.8% had lactational amenorrhea prior to commencement of the study Weight 50 μg Norgestrel users' average weight: 43.4 kg 75 μg Norgestrel users' average weight: 44.7 kg
Tyler [65]	1968	United States	Norgestrel	Nonrandomized comparative study (comparing two doses)	High	–
Vessey [66]	1972	Yugoslavia	Chlormadinone acetate Norethisterone acetate Norgestrel	Randomized control trial	Moderate	Age Chlormadinone acetate users' mean age: 30.4 years Norethisterone acetate users' mean age: 30 years Norgestrel users' mean age: 30.1 Fertility All participants of proven fertility Chlormadinone acetate users mean number of full term births: 1.7 Norethisterone acetate users' mean number of full term births: 1.8 Norgestrel users' mean number of full term births: 1.8 Weight Chlormadinone acetate users' mean weight: 65.8 kg Norethisterone acetate users' mean weight: 65.6 Norgestrel users' mean weight: 66.1 kg

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Table 1 (*continued*)

First author	Year published	Study location (country)	Progestin(s)	Study design**	Risk of bias assessment	Participant characteristics
Vessey [67]	1985	United Kingdom	Norethisterone Norgestrel Levonorgestrel Ethynodial diacetate	Nonrandomized comparative study (comparing different POP formulations)	Moderate	Age Range: 25–39 years Marital Status All participants were married Race All participants were White
Whyte [68]	1973	Canada	Norethindrone	Noncomparative study	High	Age Mean: 23.3 years Fertility 98% of participants had at least one previous pregnancy Previous Contraceptive Use All participants had previously used a type of oral contraceptive Other One third of patients were either contraindicated to estrogen or found the combined pill unacceptable due to side effects. The remaining sample had never used any oral contraceptive before and had no contraindications to a combined or progestin-only pill.
Zañartu [69]	1968	Chile*	Chlormadinone acetate	Nonrandomized comparative study (comparing two groups of participants of different socio-economic statuses)	High	Age Minimum: 16 years Fertility All participants had been pregnant at least once Lactating or postpartum 110 women started use after childbirth while lactating and/or experiencing amenorrhea Other 45 women were came from families with an above-average income 345 were from low-income groups Combined oral contraceptives or sequential oral contraception was either poorly tolerated or not acceptable to all women from low-income group and in the majority (40) among women from families with an above-average income
Zanartu [71]	1974	Chile*	Ethynodiol diacetate Norgestrienone	Nonrandomized comparative study (comparing different formulations among two different groups of patients -continuous use with precoital use)	High	Age Mean:28.8 Range: 18–41 Fertility Mean parity:5.5

* Study location was not reported in the article so the country where researchers were based are listed instead.
^ This study reports on results from two studies; the first of which are already reported in the study by Archer et al. Only results from the second study, and any pooled results, are reported here. **Studies that did not explicitly say they were randomized are categorized as nonrandomized.
*** Korver T is listed as the corresponding author. The study was written by a collaborative study group.

Table 2
Summary of Pearl Index measures by study risk of bias level

	Number of studies	Number of Pearl Index rates	Average Pearl Index	Median Pearl Index	Pearl Index range	Interquartile range
Low risk	2	5	0.85	0.73	0.41–1.55	0.45
Moderate risk	11	21	4.11	2.00	0.00–14.12	7.1
High risk	34	50	2.19	2.00	0.00–8.60	1.7

