Preventing Preterm Birth: New Pharmacological Strategies

Preterm birth is now officially the leading cause of death in children under the age of 5 years. In Australia our rates of preterm birth are around 7 – 8%, resulting in around 25,000 preterm deliveries annually at a cost to the healthcare system of around half a billion dollars a year.

THE UNIVERSITY OF WESTERN AUSTRALIA

women & infants research foundation Western Australia

A new initiative was launched in WA in 2014 with the aim of reducing the rate of preterm birth in the state over the next five years: The Western Australian Preterm Birth Prevention Initiative (www.thewholeninemonths.com.au). Central to this initiative is a programme of on ongoing research into prediction, treatment & prevention of prematurity, combined with monitoring of preterm birth rates over the course of the initiative.

Babies born more than two months preterm have the greatest risks of adverse outcomes, and the majority of such deliveries arise as the result of intrauterine infection and inflammation. In these pregnancies, bacteria residing in the vagina ascend and breach the cervical barrier, colonise and invade the fetal membranes and amniotic fluid, and elicit an intraamniotic inflammatory reaction (manifested as histologic chorioamnionitis) that triggers preterm labour. This can also result in associated morbidities such as cerebral palsy. The bacteria most commonly isolated from the amniotic cavity in preterm deliveries are the *Ureaplasma* species, commensal organisms found in the reproductive tracts of around 50% of pregnant Australian women. A related bacterium, *Mycoplasma hominis*, is also a relatively common isolate from infected amniotic cavities. Collectively, these 'genital mycoplasmas' are a major cause of early preterm birth, although a wide variety of other bacteria can also trigger inflammation-driven preterm birth.

In order to develop effective therapies to treat and prevent infection-associated preterm birth we must overcome two main hurdles: 1) how to identify women at risk who would benefit from treatment, and 2) how to treat intraamniotic and fetal infection and inflammation effectively and safely. To address the first issue, we are currently undertaking a large NHMRC-funded study to employ microbiological, biochemical and metagenomic approaches to identify asymptomatic women who are at high risk of preterm birth arising from intrauterine infection.

With respect to the second hurdle, one might presume that antibiotic therapy would be a simple solution. Somewhat surprisingly, however, attempts to date to prevent preterm birth using antibiotics have been largely unsuccessful, due in part to deficiencies in the pharmacokinetics and pharmacodynamics of currently available antibiotics. We recently made a major discovery that could change the antimicrobial therapeutic landscape in pregnancy. Using our pregnant sheep model we discovered that a new fluoroketolide antibiotic called solithromycin is capable of crossing the placenta and reaching effective concentrations in the fetal circulation and amniotic fluid within 4 hours of a single maternal dose. Solithromycin is the first macrolide-like antibiotic that is active against all the major microorganisms known to be associated with preterm birth and able to effectively treat intrauterine/fetal infections via oral maternal administration (other macrolides do not readily cross the placenta). Importantly, it is highly effective against a wide variety of antibiotic-resistant bacteria and is particularly potent against all genital mycoplasma species and strains. Its high oral bioavailability (~70%), ease of administration (400 mg p.o. once per day), potency, ability to overcome antibiotic resistance and favourable tolerability/side-effect profile make it a convenient and extremely attractive therapeutic option. In this regard, solithromycin is markedly superior to widely used antibiotics such as azithromycin, erythromycin, clindamycin and metronidazole for this indication in pregnancy.

Not only is it highly effective, but solithromycin is also an effective anti-inflammatory agent, significantly more potent than existing macrolides in terms of suppressing macrophage/monocyte activation. Studies are also ongoing on the use of more potent agents that block cytokine signalling in the amniotic cavity in response to microbial triggers. It is now widely accepted that the fetal inflammation which occurs as a consequence of intrauterine infection must be prevented in order to protect the fetus and maximise the benefits of antenatal/perinatal antimicrobial treatment. Cytokine-blocking agents can be given intra-amniotically to ensure that amniotic and fetal inflammation is inhibited without compromising the maternal immune system and risking persistence of infection.

Solithromycin is not currently available; it is expected to be licensed for use in 2016. In the meantime, its pharmacokinetics and potential use in pregnancy will be investigated in a series of clinical trials planned for later this year.

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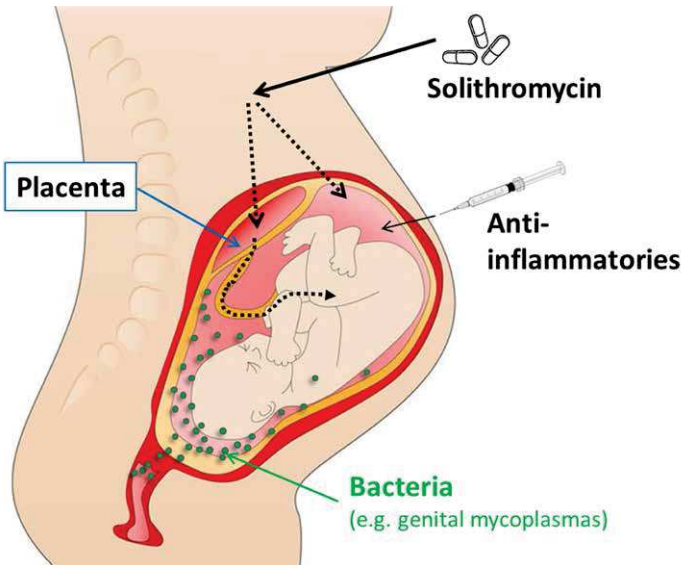

Pharmacological strategies for the treatment and prevention of preterm birth