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COMMENTARY

The assessment of drug safety for the fetus

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Abstract
Long standing concerns regarding the use of medications during pregnancy and their unknown effects on fetal development and child health suggests the need for modified study methods regarding the establishment of drug safety for the fetus. This Current Commentary highlights several pharmacological study method limitations and offers suggestions for the establishment of drug safety for the fetus. For example, extensive phase 1 pharmacology studies are needed to assess the complex pharmacokinetic relationships between mother and fetus in order to determine injurious doses to the fetus throughout pregnancy. In addition, long term randomized clinical trials are needed to assess the effects medications may have on children following exposure during gestation.

Keywords Drug related side effects · Fetus · Pharmacology · Pregnancy

Impact on practice

- The assumption that medications used in pregnancy have previously undergone rigorous pharmacological fetal safety testing is wrong.
- There are undefined long-term health risks to a developing child following gestational exposure to some medications.
- Fetal safety information is possible following the enrollment of pregnant women into phase 1, 2 and 3 clinical trials designed to study the safety of medications. Clinicians should encourage enrollment into such trials.
- Long term follow-up data from randomized clinical trials are needed in order to determine that children are not adversely affected from gestational exposure to medications.

Medication usage during pregnancy has increased substantially over the last several decades. For example, 80% of pregnant women in the US, Europe, and Australia, now use at least one medication during pregnancy [1]. In addition, almost 50% of women use 4 or more drugs at some point in their pregnancy [2] with many of these drugs having D or X former FDA classification labels [3]. Over a similar period of time, numerous childhood chronic illnesses have increased including neurodevelopmental delay, autism, asthma, ADHD and autoimmune illnesses. A relationship between these two trends has been suggested [4]. This Current Commentary highlights several methodological limitations regarding the establishment of drug safety for the fetus and suggests needed changes.

Less than 10% of all FDA approved drugs obtain direct pharmacological data from pregnant women and their fetus, despite the fact that most drugs pass through the placenta [5, 6]. Instead, what are obtained are animal reproductive toxicity data, which are well known to be inadequate, as animal species pharmacokinetic data do not extrapolate well to humans [5, 6]. The vast majority of drugs are therefore missing the data needed to obtain fetal circulatory drug levels, tissue level drug exposure, dose response curves and injurious drug doses for a fetus. Biological changes to the mother and fetus over the course of pregnancy impart effects on all aspects of pharmacology including GI absorption, first pass effects, volume of distribution, metabolism, plasma protein binding, placenta crossing, residence time in amniotic fluid,

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drug reabsorption and drug excretion [6]. Obtaining this data is challenging, but without it there can be no scientific basis for the establishment of drug safety for the evolving fetus.

Another methodological limitation regarding the study of fetal effects from drugs is that it is uncommon for drugs to be tested in pregnant women in randomized clinical trials (RCTs) [7]. In fact, most RCTs for prescription drugs exclude pregnant women from clinical trials [5]. Instead, safety data for drugs used in pregnancy are almost always the result of observational studies including case reports, case control studies, cohort, population-based birth defect surveillance and registration studies [7]. While these methods can have certain strengths over RCTs including very large sample sizes that offer sufficient statistical power to detect adverse study effects, better compliance with long term follow up periods, and the ability to study exposure variables that might be unethical to administer in an experimental fashion, they also have significant limitations including information, selection and confounding biases [6]. RCTs are best at controlling these biases and can offer a higher level of evidence regarding a causal relationship between a drug and a side effect.

The safety goals of observational studies and RCTs are to establish causal inference between drug exposure and an adverse outcome. Both study types rely upon not only a statistical association but also the strength of association, the consistency of effect, biological plausibility, dose response and temporality. However, while observational studies can offer suggestions regarding causal evidence of adverse drug effects, more definitive statements regarding these effects require RCT data. [8] To combat the problem of causal inference associated with observational studies, meta-analyses of observational studies are often done, but these types of studies run the risk of adding biases common to meta-analysis including publication bias and the combining of differing quality primary studies [9].

Another drug safety study limitation in the setting of pregnancy is that harmful exposures to a fetus occur during discrete windows of time and may not be toxic throughout all of pregnancy [6]. When evaluating drugs for toxicity via observational studies, periods of exposure must be known and considered. If the investigators define exposure as a period of time that is greater than the period of vulnerability an underestimation of any true association between drug and side effect can occur.