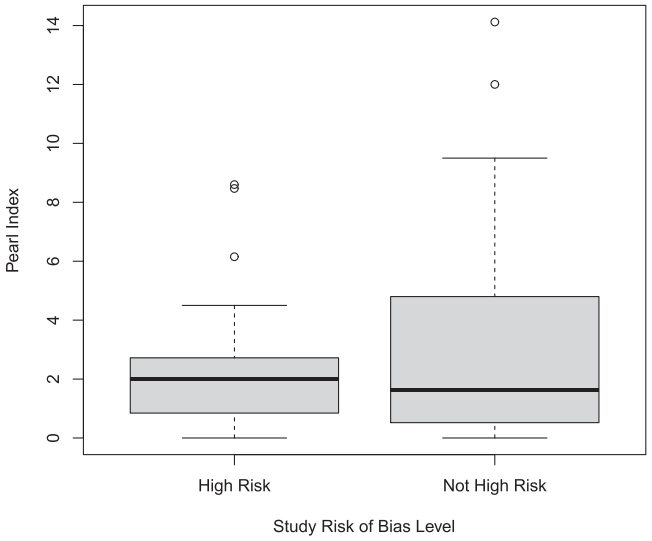

Fig. 1. Pearl Index rates by study risk of bias level (high risk and not high risk).

3.3.2. Pearl Index rates by study size

All but two studies [67,74] reporting a Pearl Index rate provided details on the number of participants in the study. The number of participants in any given treatment arm or pooled analysis ranged from 23 participants to 1571 participants, with a median of 183 (IQR 254.50). Pearl Index rates were consistently low in studies that have at least 250 participants as shown by Figure 3.

3.3.3. Pearl Index rates by progestin

Among non–high-risk studies with Pearl Index data, the progestins most frequently studied were Norgestrel (5 studies) [32,36,53,66,67] and Chlormadinone acetate (5 studies) [34,48,53,66,78]. The median Pearl Index rates for Norgestrel and Chlormadinone acetate were 1.73 (range 0.00–9.00, IQR 1.50) and 6.95 (range 1.20–12.00, IQR 5.20), respectively. Neither of the two low-risk studies studied Norgestrel or Chlormadinone acetate. Three studies reported Pearl Index rates for the formulation currently under review by the FDA for OTC status (Norgestrel 0.075 mg), and the Pearl Index rates for that formulation ranged from 0.50 to 2.00, with a median of 1.73 [36,66,67]. For Desogestrel and Risperidone, five Pearl Index rates reported by three studies were all less than 1.00 (median 0.52, range 0.41–0.97, IQR 0.22). Across all POPs, there were 26 Pearl Index rates and 17 of these were 2 or less. Figure 4 shows Pearl Index rates by progestin and study duration.

3.3.4. Additional pearl index rates accounting for participant characteristics or behaviors

In addition to reporting Pearl Index rates, four studies also reported effectiveness rates stratified by participant characteristics or behaviors that could potentially impact effectiveness [21,37,43,67]. Two studies [37,67] reported Pearl Index rates stratified by age and, comparing these rates by formulation, these rates were the same or slightly higher (by an average of 0.15) than unstratified rates. One of these studies [67] analyzed failure rates by multiple age groups and duration of study participation and found that failure rates in their sample declined as age increased but that across all ages, participants using their method for 37 months or longer had a low Pearl Index rate (0.20). Two studies [21,37] reported Pearl Index rates adjusted for additional contraception and sexual activity status, and these adjusted rates were higher than unadjusted rates by an average of 0.07. One study [37] reported Pearl Index rates adjusted for breastfeeding participants and when excluding these participants from calculations, the adjusted rates were lower by an average of 0.19. Table 3 displays stratified and adjusted rates.

3.4. Efficacy rates

A method failure Pearl Index is a measure of contraceptive efficacy because it only includes pregnancies resulting from a method failure among perfect users. Only three studies assessed to be at low or moderate risk of bias reported method failure Pearl Index rates [21,36,78], and the median of the five reported rates was 0.97 (range 0.40–6.50, IQR 0.68). Without rates for Drosperinone and Desogestrel, there were only two efficacy rates from two studies – one reported an efficacy rate of 6.5 [78] and the other reported a rate of 0.40 [36]. Including studies assessed to be at high risk of bias, there were a total of 33 method failure Pearl Index rates from 21 studies. Rates ranged from 0 to 221.95 and the median rate was 1.10 (IQR 1.50). The high rate of 221.95 was calculated from a small study testing the lowest dosage of a POP formulation that would

