Premature births, protease inhibitors and progesterone

As mentioned earlier in this issue of TreatmentUpdate, in Canada and other high-income countries the use of potent anti-HIV therapy (commonly called ART or HAART) during pregnancy along with other steps can greatly reduce the risk of mother-to-child transmission of HIV.

Protease inhibitors are a commonly prescribed class of anti-HIV drugs for pregnant women in high-income countries. Examples of protease inhibitors in common use today include the following:

- a fixed-dose combination of lopinavir + ritonavir (Kaletra)
- darunavir (Prezista) + ritonavir (Norvir)
- atazanavir (Reyataz) + ritonavir

Researchers in Toronto and elsewhere in Canada have found that “the benefits of ART far outweigh the potential adverse effects” for both the mother and the fetus. However, in recent years, as treatment guidelines in high-income countries shift toward encouraging all HIV-positive people, regardless of CD4+ count, to initiate ART, and new drugs have become available, more research is needed to help doctors better understand the safety of ART during pregnancy.

Some studies have found an increased risk for the following problems in HIV-positive pregnancies:

- preeclampsia – a syndrome of higher-than-normal blood pressure and excess protein in the urine that can develop during pregnancy
- premature birth
- infants with less-than-ideal birth weight

The cause of these problems is not clear.

Canadian research

Researchers in Toronto have been investigating the potential impact of protease inhibitors on pregnancy. In a series of complex experiments, researchers studied the impact of ART on cells, mice and pregnant women. Their findings suggest that a particular component of ART—the class of anti-HIV drugs called protease inhibitors—reduces levels of the hormone progesterone. This hormone is important for the growth and survival of the fetus. The researchers are planning a pilot study of a progesterone cream with pregnant HIV-positive women who use protease inhibitors.

Lab studies with cells

In experiments in the lab with cells that can develop and form the placenta, researchers studied the impact of anti-HIV drugs, either singly or in combinations commonly used in pregnancy. The researchers tested three main classes of anti-HIV drugs as follows:

Nukes (nucleoside analogues)

- AZT (Retrovir, zidovudine and in Combivir and Trizivir)
- 3TC (lamivudine and in Combivir, Kivexa, Trizivir and Triumeq)

Non-nukes

- nevirapine (Viramune)

Protease inhibitors
The three main protease inhibitors—atazanavir, darunavir and lopinavir—are generally taken with a small dose of another protease inhibitor, ritonavir. The purpose of the small dose of ritonavir is to raise the concentration of the main protease inhibitor in the blood and keep it elevated for about 24 hours. In this way, many regimens containing protease inhibitors can be taken just once daily. Ritonavir has this effect in a large part because it impairs the activity of enzymes in the intestine and liver that can break down protease inhibitors. It also impairs the activity of tiny pumps inside of cells that attempt to flush foreign substances out of a cell. Ritonavir and other drugs that have a similar effect are commonly called boosters.

As protease inhibitors are generally used with a booster, researchers tested combinations of protease inhibitors with low-dose ritonavir.

**Experiments with cells**

The researchers used cells that develop into the placenta. They found that, in general, exposure to protease inhibitors (singly) reduced the cells’ production of progesterone. The strongest effect was seen with exposure to ritonavir. However, atazanavir and lopinavir also reduced progesterone production. Exposure to darunavir did not reduce progesterone production.

Similar effects were seen when protease inhibitors were used in combination with ritonavir. Neither nukes nor non-nukes affected progesterone levels.

**Experiments with pregnant mice**

Researchers gave pregnant mice doses of protease inhibitors that resulted in drug concentrations similar to those seen in pregnant women who use such drugs. The researchers found that protease inhibitor–based regimens significantly reduced progesterone concentrations in mice. Furthermore, by reducing the level of progesterone in the pregnant mice, protease inhibitors indirectly affected fetal health by reducing the chances of survival. A mouse’s body can absorb a dead fetus in a process called resorption. Among the fetuses that did not undergo resorption, most did not achieve a normal weight while in the wombs of pregnant mice.

It is important to bear in mind that mice in this experiment received very high concentrations (for mice) of protease inhibitors. As such, it should not be surprising that they experienced adverse reactions, both biochemically and physically. However, such concentrations of protease inhibitors are within the normal and safe range for humans and there have not been any reports of fetal resorption in HIV-positive pregnant women treated with protease inhibitors.

In contrast, pregnant mice given a combination of ATZ + 3TC did not develop problems with progesterone and their fetuses were of normal weight. However, the survival of the fetuses was affected as resorption still occurred for some reason.

Researchers gave some pregnant mice on protease inhibitors supplements of progesterone. As a result, the weights of their fetuses increased but did not reach the normal range. Furthermore, some fetuses continued to die and undergo resorption by the mother.

**Studies in women**

Researchers collected blood samples from 27 HIV-positive pregnant women, most of whom (22 of 27 women, or 82%) were taking protease inhibitor–based ART. Among these 22 women, a majority (55%) was taking Kaletra (lopinavir + ritonavir). None of the women smoked tobacco or used street drugs.

For general purposes of comparison, researchers also observed the pregnancies of 17 HIV-negative women.
On average, all the women in the study were in their 26th week of pregnancy and were of similar age (33 years) and ethno-racial background.

In general, babies born to HIV-positive women weighed less than those born to HIV-negative women. Rates of premature delivery were not different between the two groups of women.

However, HIV-positive women tended to have statistically significantly less progesterone in their blood (132 ng/mL) than HIV-negative women (180 ng/mL).

Among HIV-positive women, progesterone levels were lower in users of protease inhibitors than in women who used other components of ART.

**Points to consider**

1. The Toronto research consists of a series of complex experiments with cells, mice and pregnant women. The data from the experiments strongly suggest that the use of certain protease inhibitors during pregnancy is linked to lower progesterone levels and lower birth weight.

2. ART improves the overall health of HIV-positive women and greatly reduces the risk of transmitting HIV to the fetus and to the baby during birth. However, protease inhibitor–based ART may, in some cases, cause the placenta to produce less progesterone and possibly increase the risk of the mother giving birth prematurely.

3. The present study in pregnant women was small, observational in design and not a randomized controlled clinical trial (RCT). Bear in mind that an RCT would require a large number of women, likely from many countries, would be complex and take several years to complete, and therefore would be an expensive and labour-intensive undertaking. Due to the limitations with observational studies, the researchers cannot be certain that protease inhibitors were responsible for the low birth weights noted in the offspring of HIV-positive women.

4. It is also possible that there were immunological issues that have not been fully explored that could have played a role in the pregnancy results that the Toronto researchers found in HIV-positive women. For instance, the placenta produces hormones, including progesterone, that somewhat weaken the immune system of the mother so that the fetus (which contains genetic material from both its mother and father) can survive. It is possible that protease inhibitors could have an effect on the immunological balance between the mother and fetus. This could, in theory, affect fetal health and outcomes, such as low birth weight.

5. The Canadian researchers with the help of the Canadian HIV Trials Network (CTN) are going to be exploring a pilot study—code-named CTNPT 025— of progesterone supplementation in pregnant HIV-positive women. In part, researchers will assess if it is possible to recruit women for such a study in Canada. For further details about this, contact the CTN.

Clinical trials in HIV-negative pregnant women have found that progesterone supplementation can help to reduce the risk of premature birth in some women.

6. The apparent lack of effect of darunavir on progesterone levels is intriguing and needs to be assessed in further studies.

—Sean R. Hosein

**REFERENCES:**


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