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Pregnancy, Substance Use, and Research: How do We Protect Women while Increasing their Participation in Research?

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The opioid epidemic is a burgeoning public health crisis. The 2017 National Survey on Drug Use and Health (NSDUH) estimated 2.1 million persons in the United States have opioid use disorder (OUD) (Center for Behavioral Health Statistics and Quality, 2018). Many resources have been allocated to curbing it, including funding for research. In April, 2018, the NIH introduced the HEAL (Helping to End Addiction Long-term) initiative, to fund specific opioid-related research (National Institutes of Health, 2018), and in September, 2018, HHS awarded over \$1 billion in additional funding for opioid-specific grants. Researchers have identified gaps in research involving substance use among women (eg, addressing mental health; treatment of substance use during pregnancy) and outline ways in which this can be mediated (Meyer et al., 2019; VanHouten et al., 2019). As opioid use disorder research increases, it is anticipated that the number of women participants will also increase, making it crucial for researchers to be aware of and anticipate potential issues, especially those that relate to sex and gender. We focus on opioid use due to the widely publicized national opioid epidemic, the increased funding for research focusing on the opioid epidemic nationally, and because opioid use is typically illicit, often bearing greater societal consequences. However, the issues discussed in this article can apply broadly to all substance use research.

The 2017 NSDUH estimated that 1 million women used opioids (heroin or opioid pain relievers) in the previous month, and 32,000 were pregnant. Additionally, from 2004 to 2014, there was a 5-fold increase in the number of babies born with neonatal abstinence syndrome (Winkelman et al., 2018). Unplanned pregnancies in women with OUD are more common compared with the general population; thus there is a strong possibility of pregnancy occurring during substance use research (Heil et al., 2011). This illuminates a group that requires additional considerations when conducting research. Researchers must acknowledge the probability that women using illicit substances (opioids or other drugs) may be or become pregnant while participating in research studies, and critically think about potential ethical and legal issues that may arise. One critical issue regards research participation, pregnancy testing, and the required documentation and reporting of results. This bears consideration of confidentiality and legal implications as it creates risks for research subjects and a potential need for greater protection, and also broader research

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considerations, including how the number of women enrolled in research may be affected. Given that there is a need for greater participation of women in research studies, especially studies of substance use disorders (SUDs), the issues surrounding pregnancy during research should be carefully considered to minimize participant risk and ensure that risks related to pregnancy and substance use do not deter women from enrolling in research studies.

Historically, pregnancy testing as part of research participation is typically discussed in relation to preventing adverse fetal outcomes, especially in clinical trials where pregnancy testing is required (Rohan et al., 2011). However, as highlighted in a recent New York Times Opinion piece (Editorial Board, 2018), illicit drug use during pregnancy can lead to prosecution as it is subject to laws in some states, which range in severity. These include, but are not limited to: Criminal Law (2 states), although 45 states have pursued prosecuting women for drug use during pregnancy; Child Welfare Laws (23 states and DC consider drug use during pregnancy as child abuse); and Civil Commitment (3 states allow pregnant women using drugs to be involuntarily committed to drug treatment programs) (Miranda et al., 2015; Guttmacher Institute, 2019).

Prenatal drug laws in combination with granting fetuses the same rights as a person is gaining momentum in state regulations, making this issue of utmost importance. As researchers, we must consider how this will affect research design, recruitment, procedures, and most importantly the participants who are afforded certain protections for study participation. Child welfare cases involving drug use during pregnancy have led to loss of parental rights based on 1 positive drug test. All states require child abuse reporting, and some consider drug use during pregnancy as child abuse, posing both ethical and legal issues for researchers. Certificates of Confidentiality (CoCs) are issued to protect subjects from legal jeopardy and were authorized in the United States for research involving drug use to allow the study of this population. CoCs permit disclosure of protected information when required by Federal, State, or local laws, which could create gaps in coverage and protection (Wolf and Beskow, 2018). Although there are a few cases where CoCs have been challenged, the authority of CoCs has historically been upheld.