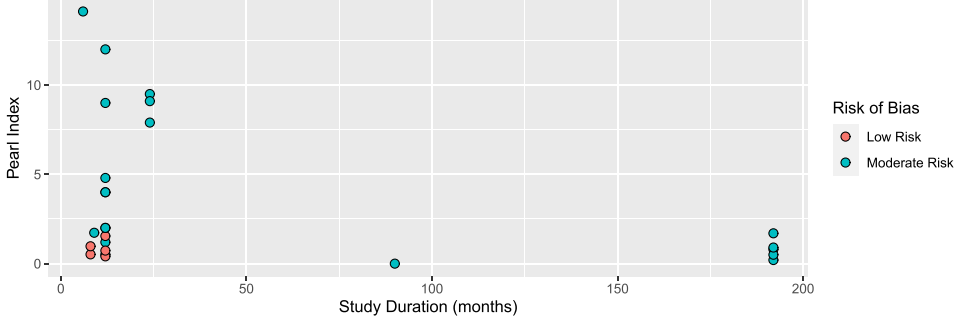

Fig. 2. Pearl Index rates by study duration (reported by low- and moderate-risk studies).

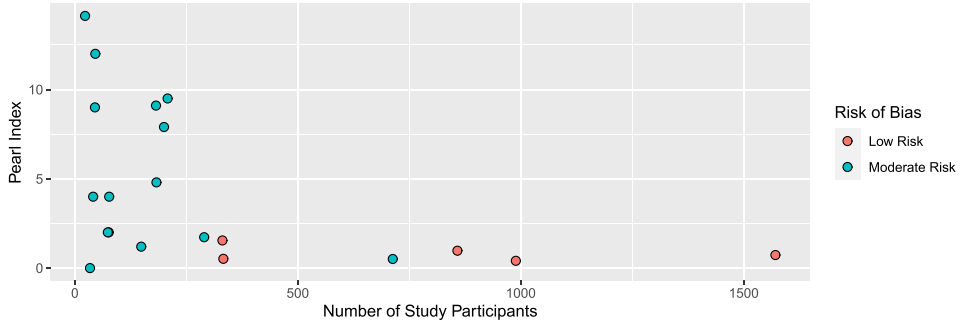

Fig. 3. Pearl Index rates by study size (reported by low- and moderate-risk studies).

