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Contraindications to progestin-only oral contraceptive pills among reproductive aged women

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Abstract

Background—Progestin-only oral contraceptive pills (POPs) have fewer contraindications to use compared to combined pills. However, the overall prevalence of contraindications to POPs among reproductive aged women has not been assessed.

Study Design—We collected information on contraindications to POPs in two studies: 1) the *Self-Screening Study*, a sample of 1,267 reproductive aged women in the general population in El Paso, Texas, and 2) the *Prospective Study of Oral Contraceptive (OC) Users*, a sample of current OC users who obtained their pills in El Paso clinics (n=532) or over the counter (OTC) in Mexican pharmacies (n=514). In the *Self-Screening Study*, we also compared women's self-assessment of contraindications using a checklist to a clinician's evaluation.

Results—Only 1.6% of women in the *Self-Screening Study* were identified as having at least one contraindication to POPs. The sensitivity of the checklist for identifying women with at least one contraindication was 75.0% (95% CI: 50.6–90.4%), and the specificity was 99.4% (95% CI: 98.8–99.7%). In total, 0.6% of women in the *Prospective Study of OC Users* reported having any contraindication to POPs. There were no significant differences between clinic and OTC users.

Conclusion—The prevalence of contraindications to POPs was very low in these samples. POPs may be the best choice for the first OTC oral contraceptive in the US.

Keywords

oral contraceptives; contraindications; self-screening; over-the-counter status

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1. Introduction

Oral contraceptive pills (OCs) are the most common method of contraception in the United States (US) [1]. Although the relative safety of this method has been well-established and some have advocated for making OCs available over-the-counter (OTC) [2,3], women interested in starting or continuing with this method must still obtain a prescription from a health care provider in the US. One of the justifications for maintaining the prescription-only status is that, during their clinician visit, women are screened for health conditions such as hypertension and diabetes, which may increase their risk of myocardial infarction, stroke or other complications while taking OCs [4]. However, these rare complications are associated with the use of combined oral contraceptives (COCs) and not progestin-only pills (POPs) [5].

According to the US Medical Eligibility Criteria (MEC), many more conditions are considered relative (category 3) and absolute (category 4) contraindications to COCs compared to POPs [6]. For example, hypertension, migraine headache with aura, and smoking among women age 35 years and older – conditions with the highest prevalence in studies of reproductive aged women – are not considered contraindications to POPs [6–9].

In addition, conditions that are contraindications to POPs, such as past or current breast cancer, cirrhosis, and use of anticonvulsants, have been found to be relatively uncommon in several studies examining the prevalence of OC contraindications among reproductive aged women in the US. Using data from the National Health and Nutrition Examination Survey (NHANES), Shortridge and Miller [7] found that less than 2% of women reported having breast, cervical or uterine cancer or current liver disease. Although some contraindications were broadly defined in this study and data on others were not available in the NHANES, several other studies also found that the prevalence of individual contraindicated conditions was low - less than 1% among both women in the general population and women seeking reproductive health services [8–10]. However, none of these studies reported on the overall prevalence of having any POP contraindication.

There is growing evidence that women can accurately screen themselves for most health conditions that would contraindicate them for OC use. For example, women attending family planning clinics in Washington completed a self-assessment of 20 health conditions that would pose a risk to OC use, and the accuracy of this assessment was then compared to their providers' separate evaluation of these same conditions [10]. Patient-provider agreement was ≥ 90% on 17 of these items. In another study conducted in Texas, researchers also found a high level of agreement between contraindications identified through providers' assessment and those women reported in a self-administered checklist [8]. Disagreement between women and providers on eligibility for OC use was largely due to misclassification of migraine headaches and unrecognized hypertension, conditions that would not impact women's eligibility for POP use.

The purpose of this analysis was to provide a more focused examination of the prevalence of contraindications to POPs. Specifically, we assess the prevalence of individual POP contraindications as well as the overall prevalence of having any POP contraindication in a convenience sample of reproductive aged women and in a sample of current OC users – including those who have the option to obtain OCs over-the-counter in a counter in a real-life setting. We also examine how well women's self-assessment of these contraindications compares to that of a health care provider.

