Barriers to contraceptive use in product labeling and practice norms

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Introduction

Both in the United States and internationally, unmet need for contraception remains significant. Difficulty of use, concerns about side effects or long-term health effects, and barriers to access may deter utilization.[1-5] New contraceptives under development may be easier to use with fewer side effects, but in the interim, it may be possible to increase uptake and continuation of existing methods. Eliminating restrictions in how contraceptives are provided has great potential to increase access.

Two sources provide clinicians and consumers with information and regulations about appropriate contraceptive use: product labeling (the information that the US Food and Drug Administration officially permits the drug companies to use in their packaging and marketing) and practice guidelines (typically set forth by public sector groups, such as the International Planned Parenthood Federation or the World Health Organization). Sometimes labeling and practice guidelines are in consonance; however, they often differ. Product labeling is often based on outdated data, potentially misinforming both the public and healthcare providers. In many cases this misinformation hinders direct consumer access to contraceptives.

In contradistinction to the ease by which manufacturers may strengthen pharmaceutical product labeling is the comparative difficulty of reducing safety information or adding indications for use. The latter change generally requires that the manufacturer support the proposed change with two adequate and well controlled studies.[6] There are, however, few incentives for manufacturers to submit additional paperwork to simplify labeling due to

the cost of conducting the clinical studies unless there is a potentially significant increase in market share to be derived from the changes. In the case of oral contraceptives (OCs), manufacturers are generally proscribed from distinguishing products through promotional campaigns or labeling, because OCs are regulated under class labeling guidelines. Therefore it is unlikely that a reduction in safety information will be initiated by manufacturers. As a result, labeling often includes unnecessary and outdated information, much of which was grandfathered in when the regulations were established.

Rarely updated labeling concerned primarily with liability issues is troublesome for several reasons. First, inaccurate information in labeling may lead women to overstate the dangers associated with a given contraceptive[7] and thus deter eligible women from using what are in fact widely studied, safe and effective methods. Indeed, previous research has shown that the misinformation provided in OC labeling led women to believe they had medical contraindications to use or that the pills entailed health risks so grave as to render use unsafe.[8] Perhaps most importantly, labeling that focuses primarily on liability obfuscates particularly useful and important information for women. Valid concerns regarding legitimate potential complications get over-shadowed by the medically unwarranted emphasis on the extremely rare complication (*e.g.* hepatic cancer for OCs).[9]

Given that the FDA-approved labeling is often out-of-date or not based on current scientific evidence, physicians often utilize medications and devices in ways not listed in the labeling, so-called "off-label" use. Off-label use is common, and even the FDA recognizes that advances in medicine often precede changes to the labeling.[10] It is

assumed that the physician prescribing a drug or device off-label is well informed and bases the decision to do so on sound medical evidence.[11] While off-label use is helpful in that it allows physicians to use medications in innovative ways, the practice transfers liability risk to the provider, and some clinicians may be reticent to use drugs in this manner. Women without access to clinicians with the latest research, particularly women in developing countries, are at a disadvantage because their provider is less likely to be aware of innovative or less restrictive uses of drugs or devices. Because of the dearth of clinical trials including pregnant women and children, off-label use is extremely common among pediatricians and obstetricians. In one study of women attending prenatal clinics, physicians prescribed medications for an off-label indication to 23% of the pregnant women.[12]

When physicians prescribe off-label, they often look to the other main source of information: expert recommendations or practice guidelines. At their best, practice guidelines are systematically developed statements intended to help clinicians make decisions about specific patient circumstances. These guidelines are often developed by experts brought together by professional organizations, such as the Royal College of Obstetricians and Gynaecologists or the World Health Organization, and either published by the organization or in peer-reviewed journals.

In this paper, we review the labeling of the major contraceptives available on the market worldwide, as well as the contraceptive practice guidelines of the leading professional and public sector organizations active in family planning. We hypothesize that current

models of contraceptive provision, included in both the medication and device labeling as well as practice guidelines, create barriers to access, which if removed, could increase the number of users of these methods. We identify research priorities to help solidify the evidence to support more liberal contraceptive provision.