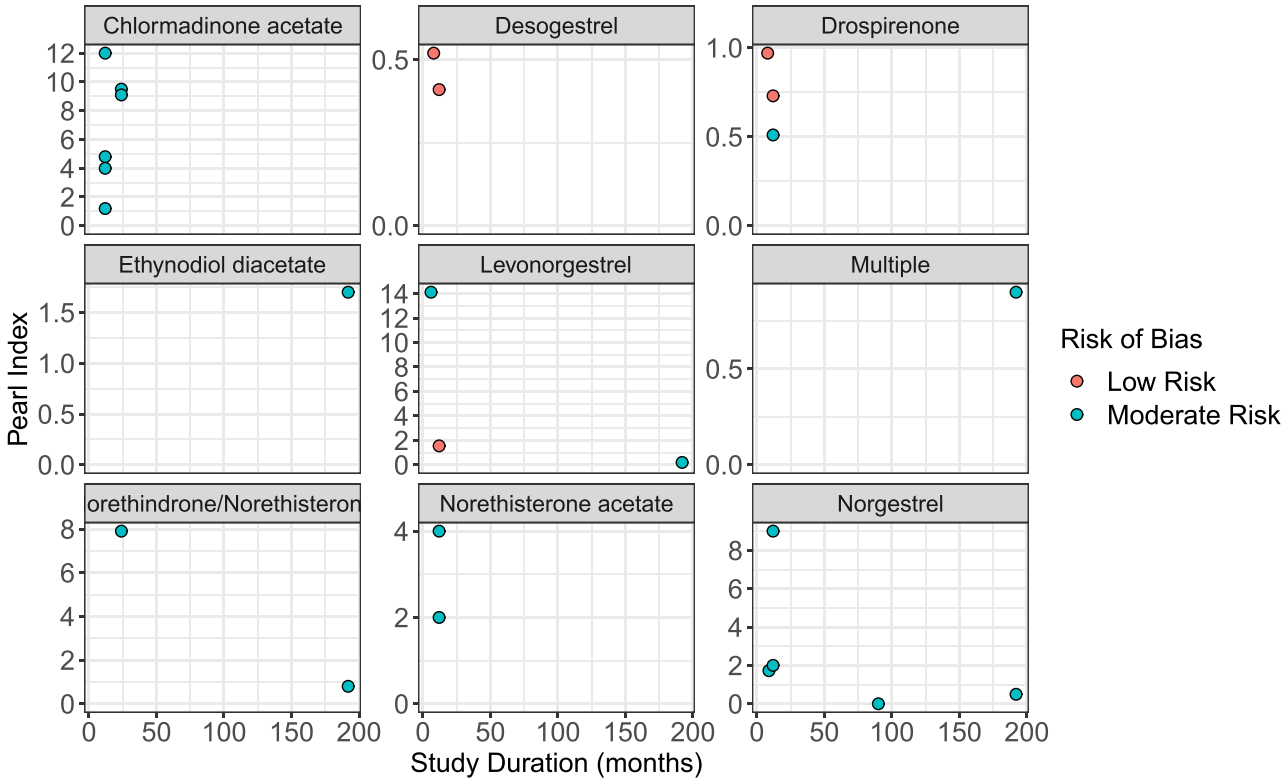

Fig. 4. Pearl Index rates by progestin and study duration (reported by low- and moderate-risk studies).

change cervical mucus enough to still be an effective contraceptive method.[49] The highest dose given to patients was half the dosage used in other studies testing this formulation, so rates of pregnancies due to method failure reported from this study were anticipated to be high and participants were forewarned that the pill may not protect them from pregnancy. The remaining efficacy analysis will focus on rates reported by studies not at high risk of bias.

3.4.1. Method failure pearl index rates by study duration, size, and formulation

Study duration of the three studies reporting efficacy rates ranged between 8 and 24 months. The number of participants in a treatment arm or pooled analysis ranged from 208 to 1571, with a median of 333 participants. There were not enough data to analyze efficacy rates by formulation, but across all formulations, all rates but one were less than 1.5.

3.5. Life table

Fourteen studies [21,27,30,31,34,40,54,56,59,62–64,66,73] reported life table rates but different types of rates (gross cumulative, net cumulative, standardized net, among other types of rates) were reported over various periods of times, making comparisons difficult. Five studies were assessed to be at low or moderate risk of bias [21,34,54,62,64]. Table 4 displays life table rates and their descriptions reported by studies. Periods of time used in analyses ranged from 2 months to 36 months and pregnancy rates per 100 women ranged from 0 to 8.4.

4. Discussion

4.1. Main findings and interpretation

Our review shows that the median Pearl Index rate for typical use of POPs reported by studies not at high risk of bias published over the course of five decades is about 2 (1.63). Al-

Table 3
Stratified or adjusted[a] Pearl Index rates reported by studies at low or moderate risk of bias

