CHALLENGES IN DRUG USE NEAR TERM AND DURING DELIVERY

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This article will try to provide an overview of issues related to prescribing medications during pregnancy. Therefore it will cover several different but related issues.

There are currently many sources for information ranging from standard textbooks going through the ten of thousands of peer reviewed article and ending with the huge amount of data accessible through the Internet. However, a crucial issue is if we have better data or just better access to more inconclusive data?

Physicians do not like to prescribe drugs in pregnancy.[1] This is partly because of the past experience of the Thalidomide catastrophe.[2] That experience made us all aware that exposure to new drugs may at least theoretically result in anomalies and other major consequences. It is clear that extrapolation of non pregnant data is a poor predictor for catastrophic teratogenic outcomes. This resulted in a justified reluctance of prescribing new drugs during pregnancy and prevents acquisition of data on their safety. Furthermore, a busy and overbooked clinician may not explore the need for therapy during pregnancy without being prompted by a patient. Likewise, the patient may want to avoid reporting symptoms to prevent her perceived risks of drug exposure in pregnancy.[3] This eliminates at times reassurance that the drug therapy is both effective and safe. These concerns reduce compliance with drug therapy in pregnancy. Most pharmaceutical companies have little interest in drug therapy during pregnancy. Therefore, they generally tend to protect themselves medico-legally with label warnings. Most state that their drugs should not be used in pregnancy unless the expected benefits outweigh the risks.

This results in a negative impression of these undescribed and often undefined risks. There are very few drug companies targeting pregnant women and only these ones avoid this type of labelling.

Physicians have urged pharmaceutical companies to add indications for use in pregnancy (e.g. the use of misoprostol for termination of anomalous pregnancies).[4] Such requests are usually denied. Drug therapy in pregnancy is often skewed to use in sicker patients. This further obscures the distinction between the effect of the disease and its therapy.

There are other issues that further complicate the issue of drug therapy in pregnancy. For example, most human data on drugs is generated from male patients. There are very few studies done exclusively or predominantly on females. Thus we have little data on women specifically; less data on pregnancy in general and even less data on therapy at specific time frames in pregnancy (e.g. early pregnancy and organogenesis, late pregnancy and peripartum).

The third trimester involves several changes that would include:

1. Major maternal increases in volume (5-6 Litres).
2. Fluid shifts with more fluid in both intravascular and the extracellular space.
3. High levels of estrogen and progesterone that alter drug pharmacokinetics by different mechanisms such as metabolism, binding, competition with receptors and excretion.
4. Placental hormones levels peak in maternal circulation and modulate a variety of cell functions (e.g. Prolactin, GH and HPL).

Demerol is an illustrative example of these issues. Demerol was administered for labour pains to most women prior to the regional analgesia era. Most mothers and babies that were exposed to Demerol in labour did well. However, its metabolites stay in the fetal circulation for a longer period of time and are associated with higher CNS[6] and respiratory[7] depression of the newborn after birth and a higher risk of poor breast feeding. The fetal compartment undergoes

major changes in late pregnancy. It generally increases, but this increase could be variable. For example IUGR (intrauterine growth restricted) babies, weigh 1-2.5 kg, and in contrast macrosomic babies weigh more then 4 kg. Obviously, the large fetus at term is quite different from the growth restricted one in a variety of different ways and not only in distribution volume. The growth may reflect a fundamental difference in placental function such as transport mechanisms as well as placental hormonal function. There is an interaction between the placental and fetal hormones, especially at the initiation of labour. But these hormones have a variety of other effects, including stress in the fetus. These are not very well studied overall, and are less studied in late pregnancy.

Not all babies are alike in other ways. A small but interesting group are the babies that require resuscitation at birth. About 10% of babies are growth restricted (IUGR); 80% of these babies have metabolic acidosis. These babies generally require major resuscitation. Other babies are exposed to a more acute respiratory acidosis during labour. These babies are likely to recover faster after a relatively short event. However, the growth restricted baby may have developed mechanisms to cope better with acidosis. Regardless of the type of acidosis, it generally causes most drugs used in labour to cross preferentially to the fetal compartment just prior to delivery. These babies are then likely to be even more depressed because of higher drug levels (e.g. narcotics) than just from the acidosis per se. This is a well known fact to paediatricians, neonatologists and anaesthetists.