Methods

We reviewed the prescribing information (referred to here as labeling) for the following contraceptives: combined oral contraceptives (specifically that of Ortho-Novum and Modicon tablets), Depo-Provera contraceptive injection, the Ortho Coil Spring and All-Flex diaphragm and fitting set, and the ParaGard T380A intrauterine copper contraceptive. In addition, we reviewed the most recent practice guidelines from the following organizations: the World Health Organization (WHO), the International Medical Advisory Panel (IMAP) of the International Planned Parenthood Federation (IPPF), the Planned Parenthood Federation of America (PPFA), the Maximizing Access and Quality Initiative (MAQ) of the US Agency for International Development (USAID), the Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit of the Royal College of Obstetricians and Gynaecologists (RCOG), and the American College of Obstetricians and Gynecologists (ACOG), as well as those from *Contraceptive Technology*.

Results

We identified barriers to use for each contraceptive method: restrictions about how the product can be dispensed, limitations in the type of provider who can dispense it, and excessive or unproven rules about use and clinician follow-up.

Hormonal methods

A number of practices associated with hormonal methods (*i.e.* combined oral contraceptives (COCs), contraceptive patch, vaginal ring, injectables) could be eliminated to improve access to these methods. The labeling for all hormonal methods recommends a physical examination prior to provision, although a relatively recent modification allows deferral of this exam until after initiation.[9] While regular physician visits are advisable for a number of preventative health procedures such as breast exams and pap smears, clinicians should not prevent women who decline these services from receiving contraceptives.[13]

At issue is whether women can adequately self-screen for COCs, as well as absorb the relevant information necessary for good compliance and continuation, without a clinician visit. Very few studies have examined whether women can screen themselves successfully for medical contraindications to COC use. One of the rare studies to tackle this topic was conducted in Mexico, where a prescription for COCs is not required, and provides some evidence that woman can screen themselves well.[14] More definitive studies are necessary to inform the debate about over-the-counter provision in countries where this is not the norm.

Direct clinician counseling about how to use hormonal methods is routine in countries where they are available only by prescription. However, a recent review of studies of contraceptive counseling found little evidence demonstrating a benefit to this practice.[15] Even with physician counseling, patient compliance is relative low. A clinic-based study in the US found that 58% of women did not take their pills every day,[16] and similar proportions of women missing pills have been reported in other settings.[17,18] Poor compliance may be even more common among adolescents, with or without a doctor's visit.[19] One study of 6,676 European pill users found that poor compliance was significantly related to a lack of an established routine for pill-taking, experiencing side effects, and a failure to read and understand written materials that came with the COC package.[20] The latter result could indicate that current COC labeling is too complex, or that women who already receive personal consultation are disinclined to read written materials. Simplified patient instructions for COCs are urgently needed, and studies should address women's comprehension of this material, as was done for an emergency contraception product.[21] Little research specifically analyzes the effect of a doctor's consultation on continuation. One study from Kuwait found similar continuation rates among women who consulted a physician and women who did not.[22] More research is needed to understand the effect of over-the-counter provision on compliance, continuation and overall efficacy.

The FDA labeling for hormonal contraceptives emphasizes the importance of blood pressure screening during the physical exam.[9] Screening for uncontrolled hypertension is important, as it is a contraindication to COC use; it is also important at follow-up visits as

some women develop hypertension while on COCs.[23-25] All of the practice guidelines we reviewed stressed the importance of blood pressure screening prior to dispensing COCs,[26-29] although the WHO recognizes that in settings where such measurement is not possible, this should not be a barrier to dispensing the method.[30] But in settings where blood pressure measurement is available, must women see a clinician to be screened for hypertension? Research outside of the field of contraception has demonstrated that blood pressure self-determination is feasible.[31,32] Although some studies have suggested that blood pressure kiosks in drug and grocery stores are inaccurate,[33,34] as this technology improves, women may be able to self-screen for hypertension in settings other than clinicians' offices. The accuracy and feasibility of this approach to blood pressure screening prior to and while on COCs needs to be tested prospectively.