First author	Formulation	Pearl Index	Adjusted Pearl Index	Variable that Pearl Index was stratified by or adjusted for
Archer [37]	Drospirenone 4 mg	0.51	0.71	Age: <35 years
Vessey [67]	Norethisterone 0.35 mg	0.8	0.8	Age (no other details)
Vessey [67]	Norgestrel 0.75 mg	0.5	0.7	Age (no other details)
Vessey [67]	Ethynodial diacetate 0.50 mg	1.7	1.8	Age (no other details)
Vessey [67]	Levonorgestrel 0.03 mg	0.2	0.3	Age (no other details)
Vessey [67]	Multiple formulations[b]	0.9	0.9	Age (no other details)
Vessey [67]	Multiple formulations[b]	3.1	2.7	Age 25–29 and 1–12 months of use
Vessey [67]	Multiple formulations[b]	3.1	4.5	Age 25–29 and 13–36 months of use
Vessey [67]	Multiple formulations[b]	3.1	0	Age 25–29 and 37 months or more of use
Vessey [67]	Multiple formulations[b]	2	1.8	Age 30–34 and 1–12 months of use
Vessey [67]	Multiple formulations[b]	2	3.1	Age 30–34 and 13–36 months of use
Vessey [67]	Multiple formulations[b]	2	0	Age 30–34 and 37 months or more of use
Vessey [67]	Multiple formulations[b]	1	0.7	Age 35–39 and 1–12 months of use
Vessey [67]	Multiple formulations[b]	1	1.4	Age 35–39 and 13–36 months of use
Vessey [67]	Multiple formulations[b]	1	0.8	Age 35–39 and 37 months or more of use
Vessey [67]	Multiple formulations[b]	0.3	0.6	Age 40+ and 1–12 months of use
Vessey [67]	Multiple formulations[b]	0.3	0	Age 40+ and 13–36 months of use
Vessey [67]	Multiple formulations[b]	0.3	0	Age 40+ and 37 months or more of use
Vessey [67]	Multiple formulations[b]	0.9	1	Duration of progestin-only pill use: 1–12 months
Vessey [67]	Multiple formulations[b]	0.9	1	Duration of progestin-only pill use: 13–36 months
Vessey [67]	Multiple formulations[b]	0.9	0.2	Duration of progestin-only pill use: 37 or more months
Palacios [21]	Desogestrel 0.075 mg	0.52	0.58	Additional contraception and sexual activity status
Palacios [21]	Drospirenone 4 mg	0.97	1.09	Additional contraception and sexual activity status
Palacios [21]	Drospirenone 4 mg	0.73	0.79	Additional contraception and sexual activity status
Archer [37]	Drospirenone 4 mg	0.51	0.54	Additional contraception and sexual activity status
Korver [43]	Desogestrel 0.075 mg	0.41	0.17	Breastfeeding—excluded exposure during breastfeeding participants in calculations
Korver [43]	Levonorgestrel 0.03 mg	1.55	1.41	Breastfeeding—excluded exposure during breastfeeding participants in calculations

[a] Pearl Index rates were stratified by or adjusted for participants' age, duration of progestin-only pill use, additional contraception and sexual activity status, and breastfeeding status. Details on stratification or adjustments are listed in the last column of the table.
[b] This included Norethisterone 0.35 mg, Norgestrel 0.075 mg, Ethynodiol diacetate 0.5 mg, Levonorgestrel 0.03 mg, and "other" progestin-only pills, some of which were trial preparations.

though four moderate-risk studies [34,44,53,78] reported six relatively high Pearl index rates ranging from 7.90 to 14.12, three of these rates may have occurred due to the small number of study participants (between 23 and 46 participants in each study arm) [44,53] and short study duration (6 months) [44]. It is unclear why the other three rates ranging from 7.90 to 9.50 reported in the other two studies are high. Authors of the study reporting a rate of 9.50 hypothesized that the relatively high rate may have been due to the high fertility in their study population [78].

The median Pearl Index rate of 2 is the median rate of unintended pregnancies per 100 person-years of taking the POP. Or, to put it another way, two pregnancies are expected to occur if 100 people (both perfect and imperfect users) took the pill for 1 year. This rate is much lower than the currently accepted estimation that 7% of pill users will have an unintended pregnancy during their first year of use [9]. This comparison is limited by the fact that our study's effectiveness estimation is based on Pearl Index rates reported by studies of varying durations, whereas the currently accepted estimation is based on first year of use only; the estimation from this study may be biased downward because we included effectiveness rates reported by studies lasting longer than a year. In addition, failure rates from our review come predominantly from clinical trials in which participant behavior may be influenced by study participation, and the current estimation that 7% of pill users will have an unintended pregnancy during their first year is based off of national survey data from mostly COC users [9]. Despite the limitations in comparing these two estimations of unintended pregnancies, the discrepancy between two and seven pregnancies is notable, especially given the belief that POPs are less forgiving of delayed pill intake, which would lead one to expect more than seven pregnancies over the first year with typical use.

