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Performing research in pregnancy: Challenges and perspectives

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Abstract There are numerous barriers to conducting clinical research in pregnancy, including ethical considerations, logistical difficulties, and federal regulations. Due to these challenges, there is a paucity of data on the safe and appropriate use of dermatologic therapies in pregnancy, even for easily accessed over-the-counter topical products, as well as for commonly prescribed medications. Given the lack of human safety data, the Food and Drug Administration pregnancy labeling system previously placed a high priority on animal data but was recently revised to highlight human data and pregnancy registries. The latter can provide prospective observational data on medication use in pregnant women, while avoiding many of the pitfalls of conducting clinical trials in this population; nevertheless, registry enrollment for dermatologic drugs remains low. Dermatologists must increase awareness of pregnancy registries and encourage patient enrollment to close this knowledge gap.
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Introduction

Approximately 6 million women will become pregnant annually in the United States, the majority of whom will take a medication during pregnancy.[1] Nine in ten women take at least one medication while pregnant, and one in two pregnant women take at least four medications.[1] Because more than half of all pregnancies in the United States are unplanned, medication use often occurs before a woman is aware she is pregnant.[2] Physiologic changes in pregnancy affect drug metabolism, such that dosing and interval recommendations derived from nonpregnant women are not necessarily appropriate for pregnant women.[3] Unfortunately, there is a paucity of data on medication safety and dosing during pregnancy. One study found that among Food and Drug Administration (FDA) approved medications from 1980 to 2010, more than 90% lacked sufficient safety data on use in pregnancy.[4,5] This lack of knowledge is in part due to complex ethical issues surrounding research in pregnancy, including the role of the fetus as a research participant who cannot consent, the high priority of neonatal safety, and the obligations of a pregnant woman to her offspring.[6]

In response to the devastating effects of diethylstilbestrol and thalidomide use in pregnancy, the FDA banned women with reproductive potential from clinical trials in 1977.[7,8] This policy remained in place until 1993, when federal regulations lifted this exclusion.[9] One year later, the Institute of Medicine recommended that clinical trials include pregnant women if there is the potential for medical benefit for the woman and no risk of significant harm to the fetus.[10] This scenario is of course difficult to predict, and few randomized clinical trials today include pregnant women due to the previously stated ethical considerations and the ease of omitting pregnant

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Table 1 Subpart B of the Common Rule (45 CFR 46)[5,11]

Research involving pregnant women or fetuses
Pregnant women or fetuses may be involved in research if all of the following conditions are met:
a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies, have been conducted and provide data for assessing potential risks to pregnant women;
b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus; or, if there is no prospect of benefit, the risk to the fetus is not greater than minimal;
c) Any risk is the least possible for achieving the objectives of the research;
d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when the risk to the fetus is not greater than minimal, and her consent is properly obtained;
e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is properly obtained, except if the father is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
f) Each individual providing consent here is fully informed regarding the reasonably foreseeable impact of the research on the fetus;
g) Pregnant children must assent and obtain permission in accord with subpart D;
h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
i) Individuals engaged in the research will have no part in any decisions as to timing, method, or procedures used to terminate a pregnancy.
j) Individuals engaged in research will have no part in determining viability.

women from research studies. Current federal regulations, most recently revised in 2001, allow pregnant women to participate in research under the Common Rule Subpart B (Table 1). Justification must be provided to conduct clinical research on pregnant women, but there is no requirement to justify their exclusion. Pregnant women remain the only population that can be excluded from clinical studies without explanation, a concerning scenario given the lack of data on medication safety and the high likelihood of medication use in pregnancy.[3]

Quality of data

There is a paucity of clinical data on dermatologic treatments in pregnancy with respect to both systemic and topical medications. Current understanding of embryogenesis suggests systemic therapies should be avoided in the first trimester if possible.[12] Topical application, a unique mainstay of dermatology, is often assumed to be safer than the systemic route, but in some ways is more challenging to assess because access to over-the-counter products is ubiquitous, dose can vary dramatically depending on amount of surface area treated, and absorption rates may also differ across people and usage patterns. For example, tazarotene is contraindicated due to retinoid-like fetal abnormalities in animal studies[13]; however, the evidence for adapalene and tretinoin use in pregnancy is mixed; early case reports suggested an association with retinoid-like malformations, but subsequent larger human studies found no such link.[13] Data are even lacking for commonly used and easily accessible over-the-counter topical acne treatments. Interestingly, benzoyl peroxide is not recommended in pregnancy, but the drug is metabolized in the skin to benzoic acid, a food additive that exhibits higher concentrations in the diet than in topical application.[13] Another over-the-counter ingredient, salicylic acid, is not recommended due to evidence of systemic absorption in nonpregnant individuals, but studies are limited.[12,14] Many pregnant women have likely conceived while using such over-the-counter agents, given their availability and ubiquity, but it is clearly difficult logistically to track use of and collect safety data on such products.

A similar scarcity of data also exists for topical steroids, although they are prescribed to approximately 6% of pregnant women and are widely available in low-potency topical forms over-the-counter.[15,16] A recent Cochrane review found only seven studies that examined topical corticosteroid use in pregnancy, none of which were randomized controlled trials.[16] Most studies found no relationship between topical steroid use and adverse pregnancy outcomes, although the quality of evidence was low to very low.[16] One study found an association between high-potency topical steroids and low birth weight,[16] and as a result, current guidelines recommend prescribing mild- to moderate- rather than high-potency topical steroids in pregnancy.[13,17] A meta-analysis could not be conducted due to significant clinical and methodologic heterogeneity among the studies, a common challenge of conducting meta-analyses in this patient population.[16] The systematic review concluded that future research on topical steroids in pregnancy must analyze more pregnancy outcomes, a difficult task because individual outcomes are rare and require very large sample sizes for detection.[16] In addition, more specific data are needed on the effects of topical steroid potency and dosage as well as the maternal indication for topical steroid use.[16]

The indication for medication use in pregnancy is critical, both in designing research studies to evaluate drug safety and when considering the risks and benefits of prescribing a medication in clinical practice. For example, data suggest that women with psoriasis are more likely to have poor pregnancy outcomes, possibly due to maternal inflammation.[18,19] Other autoimmune illnesses such as lupus have been studied more thoroughly in pregnancy, and it is well known that lupus poses significant pregnancy risks, with increased rates of maternal complications and stillborn births.[20] Small studies have found

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