Postpartum uses raises another barrier: COC labeling states that nursing mothers should not take COCs.[9] The WHO categorizes COC use during the first six months of breastfeeding as classification 3: risks usually outweigh advantages.[30] This recommendation, shared by IMAP,[26] MAQ[35] and RCOG,[27] is based on a concern that COCs might diminish the quality and quantity of breast milk; however, the data are not convincing. The studies that have examined the effect of COCs on lactation are conflicting and of poor quality.[36] What is clear is that some women prefer COCs as a form of contraception and even stop breastfeeding to use them.[37] When stopping breastfeeding is not an acceptable alternative, some women may use no or less effective forms of contraception, putting themselves at risk of an unintended pregnancy. Of the practice guidelines we reviewed, only ACOG,[38] PPFA[28] and *Contraceptive Technology*[29]

recognize that COCs can be appropriate for well-nourished breastfeeding women after milk flow is well established. A randomized controlled trial of COCs vs. progestin-only OCs vs. placebo is needed to better understand the effects of these medications on lactation, as well as on contraceptive efficacy, continuation and satisfaction. More liberal use of COCs while breastfeeding would broaden the contraceptive options available to postpartum women.

Labeling also recommends that women commence hormonal contraceptives at the start of their menstrual cycle,[9] and most guidelines we reviewed agree.[27,28,35] If women request these methods at another time of their cycle, they either may be told to return at the time of menses, or, in the case of COCs, they may be given a pack to start with their next menses. But is this practice medically necessary and does it best serve women's needs? Many women never return for the menstrual visit, and some may not start their COCs at the appointed time.[16] *Contraceptive Technology* states that COCs may be started at some time other than at the start of the menstrual cycle as long as the woman is certain she is not pregnant and has not had sex since the last menses.[29] The WHO recommendations state that COCs can be started at other times of the cycle (after the first 7 days) if it is reasonably certain that the client is not pregnant, which for most women means not having had intercourse since the last menses.[39] While more liberal than other guidelines, even the WHO recommendations would insist that many women delay initiation of contraception until the following cycle. These guidelines aim to avoid drug exposure during early pregnancy, despite the fact that studies have consistently demonstrated that COCs have no teratogenic effect.[40-43]

Two small trials have examined starting COCs at the time of clinician visit, regardless of where a woman is in her cycle, a practice called Quick Start.[44,45] Women undergo a sensitive urine pregnancy test prior to starting the pills and receive emergency contraception if needed.[45] These trials demonstrated that Quick Start COC initiation does not worsen side-effects and may improve continuation. Larger trials are underway with Quick Start COCs, and we hope future research will address this practice in developing country settings, as well as for injectables and other hormonal delivery systems. Research also is urgently needed to provide data about when hormonal contraception may be safely started during the medical abortion process.

In many settings, women are denied direct access to injectable contraceptives by requiring clinician visits to provide the injection. One small study examined women's self-injection of Cyclofem with the UniJect device, a drug delivery system with a prefilled syringe and attached needle.[46] A large percentage of women accurately self-injected and wanted to continue to do so. For those who do not prefer self-injection, provision by pharmacy workers may be both feasible and cost-effective. However, more research is needed with other injectable contraceptives to confirm that non-clinician injection is an acceptable alternative to current practices.

Similar to limiting when hormonal methods can be started, the timing of repeat contraceptive injections is an additional barrier to use. When a woman is overdue for a repeat injection (beyond 13 weeks for Depo-Provera), the labeling states that pregnancy

must be ruled out before she can receive her next dose.[47] At its most benign, this requirement is time consuming, and in some cases the client must pay for a urine pregnancy test. At its extreme, a woman may be told to abstain or use condoms for 2 weeks and return for a repeat pregnancy test.[48]

Both the WHO[39] and RCOG[27] guidelines specifically address this issue. The WHO states that the ideal time for reinjection of Depo-Provera is 3 months, while RCOG says that it is 12 weeks, and both allow a period of up to 2 weeks beyond that, during which a woman may be reinjected without further evaluation or additional contraception. If a woman is more than 2 weeks late, the injection may be given if it is reasonably certain that she is not pregnant.[39] It is unlikely that a woman late for her injection who has had unprotected intercourse will satisfy one of the clinical criteria to exclude pregnancy,[39] and a pregnancy test would be the only way to rule out an existing (but not very early) pregnancy. As with other barriers mentioned here, this practice may end up denying women the opportunity to use a safe and effective form of contraception. Evidence suggests that women may be accurate in their diagnosis of early pregnancy,[49,50] although self-assessment of pregnancy among injectable users, perhaps using a checklist of symptoms, has not been tested. Home urine pregnancy tests are highly accurate,[51] and their use by women outside of a clinical setting could be used to replace a clinician visit. In the unlikely event that a pregnant woman receives a contraceptive injection, even the labeling for Depo-Provera recognizes the minimal risk associated with this exposure.[47]

