

## DRUGS IN PREGNANCY: ACKNOWLEDGING CHALLENGES - FINDING SOLUTIONS

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**D**ue to obvious ethical issues of experimenting drugs during fetal development, women and their unborn babies are commonly excluded from drug trials. As a result, these two groups of patients are commonly orphaned from the revolution in drug therapy witnessed in the last generation.

The removal of Bendectin<sup>®</sup> from the American market despite being safe in pregnancy sent a chilling signal to drug companies, essentially discouraging them from developing or studying drugs for pregnant patients. Even in areas which are exclusively typical of pregnancy (e.g., morning sickness or tocolysis) no new drug trials are performed. Consequently, the advance in therapeutics in pregnancy lags substantially behind the same conditions or drugs in non-pregnant women, or men.

However, this approach is highly unwarranted, as uncontrolled maternal conditions may affect adversely both the mother and her fetus. Hence, a rational approach must also incorporate estimation of the risks of the untreated maternal condition. This has been highlighted painfully in recent years, where anxiety of yet unproven fetal risks of SSRI have received much attention, leading many women to discontinue these drugs, but with very little attention to the tremendous risk of untreated maternal depression.

Because embryogenesis is completed by the end of the first trimester of pregnancy, if a drug is not affecting brain development, (which continues throughout gestation), there is no apparent reason not to study it during the second and third trimesters of pregnancy. Several recent developments may mark important milestones in changing the approach to drug trials in pregnancy.

### **Changes in Drug Disposition in Late Pregnancy**

During the last few years a large body of evidence has suggested that in late pregnancy, there is substantial increase in the clearance rate of various drugs, due to increase function of different cytochrome P450 enzymes, including nicotine (2A6), fluoxetine and citalopram (2D6), and protease inhibitors (3A4).<sup>1-2</sup>

This means that women may need larger doses to achieve therapeutic steady state concentrations. For example, using nicotine replacement therapy has failed to prevent smoking in late pregnancy when compared to placebo, probably because the dose regimen used in late pregnancy was insufficient.

Similarly, many women with depression are not controlled clinically in late pregnancy, possibly at least in part because doses that were adequate before pregnancy are grossly inappropriate in late pregnancy.<sup>3</sup> Late pregnancy is also characterized by major changes in glomerular filtration rate (GFR), hepatic blood flow, protein binding and altered drug compliance. These changes lead, in most instances, to lower systemic exposure to medications, both hepatically and renally eliminated.

### **Learning from the Glyburide Milestone**

Gestational diabetes (GD) affects up to 5% of late pregnancies. Left untreated, it may adversely affect pregnancy outcome. The hallmark of therapy is dietary control and insulin, as this naturally occurring hormone does not cross the placenta appreciably. However, insulin therapy is expensive, unavailable in many areas, and is associated with low compliance rates. The use of oral hypoglycemic drugs has been largely

contraindicated, because these drugs cross the placenta, causing fetal hyperinsulinism and increasing the risk of neonatal hypoglycemia.<sup>4</sup> In 1994, using the ex-vivo placental perfusion studies, Elliot and colleagues documented that unlike other "older" sulfanylurea, glyburide did not cross the placental barrier from the mother to the fetus.<sup>5</sup>

In 2000, the same group published the results of a randomized controlled trial on pregnancy outcome comparing insulin to glyburide. The offspring were not different in any outcome characteristics, including birth weight, rates of hypoglycemia or mortality. Critically, while maternal glyburide levels were in the therapeutic ranges (50-150 ng/mL), the drug was undetected in any of the umbilical blood samples.<sup>6</sup> The mechanisms preventing a relatively small, non-polar molecule from crossing the placenta has not been elucidated yet.<sup>7</sup> It has been hypothesized that this may be a combination of relatively short half-life with extremely high protein binding. We have recently shown that glyburide is effluxed from the fetal to the maternal circulation by several placental ATP-binding cassette (ABC) transporters, including breast cancer resistance protein (BCRP) and multi drug resistance-associated protein 3 (MRP3).

### **A Proposed Framework for Drug Trials in Pregnancy**

The objective of this section is to synthesize known principles and concepts of maternal-fetal clinical pharmacology, and to propose a framework for trials of medicines in pregnancy.

#### **Principles**

1. Studies should be conducted first in the second-third trimester of pregnancy, when embryopathy is not an issue. This may not be relevant to drug affecting brain development, as fetal brain continue to develop until birth.
2. High priority should be given to studies of agents, which can be expected to address an unmet maternal/fetal risk or improve maternal or fetal outcomes compared to existing therapy. Some examples include glyburide and metformin for gestational diabetes or labetalol for hypertension.
3. High priority should be given to agents not likely to affect CNS development, which continues throughout gestation.

4. A pharmacokinetic study should precede an efficacy-effectiveness study, as in late pregnancy women may need larger dose due to faster clearance rate.
5. Before a study is initiated during the first trimester of pregnancy, human safety data should be available. Such data should be prospective observational data with an unexposed comparison group. Because half of all pregnancies are unplanned, and due to the fact that programs collecting such studies exist – there is no excuse not to collect and analyze such data.
6. Participants in studies should consent after being made aware of the available safety data and its limitations, including the risk of the untreated condition, as well as the known risks-benefits of available data on alternative therapeutics.
7. Safety of inactive ingredients studied as much as active ingredients for drugs that are to be used during pregnancy. One cannot assume that inactive ingredients are safe to the fetus, with ethanol being a powerful example.
8. Post marketing surveillance. Without mandatory post marketing surveillance, as expected now by FDA, Canadian authorities will continue to be in the dark as to drug safety in pregnancy.
9. Hold manufacturers responsible for continuously educating the medical community, as one cannot assume that physicians will update themselves in this rapidly emerging field.

The recent breakthrough in pediatric drug trials in the USA secondary to enacting financial benefits through extension of exclusivity to products studied in children, should logically lead to similar move for drug trials in pregnancy. However, the legal-ethical equation in pregnancy is much more complex than in childhood, and it seems less likely that the pharmaceutical industry will agree to participate in the very litigious climate of today.

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