Using pharmacologic research to efficiently meet acute contraceptive needs

Before the Covid-19 pandemic, reproductive health professionals had already determined that many patients wished for contraception with the ease of a long-acting reversible method, such as intrauterine and subdermal devices, but without the long-term commitment and the need to return to a healthcare provider for discontinuation. The current global pandemic has highlighted this need (1). More women than ever have been unable to access basic healthcare, including contraception, because of Covid-19 restrictions or loss of insurance as a result of unemployment. Before the start of this pandemic, efforts were already under way to create a new 6-month injectable contraceptive method (2). These efforts stemmed directly from a strong demand for longer-acting injectable contraceptive methods among reproductive-age women, particularly in low-resource settings where the current 3-month injectable contraceptive, depot medroxyprogesterone acetate (Depo-Provera, DMPA; Pfizer, New York, NY), may be the only extended-duration or long-acting method available (2). Subcutaneous injectable contraceptives can also be self-administered, further reducing the need to interact with the formal healthcare system (1), but they are currently available only for a 3-month duration of use (Depo-SubQ, 104 mg), leaving a gap in the contraceptive repertoire. The availability of a 6-month self-administered subcutaneous injectable contraceptive could provide a direct response to the healthcare disparities this pandemic has both exposed and exacerbated.

A 6-month injectable contraceptive product could also be an ideal bridge for women waiting to access a longer-acting contraceptive, such as a subdermal implant or an intrauterine system, that requires an in-person visit to a healthcare provider. With the Covid-19 surges, we have seen many healthcare systems markedly restrict in-person visits in favor of telemedicine services. This adaptation has served to maintain healthcare access for countless patients but has not addressed the disparity in health access for women seeking effective long-acting contraceptive methods. Further, notwithstanding health care needs related to limited resources, reproductive health providers' commitment to reproductive autonomy supports the development of a broader range of methods that are person-controlled, with varying modes, effects on bleeding patterns, and durations of use.

In this issue of *Fertility and Sterility,* Halpern et al. (3) report a pharmacokinetic and pharmacodynamic clinical trial to identify a dose of DMPA that, when used subcutaneously, could act as a 6-month injectable contraceptive option. This clinical trial is notable because it represents an underutilized avenue for expanding contraceptive options: investigator-initiated pharmacokinetic and pharmacodynamic trials of modifications to approved regimens. The authors highlight that the adaptation of the existing injectable Depo-Provera could be a far more expedient solution to the demand for a reliable 6-month injectable contraceptive method. With a relatively small sample size, they demonstrated that the 150-mg dose of Depo-Provera maintained consistent ovulatory suppression for at least 7 months when administered subcutaneously, and that the pharmacokinetic differences between the single 6-month subcutaneous injection of 150 mg of Depo-Provera and the two 3-month doses of 104 mg of Depo-SubQ are likely not clinically significant (3).

Given the reassuring pharmacokinetic and pharmacodynamic findings of this study, a strong argument could be made to begin pragmatic trials of 6-month, self-administered, 150 mg subcutaneous Depo-Provera to immediately begin addressing the contraceptive access issues women face in the United States and around the world. The ongoing pandemic has forced the healthcare field to make tremendous scientific strides in short periods of time, and there is no reason that the field of contraception could not do the same. The adaptation of a currently available contraceptive product provides reassurance regarding safety, given the longstanding experience we have with the 150-mg intramuscular dose of Depo-Provera (4). Although Depo-Provera has a black box warning of its effects on bone mineral density, these effects are greatest with longer durations of use (e.g., more than 2 years) and have been found to be largely reversible after cessation of the method (4). Particularly in the context of the Covid-19 pandemic, the period between the start of the pandemic and vaccine roll-out, a little less than 1 year, represents a missed opportunity where a self-administered 6-month injectable contraceptive could have been temporarily utilized by women without access to the healthcare system.

The authors also found a potential advantage of this novel administration of the 150-mg dose of Depo-Provera in terms of return to fertility (3). With the current 150-mg intramuscular injection of Depo-Provera, the standard counseling is that fertility may not return for up to 12 to 15 months after the last injection (4). This makes intramuscular Depo-Provera a poor option for women desiring to become pregnant within a year. In this study, return to ovulation was quickest for the 150-mg subcutaneous Depo-Provera injection among the three arms, with an estimated 65% of patients returning to ovulation within 12 months, compared with only 25% and 11% in the 300-mg subcutaneous Depo-Provera injection and 104-mg subcutaneous Depo-SubQ injection arms, respectively (3). Although these figures all pale in comparison with the rapid return of ovulation and fertility found with other long-acting and short-acting reversible contraceptive methods (4), the 150-mg subcutaneous dose still potentially holds a distinct advantage compared with our current injectable contraceptive options.

The 150-mg subcutaneous Depo-Provera injection may not be the ideal option for certain populations, such as women with developmental delays, where high rates of amenorrhea have additional benefits (5). Only 1% of participants in the 150-mg subcutaneous arm achieved amenorrhea by 7.5 months, compared with 44% of participants in the 300-mg arm and a reported 55% to 68% of women using 150 mg of

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intramuscular DMPA for 12 to 24 months (3, 4). For women with developmental delays or menstrual hygiene concerns, achieving amenorrhea may be the primary reason for choosing an injectable contraceptive method (5). With lower rates of amenorrhea, this study may indicate that the 150-mg subcutaneous Depo-Provera dose has reduced pharmacodynamic effects on secondary tissues (e.g., endometrium) while maintaining a consistent primary pharmacodynamic effect (e.g., ovulatory suppression). Thus, this 150-mg subcutaneous dose may also be associated with lower rates of other bothersome side effects commonly associated with injectable contraceptive methods (e.g., weight gain, breast tenderness, mood changes) (4). Although the authors reported only bleeding outcomes in this study, future studies with this 150-mg subcutaneous Depo-Provera dose should report other pertinent side effects to determine if this subcutaneous dose has other pharmacodynamic benefits, possibly including less effect on bone mineral density.

The development of novel contraceptive methods is a time-consuming and expensive venture. This study showcases the possibilities of adapting currently available contraceptive methods to more quickly meet the contraceptive needs of women. The Covid-19 pandemic has brought to the fore the need for long-acting self-administered contraceptive methods to provide women with more options to make decisions regarding contraception when direct access to healthcare facilities is severely limited. Without these options, women are forced to use less effective short-acting methods while waiting for opportunities to access the full spectrum of contraceptive methods available. By using scientifically rigorous pharmacokinetic and pharmacodynamic research, Halpern et al. have adapted a currently available contraceptive method into a potentially self-administered option that should provide reliable contraception for up to 6 months (3). These data directly support the next step of a trial of contraceptive efficacy and side effects. If the trial is successful, we may soon be able to offer patients a woman-controlled, long-acting, self-discontinued contraceptive method using a compound with decades of safety behind it.

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