Cervical barriers

The use of cervical barriers is burdened by practices that either limit access to the method or make their use more cumbersome. Clinicians and researchers have renewed interest in these female-controlled methods because of their potential to protect against sexually transmitted infections (STIs), as well as pregnancy.[52] If cervical barriers do prevent infection, improving user access will be even more critical. Clinician provision of the diaphragm and cervical cap is currently required,[53-57] mostly to fit the devices. While fitting may be justified for the cervical cap, little evidence supports this requirement for the diaphragm, and limited data suggest that the modal diaphragm size (70 mm) works as well as a fitted one.[58-60] Historical evidence shows that physician fitting was introduced early in the 20th century, nearly 40 years after the immediate precursor of today's diaphragm had been introduced, for reasons entirely unrelated to concerns about diaphragm effectiveness or safety.[61] When the US FDA began to regulate medical devices in 1976,[62] the diaphragm's fitting rules were grandfathered into the approved labeling without empirical evidence.

The labeling of the diaphragm states that the device must be used with spermicide and should not be used for more than 24 hours continuously,[53] but neither of these recommendations are based on evidence, as IMAP[55] and *Contraceptive Technology*[57] recognize. Could liberalizing such requirements make the device more attractive to new users without significantly affecting safety or contraceptive efficacy? Several reports have documented women's dissatisfaction with using spermicide, which can be messy and irritating.[63,64] Recent evidence that nonoxynol-9 may increase HIV transmission among female sex workers provides further motivation to reexamine the use of

spermicide with the diaphragm.[65] Limited data suggest that diaphragm use without spermicide does not affect efficacy,[60,66] although more research is needed to confirm this. One study also examined continuous use of the diaphragm (as opposed to use only around the time of intercourse) and found that this practice was both safe and effective.[66] Continuous diaphragm users had a significantly lower pregnancy rate, as well as fewer side effects. While this study also needs further confirmation, it appears likely that diaphragm provision and use could be substantially simplified, thereby increasing the popularity of this method.

Intrauterine devices (IUDs)

Simplifying IUD provision, by making it available from the most accessible and affordable practitioner, could greatly increase access to and uptake of this method. Although the labeling for the ParaGard IUD does not specify that a physician must insert the device, training of mid-level providers in insertion technique is deficient in many developing countries.[67] When access to physicians is limited either by scarcity or financial barriers, women's contraceptive options narrow. In several settings, studies have shown that non-physician provision of IUDs is safe, resulting in equally low complication rates.[68-70] With an emphasis on training and quality assurance, mid-level practitioner IUD insertion could be more cost-effective than physician provision, thereby increasing user access.

A number of labeling requirements for IUDs limit women's access. Despite the fact that women may be highly motivated to begin contraception in the post-abortion and post-partum period, the ParaGard labeling proscribes insertion at these times.[71] Two recent

reviews concluded that post-abortion and post-partum IUD insertion are both safe and effective.[72,73] Expulsion of the IUD may be more common in these periods, but this needs to be balanced against the convenience of having the insertion performed at the time of the other pelvic procedure when the cervix is already dilated. In the one comparative trial of immediate vs. delayed IUD insertion after abortion, 40% of women randomized to the delayed group did not return for the insertion.[74] Some of these women may have chosen other contraceptive methods, but others may have been dissuaded altogether by the inconvenience.