Until recently obstetrical approach could be correlated to a naval mission of "search and destroy". A diligent search for anomalies resulted in termination of pregnancy once a major one was detected. Nowadays prenatal diagnose has evolved to a more complex field. There is preventive therapy for some anomalies (e.g. folic acid for prevention of neural tube defects) and there is medical and surgical therapy for other anomalies. Psychologists tell us that the first few years of life are the formative ones. It could be argued that the first few weeks and months *in utero* may be more crucial for future development Changes that occur early in pregnancy, be it nutrition, hormones or drugs, may alter the way the fetus adapts to the intrauterine environment and develops. Such changes may alter the cell differentiation, proliferation and maturation. These may lead to altered organ structure and later to changes in metabolic activity and overall function resulting in long term effects.

Barker was the first to relate intrauterine growth restriction to adult diseases such as heart attacks.[8]. In Finland, more then 50 years ago, data weight gain in pregnancy as well as data on birth weight and subsequent growth of babies was meticulously collected in the entire population. This data was correlated to the frequency of adult disease. Osmond and colleagues[9] looked at the size of the newborn and correlated it to death from coronary disease later on in life. They showed very clearly that the bigger the baby, the better off they were and that in the long run they had less cardiac disease. This may mean that "bigger is better", at least in this respect and to a limit. This set of data also showed that the children that were growth restricted at birth but became overweight later in life had the highest risk for adult disease

Much data comes from large epidemiological studies, some of which have been conducted in Toronto. Most look at interventions, few look at drugs. The ASAP[10] and MACS[11] studies are an example of a minority of studies that have focused on drugs (specifically steroids for either pregnancy losses or lung maturation).

In pregnancy, two patients are being treated. In the administration of drugs, one should evaluate whether helping the mother is at the expense of the baby or vice versa. For example, chemotherapy for maternal cancer, or thyroid radiation for ablation benefit the mother while exposing the baby to risks. In contrast, administrating steroids for fetal indication or exposing the mother to antiarrhythmic for fetal tachycardia (or bradycardia) benefit the fetus while exposing the mother to risks.

There are other effects that also need to be considered. For example, steroids administration to induce fetal lung maturation, may also induce maternal gestational diabetes.[12] Steroid administration following rupture of the membranes is likely also to induce an increase in white blood

cell count and thereby mask one of the major markers of an infection.[13] Beta-blocker administration for maternal hypertension, may affect fetal heart rate patterns by reducing its variability.

This may deprive the care givers of some of the parameters used for fetal monitoring in labour. In large studies, mortality is the main endpoint because it is well defined, is better documented and there is consensus that "it is a poor outcome". However, there is the (good) problem nowadays of having a very low mortality rate. The latest Canadian data report 6.1 deaths per 1000 live births, i.e., death is a rare outcome.[14] The recent large studies that tried to look at pregnancy outcomes, could not use mortality as the sole outcome variable. They used compound indices, where mortality is only one of many. Notably, in the last large diabetes study, there was not a single perinatal death attributed to diabetes in a cohort of 1000 women with gestational diabetes.[15] So, although it is an attractive endpoint, it is now becoming quite unpractical.

As to ultrasound, Dr. Timor Tritsch my mentor from New York taught me many years ago that there are three major developments in perinatology: number one - ultrasound; number two - ultrasound; and number three - ultrasound. Ultrasound has evolved dramatically from the first machine used about 50 years ago by Donaldson, where fetal structures were poorly seen to the latest 3D ultrasound.

Ultrasound is the cornerstone of fetal therapy. The more common form of fetal therapy is intrauterine fetal transfusions used to treat fetal anemia. There are numerous aetiologies for fetal anemia. Rh disease used to be the most common cause, but effective prevention of this condition almost eradicated the risk of fetal anemia. Nowadays anemia following parvovirus infections have become a more common aetiology. Intrauterine blood transfusions involve a needle that is inserted either into the umbilical cord or into one of the hepatic veins under ultrasound guidance.