If taken correctly and consistently, we found that the median method failure rate of POPs is 0.97 among studies not at high risk of bias, which is consistent with the lowest reported failure rate of 1% during the first year of use [9].

4.2. Limitations

This review has several limitations. The first is that, given the sparseness of detailed information on methodology, we often could not obtain complete information about data collection and analysis approaches for each included study. Previous research has documented common methodological mistakes in studies assessing contraceptive efficacy or effectiveness, including: methods of collecting data on adherence; procedures for detecting, recording, and reporting pregnancies; and definitions of, and procedures for, accounting for participant loss to follow-up [17,25,80,81]. We attempted to account for the above limitations by assessing each study for biases that could impact reported effectiveness and efficacy rates and by analyzing rates by study quality, with a focus on data reported by studies assessed to be at low or moderate risk of bias. We also checked Pearl Index calculations when adequate data were reported and found that 35% of rates may have been incorrectly calculated. We did not replace these rates with our calculations since it is possible that authors correctly did the calculations but reported person-time differently in their manuscript. Pearl Index rates rarely included confidence intervals, and although an article published in 2003 recommends a statistical model for calculating confidence intervals for Pearl Index rates [82], it is unclear if confidence intervals are currently reported in a standardized manner. Since loss-to-follow up rates could also impact efficacy and effectiveness rates, loss-to-follow up rates (20% or greater) were considered when assessing risk of bias.

Table 4
Pregnancy rates reported by studies using life table analyses

First author	Progestin	Study duration	Pregnancy rate	Pregnancy rate due to method failure	Pregnancy rate due to patient failure	Other reported rate	Description of life table rates	Risk of bias
Bernstein [59]	Chlormadinone acetate	12 months	2.5	1.7	0.8	–	Life table rates (no detailed description).	High
		24 months	1.6	1.6	0	–		
		24 months (total)	4.1	3.3	0.8	–		
		36 months (total)	4.6	3.8	0.8	–		
Canto [27]	Norgestrel	2 months	0	–	–	–	Gross cumulative life table rates	High
		6 months	0.9	–	–	–		
		12 months	3.4	–	–	–		
Cerais [73]	Norgestrel	12 months	1.1				Life table rate for pregnancy	High
Dunson [30]	Norgestrel	11 months/12 cycles	1.2	–			Gross cumulative life table rates	High
Eckstein [31]	Norgestrel	12 cycles		–	–	2.10%	Overall contraception rate using life table method (no detailed description)	High
		30 cycles		2.1	–	3.60%		
Hawkins [34]	Chlormadinone acetate	0–3 months		1.6			Standardized net life table rates per 100 women at risk	Moderate
		4–6 months		0.8				
		7–9 months		0				
		10–12 months		0				
		12 months (potentially treated)	8.3	1.6	5.8		This study standardized life table rates by including only patients potentially treated for a year, since using participants who discontinued after a few months biases life table analysis rates.	
		13–24 months		No pregnancies				
	Norethisterone	0–3 months		2.1			Standardized net life table rates per 100 women at risk	
		4–6 months		0.8				
		7–9 months		0				
		10–12 months		0.6				
		12 months (potentially treated)	8.4	3.5	4.9		Includes only patients potentially treated for a year	
		13–24 months		No pregnancies			Standardized net life table rates per 100 women at risk	
Jubhari [40]	Quingestanol acetate	3 months	0.6	0.6	–	–	Net cumulative pregnancy rate	High
		6 months	1.3	0.9	0.4	–		
		9 months	1.9	0.9	1	–		
		12 months	2.9	0.9	2	–		
Moggia [54]	Norgestrel	6 months	0.5	–	0.5	–	Cumulative life table pregnancy rate	Moderate
Moggia [56]	Quingestanol acetate	6 cycles	–	–	–	98.1	Cumulative life table rates protection against pregnancy rates	High
		12 cycles	–	–	–	96.4		
		18 cycles	–	–	–	93.5		
		24 cycles	–	–	–	89.5		
		30 cycles	–	–	–	85.2		
Palacios [21]	Drospirenone	9 cycles				0.70%	Cumulative pregnancy ratio	Low
		13 cycles				0.72%		
Sheth [62]	Levonorgestrel	360 days				9.5	Cumulative net life-table discontinuation rates for accidental pregnancy	Moderate
		676 days				9.5		
	Norethisterone	360 days				13.2		
		676 days				19.6		
Shroff [63]	Ethynodiol diacetate	12 months	1.1	0.5			Net involuntary pregnancy rate	High
Tejuja [64]	Norgestrel	6 months	3.4				Net cumulative pregnancy rate	Moderate
		6 months	2.1					