The practice guidelines we reviewed[35,75,76] followed the WHO Medical Eligibility Criteria for Contraceptive Use,[30] which generally supports post-abortion and post-partum IUD insertion. Insertion after first trimester abortion is classification 1 (use in any circumstance), and after second trimester abortion is classification 2 (generally use), with a caveat about the increased risk of expulsion with later abortion.[30] Immediate (< 48 hours) post-partum insertion of a copper IUD is classification 2, also with a caveat about expulsion.[30] Yet post-abortion and post-partum IUD insertion are not widely practiced. Clinicians are not routinely trained in these procedures, perhaps because of a lack of clear evidence that immediate insertion is better than delayed. As mentioned above, only one study directly compared immediate to delayed insertion post-abortion, and it evaluated an IUD brand no longer in use. No comparative trials exist on post-partum insertion. Randomized controlled trials of immediate vs. delayed insertion in both periods that showed equivalence or superiority of immediate insertion would be useful to help support a labeling change. They could also motivate governments and family planning programs

to promote immediate IUD provision and encourage investment in training programs for these techniques. Studies are also needed to guide clinicians about when IUD insertion is most appropriate after medical abortion.

Another barrier to the increased utilization of the IUD is the reluctance to offer this method to nulliparous women. The ParaGard labeling states that the device is recommended for women who have had at least one child.[71] The WHO recommendations and several other practice guidelines categorize IUD use among young (< 20 years old) and nulliparous women as classification 2.[30,35,75] The PPFA guidelines do not consider nulliparity a contraindication to IUD use, provided the woman is in a monogamous relationship and at low risk for acquiring an STI.[77] The hesitation to use the IUD in this population grows out of a fear of infertility in long-term users, especially in young users at risk for STIs, as well as concerns about nulliparous women having more cramping, bleeding and spontaneous expulsion with IUDs designed for parous women.[78,79] Evidence that IUD use is not associated with subsequent infertility and is safe in nulliparous women continues to accumulate,[78-80] and labeling and guidelines should keep pace. Data with new specially designed smaller IUDs suggest that these devices can be very well tolerated by nulliparous women.[81]

Motivated women at low risk of STIs can be good IUD candidates,[79] yet nulliparous women are often denied access to this highly effective form of contraception. Some argue that the data are not yet strong enough to refute the association between IUD use and infertility and that there is not enough information available about the new IUDs

designed for nulliparous women. What would it take to support a labeling change for the copper IUD or for normative bodies to encourage IUD use among women at low risk for STIs? We suspect it would require an additional case-control study, similar to one recently published,[80] examining the association between infertility and prior IUD use, as well as additional randomized controlled trials of devices suitable for nulliparous women.

Discussion

Working to make available contraceptives easier to use could be very cost-effective.[82] Ease of use was the second most important reason for choosing a contraceptive among reproductive age women interviewed at shopping malls in the US.[83] If contraceptives were available over-the-counter, more women might begin using a method or switch to a more effective method. In one study of women seeking pregnancy tests at public health clinics who said their potential pregnancy was undesired, 25% said they would be more likely to use OCs if they were available over-the-counter.[1] At the moment, few new methods are close to being brought to market. When a hypothetical new product becomes available, some proportion of current contraceptive users *might* switch to the new method, and some proportion of nonusers *might* adopt the method and become new users. Of course, a new method might also fail to attract any new users. For instance, Norplant is now used by fewer than 1% of women of reproductive age in the US and has arguably had little effect on overall contraceptive coverage.[84] Studies, reviews and advocacy efforts that attempt to improve access to the most commonly used contraceptives could make a bigger impact than focusing on new contraceptive modalities, at a fraction of the cost.

In many developing countries, prescription requirements are seldom enforced, and many women already purchase COCs essentially over the counter. There labeling serves as a primary source of (mis-)information. In such settings, carefully designed package labeling that accurately and simply describe the risks, side effects, contraindications, benefits and proper use of a given method could play a large role in improving method choice, as well as compliance and acceptability. Practice guidelines must also present the most up-to-date medical evidence, as clinicians the world over look to these for information about best practices, especially for off-label drug and device use.

Conclusion

Unnecessary medical restrictions in contraceptive labeling and practice guidelines are costly to women and society. Labeling with inaccurate or unsubstantiated information may dissuade otherwise suitable and enthusiastic users of a method, or could foster higher discontinuation rates, and elevate unintended pregnancy rates. If women do not fully understand the risks and benefits associated with use, they are unable to make informed decisions regarding uptake. Evidence-based contraceptive labeling that eliminates unnecessary barriers could increase contraceptive use and reduce unintended pregnancy.

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