2. Materials and methods

For this analysis, we use data from the Border Contraceptive Access Study (BCAS), which examined OC use along the US-Mexico border. The study design, sample size justification and characteristics of women participating in the two sub-studies of BCAS have been published previously [8,9,11]; we briefly describe the relevant methods here. In the first BCAS sub-study (the *Self-Screening Study*), bilingual (English/Spanish) female interviewers recruited a convenience sample of 1,271 women between ages 18 and 49 years at shopping malls and a flea market in El Paso, Texas, from May to July 2006. Eligible women were given a checklist of contraindications to OC use, which was based on the WHO MEC and a previously validated instrument [10], and asked to mark whether they had any of the conditions listed. After completing the checklist, women were screened for these same conditions by a nurse practitioner who was not aware of the participants' self-screening assessment. If the nurse practitioner was unsure or felt a woman needed further evaluation regarding a specific condition, she was classified as contraindicated. The questions used in each of these assessments are presented in Table 1. Women provided verbal consent to participate in the study and received a $5–$10 gift card to use at the shopping mall or flea market following completion of the interview.

In the second BCAS sub-study (the *Prospective Study of OC Users*), we recruited 1,046 El Paso resident women between ages 18 and 44 years who either obtained their OCs at US family planning clinics (n=532) or OTC from pharmacies in Mexico (n=514). In the baseline interview, which was conducted between December 2006 and February 2008, bilingual (English/Spanish) female interviewers read participants a list of medical conditions considered contraindications to OC use and asked women to report if they currently have or ever had the conditions. We assessed category 3 and category 4 contraindications according to the WHO Medical Eligibility Criteria (MEC) 3rd edition, as the US MEC had not yet been released [6,9,12]. This sub-study did not include screening by a clinician. Women who reported any contraindication to OCs were referred to a health care provider. We also asked women to report the specific brand of pill they were using and provided a pictorial guide to assist them in identifying their brand. Prior to completing the baseline interview, women provided written informed consent; they also received a $20 gift card for their participation. Both sub-studies were approved by the Institutional Review Boards at the University of Texas at Austin and University of Texas – El Paso.

In our analysis of both sub-studies, we focus on just those conditions that are considered category 3 or 4 contraindications to initiation of POPs: history of or current breast cancer, liver disease (i.e., severe cirrhosis) or liver tumors (hepatocellular adenoma or hepatoma), and use of medications to treat seizures or tuberculosis (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, or rifampicin). We did not ask women about whether they had systemic lupus erythematosus (SLE) with positive or unknown antiphospholipid antibodies, malabsorptive bariatric surgery or used ritonavir-boosted protease inhibitors or rifabutin, as these conditions were not included as contraindications to POP use in the WHO MEC [12]. Women who were missing information on any of the POP contraindications were excluded from analysis. Only four women were missing this information in the *Self-Screening Study*, yielding a final sample of 1,267 women for this analysis. None of the 1,046 participants in the *Prospective Study* were missing this information.

In the *Self-Screening Study*, we computed the frequency of each self-reported contraindication, as well as the frequency as assessed by the nurse practitioner. We also assessed the sensitivity, specificity, positive and negative predictive values for report of any contraindication in the checklist, using the nurse practitioners' assessment as the 'gold

standard.' We calculated the 95% confidence intervals for these measures using the efficient score method [13]. In the *Prospective Study*, we computed the frequency of each contraindication to POPs and report of any contraindication by women's source of OCs at baseline (clinic versus OTC). The statistical significance of differences in the proportions of clinic and OTC users with any contraindication to POPs was determined using Fisher's exact test. We also examined the frequency of contraindications among women who were using POPs at the time of the baseline assessment. All analyses were conducted using Stata 10.0 (Stata Corp., College Station, TX).

3. Results

3.1. Self-Screening Study

Of the 1,267 women included in this analysis, few reported having contraindications to POPs (Table 2). Taking medications for tuberculosis or seizures was the most frequently identified contraindication in both women's self-report and the provider assessment, followed by history of liver disease and breast cancer. Overall, 1.7% (95% CI: 1.2–2.6%) of women self-reported at least one contraindication to POPs, and a similar percentage of women with contraindications were identified in the provider assessment (1.6%; 95% CI: 1.0–2.4%).