Researchers are required to protect participants and assure that the risk of harm is minimized. A pregnant participant deserves the same privacy and confidentiality as other participants, but required reporting issues may impose upon these protections. They also deserve a sense of autonomy, which may be limited in areas where involuntary drug treatment is permitted or access to abortions is limited. Researchers must consider how to protect participants from these risks, and also legal issues that may arise when a woman using illicit substances is pregnant while screening for or participating in a research study.

We propose some guidelines for researchers conducting pregnancy testing or documenting pregnancy status in substance use research. These guidelines are not all-encompassing or fit every research study, given differences in state laws. They are meant to be general guidelines which researchers should consider.

1. Researchers should identify sponsor, IRB, or other requirements for pregnancy testing/documentation. If there are not any requirements, they should determine if pregnancy testing is necessary for a research study and question if there is

rationale for excluding pregnant women or women of childbearing potential in the research design (eg, effects on analyses, maternal health, or fetal development).

2. If a pregnancy test is required in a study that also does toxicology testing and pregnancy is exclusionary, the protocol should state that a pregnancy test will be conducted and confirmed negative before conducting any toxicology screens. This eliminates the possibility of the researcher identifying a participant who is pregnant and using illicit substances. The researcher should consider creating a protocol to address the conduct of these procedures.
3. A protocol should be in place that dictates if a research participant has a positive pregnancy test and toxicology screen (or is using drugs or alcohol), the researcher should:
 - a. Encourage the participant to seek SUD treatment and reproductive health care.
 - b. If the study is not providing SUD treatment, researchers should provide a list of treatment programs, particularly those that give priority access to pregnant women and reproductive care clinics that are available for referrals. Directly linking to healthcare providers with experience in substance use and pregnancy would be optimal. Nonjudgmental SUD treatment and reproductive health care would benefit women participating in research and foster best outcomes for both her and the pregnancy.
4. Consent language about the risks of pregnancy testing should be clear and understandable. During the consent process, participants should be:
 - a. made aware of state laws regarding illicit substance use and pregnancy.
 - b. informed that if they are pregnant or a screening pregnancy test is positive and a toxicology test is positive (or there is documentation of drug use), that members of the study team may be required to report this information to the appropriate authorities according to state law.
5. Researchers should be well-versed in all state-mandated reporting requirements for all patients and research participants, and stay up to date on laws regarding substance use and pregnancy in the states in which they are conducting research. This is particularly important in multi-center research studies.

It may be most effective for IRBs to take the lead on addressing pregnancy in substance use research, where a top-down approach can create policies and systematically address this issue. IRBs should have policies in place regarding pregnancy testing and pregnancy scenarios, such as pregnancy testing requirements, if pregnancy is exclusionary to study enrollment, or if participants should remain in the study if they become pregnant if the study poses no risk to both the participant and fetus. Additionally, IRBs can make sure that there are institutional policies and resources in place that support CoCs, such as having attorneys available that are well-versed in these issues.

Those involved in substance use research must consider how to protect participants from legal harm (while fostering entry into treatment and reproductive care in a nonstigmatizing manner); however, we should also be aware that women are underrepresented in studies of SUDs. Research is needed on women using drugs, especially those who are pregnant or are of childbearing potential. Addressing the issue of pregnancy in substance use research is important for the protection of research subjects; however, broader policy changes decriminalizing substance use during pregnancy is critical so that women can access needed health services. Our proposed guidelines are envisioned to be short-term, with the hope that policy leaders (including researchers) in combination with sociocultural changes address how substance use and pregnancy is treated. Linkage to substance use and reproductive care provides benefit to research subjects, and may also capture pregnant women who use drugs and assist them with treatment. Research studies can act as a safety net in identifying these women, but only if women can safely enter care without any legal ramifications. When we assure that this can be done, there will be greater benefit for women entering into research studies. As substance use research in women increases, it is critical for researchers and healthcare professionals to anticipate potential issues, especially those related to gender and reproduction, and find ways to mediate them.

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