Time windows of vulnerability have historically been challenging to determine because fetal age estimation is imprecise when calculated by standard methods [6]. Nevertheless, methodological advances have been made in recent years to better determine the timing and the window of exposure [10].

Finally, the vast majority of medication pregnancy studies limit their outcome evaluation to gross anatomical abnormalities present at birth while the long-term effects of fetal drug exposure are generally not sought [6]. Of the hundreds of drugs commonly used in pregnancy, few are studied for their potential effects seen well after birth [6]. Nevertheless, pharmaceutical products can potentially change fetal receptor density on cell surfaces, interfere with intra and extra cellular signal transduction and modify the expression of DNA and RNA via methylation thereby altering numerous biological processes that lay dormant until later in life [11]. For most medications, there is little information regarding the long-term adverse effects for the developing child following exposure in the womb [12] despite current knowledge that adverse effects may not appear until adulthood for the exposed fetus as was the case regarding the association between diethylstilbestrol and vaginal cancer [13].

Acetaminophen's potential effects on the fetus exemplifies the problem. A significant portion of women take acetaminophen during pregnancy, a non-prescription drug generally supported for use during pregnancy. Acetaminophen is perceived to be a safe medication and it is likely that acetaminophen is not a teratogen [14]. Acetaminophen freely passes through the placenta, but the pharmacokinetics of acetaminophen in the fetus are not known, and likely change over the course of pregnancy [14]. In animal models, acetaminophen depletes the antioxidant glutathione in alveolar fluid which in turn changes the immunological environment in the lungs of animals to a more pro-inflammatory environment [14].

Several meta-analyses of longitudinal studies have associated the maternal usage of acetaminophen during pregnancy with childhood asthma and have suggested an increase of asthma by as much as 25% for those fetuses regularly exposed to acetaminophen in the womb [15]. These data are consistent with the observation that childhood asthma rates have risen significantly since the 1980's when acetaminophen usage also increased [16]. Nevertheless, biases common to observational drug safety studies have limited the interpretation of these data [17] and a causal relationship between acetaminophen usage in pregnancy and childhood asthma has thus far not been accepted. For example, while the FDA acknowledges the data that question the safety of acetaminophen when used during pregnancy, they state that these studies have potential limitations in their design and inconsistent results which prevent them from drawing reliable conclusions regarding safety. As a result, they have recently reiterated their recommendation to health care providers that acetaminophen is indicated for use in pregnant women with pain [18].

In order to establish a causal relationship between acetaminophen use in pregnancy and subsequent asthma development in a child, the investigators of these meta-analyses recommend a well conducted long term randomized clinical trial, but no such trial is ongoing. Such long-term studies, would

be challenging anyway because of the necessity for long term follow up periods and the ambiguity regarding the choice for a comparator treatment for pain. Thus, while acetaminophen provides an excellent example of the shortcoming of observational studies and the need for an RCT, there are limitations regarding the feasibility of doing such a trial.

Given the frequency of usage of acetaminophen by pregnant women, and the meaningful effect size, the implied public health effect is potentially large and thus requires a solution. Proposed solutions to the above problems include the enrollment of women into phase 1 trials to assess pharmacokinetics and phase 3 trials to assess safety [19]. Three approaches for including pregnant in clinical trials women are the stand-alone staggered trial design, the embedded trial design and the opportunistic study design. Staggered stand-alone trials are initiated once phase 2 trials for the general population have been completed and have shown preliminary evidence of safety and efficacy. Embedded trials enroll pregnant women into phase 2 and phase 3 clinical trials while providing additional monitoring, safety evaluation and extensive pharmacokinetic data collection. Opportunistic study designs follow women in clinical trials who become pregnant while under study. [20] In each of these study designs, amniotic fluid sampling can be obtained in order to help researchers evaluate the metabolism and excretion of drugs, and extrapolate dose response curves and drug distribution maps over the course of a pregnancy [21]. Children of these pregnancies should then receive long term follow up.

Drug safety assessment for fetuses is substantially less than what is done for children and adults. Critical procedures for drug safety including a thorough pharmacokinetic profile, tissue distribution, the establishment of a potentially injurious dose, and a broad-based assessment of potential side effects over a long-term timeframe conducted in RCTs are not done. Instead, safety assessments are limited to a drug's teratogenic potential at birth. A combination of phase 1 and phase 3 RCTs conducted on pregnant women with long term follow up for the children of these pregnancies is the only reliable method toward establishing drug safety for the fetus and child.

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