Only five women (0.4%) failed to identify a contraindication to POPs when in fact the nurse practitioner determined they had one; conversely, seven women (0.6%) indicated on the checklist that they had a contraindication to POPs when they did not have a true contraindication (Table 3). The sensitivity of the checklist for identifying women with at least one contraindication to POPs was 75.0% (95% CI: 50.6–90.4%), while the specificity was 99.4% (95% CI: 98.8–99.7%). The positive and negative predictive values for the checklist in this sample were 68.2% (95% CI: 45.1–85.3%) and 99.6% (95% CI: 99.0–99.8%), respectively.

3.2. Prospective study of OC users

Among the 1,046 women currently using OCs, few reported conditions considered to be contraindications to POPs, all of which are also contraindications to COCs (Table 4). In total, 0.6% (95% CI: 0.3–1.2%) of women reported that they had at least one contraindication. The prevalence of contraindications was slightly higher among OTC users (1.0%) compared to clinic users (0.2%), but the prevalence of contraindications was not significantly different for these two groups (p=0.118).

Only 17 women (1.6% of the total sample) were using POPs at the time of the survey; seven of these women obtained their method OTC in Mexico. None of the POP users reported having any of the assessed contraindications (results not shown).

4. Discussion

We found that the prevalence of contraindications to POPs was very low both among a sample from the general population and among current OC users in El Paso. We had previously reported that the prevalence of COC contraindications was surprisingly high in this population, possibly due to limited access to medical screening services [8,9]. The fact that the prevalence of POP contraindications was so low here, and similar for individual conditions reported in prior studies, likely reflects the rarity of these conditions among reproductive aged women [7,10]. We also found that POP contraindications were rare among women who obtained OCs OTC in Mexico and were absent among current POP users.

Women were able to accurately use the checklist to identify POP contraindications. In fact, the specificity and negative predictive value of the checklist to diagnose POP contraindications were significantly higher than these measures of the checklist's ability to diagnose COC contraindications [8]. The high negative predictive value of the self-screening checklist (99.6%) indicates that it would be very unlikely for a woman to truly have a POP contraindication after screening negative with the checklist.

Even in the case of a missed true contraindication, the risk of serious harm is lower with POPs compared to COCs. Women with contraindications such as hypertension, migraine with aura and smoking at age 35 or older who use COCs are at higher risk of stroke, acute myocardial infarction and peripheral arterial disease [6]. The above conditions are not contraindications to POPs [6], and therefore, women would not be at risk for such adverse cardiovascular events as a result of POP use. Moreover, we found that the most common POP contraindication identified by a clinician was the use of certain medications for tuberculosis or seizures, occurring among 0.9% of the sample in the *Self-Screening Study*. Use of these medications reduces the effectiveness of POPs but does not otherwise harm users [6]. And while contraindicated use among women with severe liver disease or breast cancer may exacerbate these conditions, they are rare and usually known to the potential user. It is also important to consider the risk of contraindicated use of OCs—either COCs of POPs—compared to the risks of unintended pregnancy for someone with the same medical conditions. Many of the contraindicated conditions, such as hypertension, liver disease or breast cancer, would also be exacerbated by pregnancy.

In the *Prospective Study*, only about 2% of the sample was using POPs, while the remainder was using COCs. Although there are no recent reports on the proportion of OC users in the US that take POPs, it is likely similarly low nationwide. It is unclear why the use of POPs is so uncommon. There may be a perception among providers and women that POPs are less effective. However, a recent Cochrane review [14] found that the published evidence was insufficient to draw conclusions about the relative efficacy of the two formulations and recommended more research in this area. As a reflection of this lack of evidence, contraceptive labeling reports the efficacy of oral contraceptives together without differentiating between COCs and POPs [15]. In addition, current recommendations for POPs, which suggest that backup contraception must be used if a pill is taken more than 3 h later than the scheduled time, may contribute to a perception, at least among providers, that the POP regimen is less convenient than COCs [16]. Yet these recommendations are not based on firm evidence [17]. And while irregular menstrual bleeding is common with POPs, there is no evidence that it is more frequent than with COCs [14,18].