Few studies adjusted failure rates based on participant characteristics or behaviors that could potentially impact effectiveness, such as age, additional contraception, and frequency of sexual activity. Although differences between Pearl Index rates and rates adjusted for these characteristics were small on average, more research is needed to understand the extent to which participant characteristics impact effectiveness rates for different POP formulations.

Lastly, few studies reported life table rates, and those that did provided rates that were incomparable due to different durations or types of rates [25]. Our analysis therefore relied heavily on Pearl Index rates, which are impacted by the length of participant exposure to pill use. To account for this limitation, we grouped studies of similar durations together to better compare rates. Future studies should report effectiveness and efficacy using both life table analyses and Pearl Index rates (to comply with regulatory guidelines) in a standardized manner to allow for comparability across studies.

Our review aimed to synthesize POP effectiveness and efficacy rates available in the literature, acknowledging that much of the data are from nonrandomized studies published 20 to 50 years ago, and that study design and use of the Pearl Index may have influenced the accuracy and precision of reported rates. Our review finds that the median rate of unintended pregnancy during typical POP use when estimated with a comprehensive synthesis of the available literature is lower than what is currently expected for POPs, and that this holds true even when excluding failure rates from newer formulations that prevent pregnancy in a simi-

lar manner to COCs. Future research should investigate the possibility that POPs may be more effective than currently documented and explore the extent to which participant characteristics or behaviors influence the previously estimated effectiveness or efficacy of POPs. This information will help inform future efforts to make different POP formulations available OTC and help potential users decide which OTC POP is best for them.

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Declaration of Competing Interest: C.H. and J.H. report no competing interests. A.W., C.Z., K.B., and K.K. are staff at Ibis Reproductive Health, which has a partnership with HRA Pharma in which Ibis provided financial support for some of the research that will be part of an application to the US Food and Drug Administration to switch a POP from prescription to over-the-counter status. Ibis receives no monetary compensation or ownership of any rights to the product. Ibis raised the funding for this partnership from a private foundation and selected HRA Pharma as its partner through an open process overseen by the steering committee of the Oral Contraceptives Over-the-Counter Working Group in an effort to incentivize a pharmaceutical company to complete the work to make a birth control pill product available over the counter.

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Author contributions

A.W.: conceptualization, literature search and screening process, data extraction, review and editing manuscript; C.H.: analysis planning, reviewing, and editing manuscript; C.Z.: conceptualization, literature search and screening process, data extraction, analysis, writing of original draft, reviewing and editing manuscript; J.H.: analysis planning, reviewing and editing manuscript; K.B.: conceptualization, reviewing and editing manuscript; K.K.: data extraction, analysis, reviewing and editing manuscript. All authors have read and approved the manuscript.

Details of ethics approval

This is a comprehensive review and did not require ethical approval.

Data availability statement

Data available on request from the authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2022.109925.

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