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Editorial

Drug Development for Maternal Health Cannot Be Left to the Whims of the Market

The *PLoS Medicine* Editors

In an essay published in this month's *PLoS Medicine*, Nicholas White and colleagues [1] lament that an insufficient understanding of even well-established drugs has led to a lack of effective treatments in pregnancy. They conclude that "we do not know how best to treat most tropical infectious diseases in pregnancy"—an alarming and shameful situation—and lay out causes of this ignorance. For example, concern about teratogenicity has led to the exclusion of pregnant women from clinical trials regardless of their stage of pregnancy, resulting in a crucial lack of evidence even in late pregnancy, when teratogenicity is not a concern. Gaps in the evidence on pharmacokinetics of some antimalarial drugs have often led to under-dosing of pregnant women, and in some cases the erroneous conclusion that such drugs are not effective in pregnancy. The authors note that "'better safe than sorry' is the mantra of our risk-averse age." But since severe malaria has a mortality approaching 50% in late pregnancy, we concur with the authors that this mantra has actually produced harm.

But if the situation is bad for tropical diseases in pregnancy, the lack of new therapies can only be considered dire for diseases that result from pregnancy itself. In a policy paper published in January of this year, Nicholas Fisk and Rifat Atun [2] concluded that "the market has failed pregnant women." Their analysis of the drug pipeline for obstetric disease between 1980 and 2007 found just 17 new drugs undergoing evaluation between the preclinical and preregistration phases. This number compares with 660 new drugs for cardiovascular diseases and 34 for amyotrophic lateral sclerosis—a rare disease affecting two to five per 100,000 people. Even worse, of these 17 obstetric drugs, only one represents a new class of drug.

Further, many maternal deaths are due to potentially avoidable non-obstetric causes, as highlighted by Clara Menéndez and colleagues, who analyzed deaths from a tertiary hospital in Mozambique [3] and found that infectious diseases accounted for at least half of all maternal deaths, "even though effective treatment is available for the four leading causes, HIV/AIDS, pyogenic bronchopneumonia, severe malaria, and pyogenic meningitis." For surgical treatments that are known to be effective for obstetric complications, another *PLoS Medicine* article this month [4] argues that "the lack of basic surgical supplies and equipment limits the delivery of surgical services" in sub-Saharan Africa, for obstetrics as well as for other surgical conditions.

In developed countries, with low rates of maternal and perinatal deaths, it is perhaps easy to be complacent about the lack of new drugs for pregnancy and the perinatal period, but globally the situation is urgent. According to the World Health Organization, there were more than half a million maternal deaths in 2005 and over 6 million child deaths in the perinatal and neonatal periods [5]. Most of these deaths are in low-income countries—a huge, and potentially avoidable, loss of life. Appropriately, therefore, maternal and child health are part of the United Nations Millennium Development Goals, with specific goals between 1990 and 2015 to reduce the under-five mortality rate by two-thirds and the maternal mortality ratio [6] by three-quarters. Unfortunately, 18 years into the program, it seems unlikely that these goals will be met.

No one would suggest that improving the health of pregnant women and their infants is easy. For millions of women, even the most basic determinants of maternal and child health are still lacking: access to basic health care and nutrition, autonomy over reproductive choices, and freedom from violence and poverty. When it comes to drug development, however, innovations that work for other areas of health care simply do not suffice for maternal and infant health, and new ways of thinking are needed. As Fisk and Atun argue, the current business model of the pharmaceutical industry provides no real incentive but rather, because of potential litigation in developed countries, confers strong disincentives to produce novel drugs for pregnant women.

For pregnancy-related disorders, the development of drugs is perhaps further hindered by issues that rarely arise in other conditions. Although childbirth remains hazardous in all countries, there is an increasing expectation in developed countries that nowadays birth should be a "natural" event for both mother and child and that medical interventions are to be discouraged. Such expectations make doing clinical trials uniquely difficult when any suggestion of risk appears unacceptable. A qualitative study [7] of participants in the ORACLE trial of antibiotics in women presenting with preterm rupture of membranes, for example, concluded that "the main motivation for trial participation was the possibility of an improved outcome for the baby. The second and less prominent motivation was the opportunity to help others, but this was conditional on there being no risks associated with trial participation." This expectation of no risks is unrealistic and was surely not what was explained

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to the participants; nevertheless, it was what the women themselves believed and expected. So while women in less developed countries urgently need more effective interventions in pregnancy, it may be increasingly difficult to test such drugs in ways that are acceptable to pregnant women, at least in the developed world. The market-driven pharmaceutical model has little incentive to resolve the conflict of providing the safety that women expect from trials, while at the same time accepting liability and providing compensation in cases when testing does, as it inevitably will, cause harm.

What's the answer then? The issue of the market failing to develop necessary drugs is of course not a new one. In 2004, Tim Hubbard and James Love [8] argued that reliance on intellectual property rights to finance research and development in the pharmaceutical industry was both driving up drug prices and hindering essential drug development. Recognizing this hindrance, in 2003 five public sector organizations teamed up with Médecins Sans Frontières and the Special Programme for Research and Training in Tropical Diseases to launch the Drugs for Neglected Diseases Initiative (DNDI; http://www.dndi.org/). This drug development project does not prioritize maximum profitability over medical need. Instead it adopts a "needs-driven" portfolio-based approach that facilitates basic science, preclinical, and clinical research on targeted diseases. Fisk and Atun present ways in which such "push" and "pull" mechanisms can provide solutions. An example of a push mechanism is DNDI's dedicated financial support to research networks for developing drugs for specific indications; pull mechanisms include an advanced market commitment aimed at creating a market for a future drug. These mechanisms have been successfully applied thus far for malaria, AIDS, tuberculosis, and neglected tropical diseases and might be applied to maternal health.

Fisk and Atun go on to urge that not-for-profit options be carefully explored and suggest that new initiatives be put in place to encourage the testing and collection of data on old and new drugs, especially for the most life-threatening conditions in pregnancy. One such mechanism is noted by White and colleagues and involves the systematic collection of data via pregnancy registries; an essential but expensive long-term investment that would, like other long-term initiatives, be unlikely to find support in the current business environment of the pharmaceutical industry. A key part of any mechanism would be the need to specifically accept liability when harm occurs. And, as an aside, the publishing industry has a part to play too. It is essential that the results, especially harms, generated by these initiatives be made widely available. Open access to all such data is not a luxury, and should be ensured by publishers.

The time has come to accept that the development of drugs for maternal health cannot be constrained by market-driven needs. There is no lack of ideas for addressing this issue; what's needed is political will.

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