Another factor contributing to the low use of POPs may be related to marketing. Currently, all POPs marketed in the US contain the same formulation of norethindrone. While formulations containing levonorgestrel and desogestrel are available in other countries, there has been no move to register these products in the US. It may be that pharmaceutical companies see the POP market as narrowly limited to breastfeeding mothers and women with contraindications to COCs. A POP formulation containing desogestrel 75 mcg has become very popular in some European countries. In a randomized controlled trial of 989 women observed over one year, desogestrel 75 mcg had a lower pregnancy rate than levonorgestrel 30 mcg, although the difference was not significant (Pearl index 0.14 (95% CI: 0.003–0.766) vs. 1.17 (95% CI: 0.240–3.406)) [19]. Desogestrel 75 mcg appears to prevent ovulation better than levonorgestrel 30 mcg [20,21]. This analysis has several limitations. We likely overestimated POP contraindications among women in the *Prospective Study of OC Users*, since they were not evaluated by a clinician to further classify reports of liver disease and discard those that are not contraindications (such as a history of hepatitis, mild cirrhosis and benign liver tumors). On the other hand, we did not

screen for several new contraindications to POPs that were added to the US MEC in 2010, such as history of SLE with positive or unknown antiphospholipid antibodies, malabsorptive bariatric surgery or use of ritonavir-boosted protease inhibitors or rifabutin. We do not know how common these conditions are in these populations, although we suspect they are rare. In addition, our two sub-studies used convenience samples, which may limit the generalizability of our findings.

Given the very low prevalence of contraindications to POPs, it may be that this formulation would be the best choice for the first OTC oral contraceptive in the US. Not only are POP contraindications rare, but women appear to be able to accurately identify them using a simple checklist without the aid of a clinician. While the launch of an OTC POP would be an opportunity to re-brand this formulation, it remains to be seen whether there would be significant uptake of a new POP. More rigorous research is needed on the efficacy and side effects of POPs compared to COCs, as well as the effectiveness and acceptability of POPs provided in an OTC setting.

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Table 1

Assessment of contraindications to progestin-only pills in the Self-Screening Study

Self-assessment	Provider screening
Do you take medicine for seizures or tuberculosis (TB)?	Do you take any of the following medications currently: Rifampicin (Rifampin) or anticonvulsants such as phenytoin (Dilantin), carbemazepine (Tegretol), barbituates, primidone (Myidone or Mysoline), topiramate (Topamax) or oxcarbazepine (Trileptal)?
Do you have liver disease or have you had liver cancer?	Do you currently have liver disease (active viral hepatitis or cirrhosis) or have you had liver cancer in the past?
Have you had breast cancer?	Do you currently have breast cancer or have you had breast cancer in the past?

Table 2

Frequency of contraindications to progestin-only pills according to self-assessment and provider screening in the Self-Screening Study(n=1,267)

	Self-assessment		Provider screening		Correctly identified	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Current use of medications for TB or seizures	9	(0.7)	11	(0.9)	7	(63.6)
Current liver disease or history of liver cancer	9	(0.7)	5	(0.4)	4	(80.0)
History of or current breast cancer	4	(0.3)	4	(0.3)	4	(100.0)
Any contraindication	**22**	**(1.7)**	**20**	**(1.6)**	**15**	**(75.0)**

TB = Tuberculosis

Table 3

Accuracy of self-assessment compared to provider screening for contraindications to progestin-only pills(POPs) in the Self-Screening Study

	Provider screening					
	Contraindicated to POPs n (%, 95% C.I.)		**No contraindications n (%, 95% C.I.)**		**Total n (%, 95% C.I.)**	
Self-assessment						
Contraindicated to POPs	15	(1.2, 0.7–1.9)	7	(0.6, 0.3–1.1)	22	(1.7, 1.2–2.6)
No contraindications	5	(0.4, 0.2–0.9)	1,240	(97.9, 96.9–98.5)	1,245	(98.3, 97.4–98.9)
Total	20	(1.6, 1.0–2.4)	1,247	(98.4, 97.6–99.0)	**1,267**	**(100.0)**

C.I. = Confidence Interval

Table 4

Frequency of contraindications to progestin-only pills according to source of pills at baseline in the Prospective Study of OC Users (n=1,046)

	Clinic		OTC	
	n	**(%)**	**n**	**(%)**
Current use of medications for TB or seizure	1	(0.2)	1	(0.2)
Current liver disease or history of liver cancer	0	(0.0)	3	(0.6)
History of or current breast cancer	0	(0.0)	1	(0.2)
Any contraindication	**1**	**(0.2)**	**5**	**(1.0)**

TB = Tuberculosis