The fetal mortality of this procedure is about 0.2-5%, and it carries a risk of <1% of an immediate C-section because of fetal bleeding[16] Fetal drug therapy is usually through maternal administration and placenta transfer. Drugs can also be given directly to the fetus. Large molecules can be injected to the amniotic cavity to be swallowed by the baby, or injected directly into the fetal circulation. Fetal obstructive uropathies could be managed in utero by shunting the bladder into the amniotic cavity. The vascular anasthomosis of twins with twin-to-twin transfusion could be ablated using laser procedures *in utero*. Open fetal surgery is now possible, with some success in closing open neural tube defects in utero. Interestingly, open fetal surgery usually does not result in fetal scarring, a situation which intrigues our plastic surgery colleagues. Lastly, there have been by now many attempts to treat monogene diseases of the fetus by gene therapy. None of these have been successful so far, but it is clear that this modality will become available in the future.

Several examples will be given to illustrate the complexity of ethical issues in pregnancy. The first involves three patients, and not only the fetus and the mother. A few years ago a mother of a child with leukemia discovered that she was pregnant. She approached one of my colleagues asking for a cordocentesis in order to get stem cells from the fetus to treat her other child with leukemia. We had a major ethical issue: should we expose the fetus to the risk of death for the benefit of the other child? The ethicists we consulted all agreed that we should respect the wishes of the mother.

The next example is a legal issue. Cow fetuses are transported in rabbit uteri from one country to another. If an ape were to give birth to a human baby transplanted in its uterus (which is technically possible but was never attempted for obvious reasons), it would legally be an ape and not a human and this throws some interesting angles into our current definitions.

A further example illustrates a common dilemma that we encounter. It involves decision making for the extremely premature infant. The survival rate at 23 weeks gestation is 5 - 15%. The odds are slightly improved if the birth is by C-section. However, performing a classical C-section is likely to complicate future pregnancies. What should be done in this kind of situation? Recent Dutch guidelines clearly outline that such a surgery should not be performed even at 25 weeks gestation while Canadian and American

guidelines set the cut off point at a lower gestational age. The last controversial issue was clearly shown in a survey we conducted asking women about their perception of risk and management of gestational diabetes mellitus (GDM). We were surprised to find that 42% of the women surveyed stated that performing more than 1 million caesarean sections is justified to save one single baby. This perception should be contrasted in the setting of vaginal delivery that carries the risk of about 1:1000 of a compromised baby as a result of labour.

The last topic to be discussed is steroid administration in pregnancy. Steroids are very potent drugs, affecting a variety of systems and organs. The fetal effects are not very well known, however the drugs are used in about 7% of cases for preterm labour and in about 3% for treatment of medical diseases. About 30 years ago, Liggins found that steroids enhance lung maturity and prevent respiratory distress syndrome. Later studies also showed reduced intracranial bleeding in neonates. And 15 years ago, we found that even when surfactant is given, steroids *in utero* have an added benefit. This led to a universal policy of steroids administration to women who are at risk for premature labour. When some studies showed that the steroid effects last for about a week, many centres started prescribing these steroids weekly, as there was no data at the time to suggest any harmful effects caused by steroids.

A confounder to be considered is that preterm labour accounts for about 70% of perinatal mortality and morbidity. It is difficult to distinguish between the effect of the therapy or the primary condition. However, animal studies have shown the following effects: smaller babies, smaller lungs, smaller brains, hippocampal volume reduced by 40% (possibly affecting short term memory). There is also some data that steroids alter cell programming and apoptosis. This raised the question whether repeated administration of steroids is indicated or not. The MAC study (n =1900) that will be completed soon will hopefully provide the answer to this question.[11]

We are currently working with Motherisk and a cohort of 100 women who had recurrent pregnancy losses in the past. They were treated 15 years ago with very high doses of steroids throughout most of their pregnancies.[10] These are considered healthy women and their children are supposedly healthy. We intend to study the effect on long term outcome of high doses of steroids throughout gestation. We also intend to look at diabetes, sex hormones, and the pituitary-adrenal axis. Hopefully we will soon have some information on the long term effect of fetal exposure to steroids.

The bottom line is that we need to have a systematic approach. We need to use clinical pharmacology and basic principles to assess the data we have, set goals for future research and provide optimal and individual care to our patients.

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