Fighting the good fight: antibiotics and prevention of preterm birth

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Preterm birth is now officially the leading cause of death in children under the age of five years. Several major international initiatives are underway to lower the rates of preterm birth around the world, and considerable financial resources have been mobilised to promote research and coordinate development of new and effective interventions and prevention strategies.

In Australia, our rates of preterm birth are similar to many developed nations, around 7-8 per cent. In third world countries, preterm birth rates are much higher, however; 16-18 per cent in sub-Saharan Africa, for example. Like many other countries, our rates have been steadily increasing for decades. Much of this increase has been due to increased rates of late preterm birth (36-37 weeks) due – at least in part – to an increase in numbers of surgical or iatrogenic deliveries prior to 37 weeks' gestation. Early preterm birth rates (<34 weeks) have not changed appreciably during this time, although infant morbidity and mortality rates have improved with advances in neonatal care.

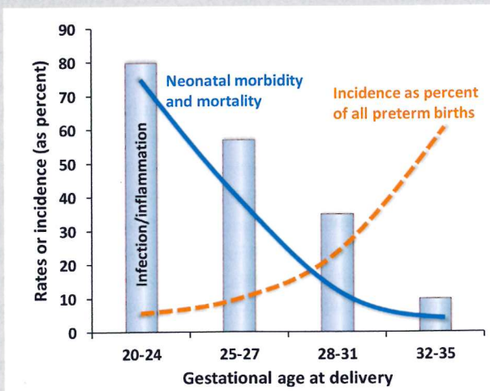
Here in Western Australia, a new initiative was launched in November 2014 with the aim of reducing the rate of preterm birth in the state by a third over the next five years. ***The Western Australian Preterm Birth Prevention Initiative*** (**www.thewholeninemonths.com.au**) is comprised of a dedicated team of clinicians, researchers, public health professionals and patient advocate groups. The Initiative is composed of five main pillars:

I. A dedicated preterm birth prevention clinic for at-risk women based at King Edward Memorial Hospital in Perth.
II. A public health and social media campaign to alert healthcare providers and patients to the importance of *"going the whole nine months"*.
III. Statewide rollout of a cervical ultrasonography screening program to identify women at risk of preterm birth for targeted treatment.
IV. An outreach program to promote the 'whole nine months' message to women in rural and remote areas and their antenatal healthcare providers.
V. Ongoing research into prediction, treatment and prevention of prematurity, combined with close monitoring of rates of preterm birth and screening compliance over the course of the initiative.

Proven interventions such as smoking cessation, cervical length screening, progesterone supplementation therapy and cervical cerclage, all of which have been included in new clinical guidelines, have been shown to be effective in reducing the rates of prematurity in particular patient groups. However, the collective impact of their introduction on the overall rate of preterm birth is likely to be modest – less than a 7 per cent decrease according to some calculations.

Research holds the key to further advances in preterm birth prevention and, importantly, significant reductions in the neonatal morbidity and mortality associated with prematurity. The area where perhaps the greatest gains can be made is in the reduction in the rate of early preterm births; babies born <32 weeks (around 1 per cent of all deliveries in WA) have the greatest risks of adverse outcomes and the greatest need for neonatal intensive care facilities. The majority of such deliveries are the result of intrauterine infection and inflammation, with the likelihood of an infective aetiology increasing significantly as gestational age decreases (*Figure 1*). The most common pathophysiological scenario occurs when bacteria residing in the vaginal mucosa ascend and breach the cervical barrier, colonise and invade the fetal membranes and amniotic fluid, and elicit an intraamniotic inflammatory reaction (manifested as chorioamnionitis) that triggers preterm labour. In some pregnancies this also results in fetal inflammatory response syndrome and associated morbidities such as cerebral palsy.

Figure 1: Relationship between gestational age at delivery and preterm birth incidence (dotted line), chorioamnionitis (bars) and neonatal morbidity and mortality (solid line)



Antibiotic	Pharmacokinetic properties: Oral bio-availability	Placental transfer	Amniotic fluid accumulation	Anti-microbial potency against bacteria commonly associated with PTB: Ureaplasma spp.	Mycoplasma hominis	Fusobacterium nucleatum	Streptococcus spp.	Staphylococcus spp	Enterococcus spp.	Pepto-streptococcus	Gardnerella vaginalis	Bacteroides spp.
Clindamycin	✓✓✓	✓✓✓	✓	✓	✓✓	✓✓✓	✓✓✓	✓	✓	✓✓	✓✓	✓✓
Metronidazole	✓✓✓	✓✓✓	✓✓	X/✓	X/✓	✓✓✓	✓✓✓	✓✓	✓	✓	✓	✓✓
Azithromycin	✓	X/✓	✓	✓✓	X/✓	✓✓	✓✓✓	✓	✓✓	✓	✓✓	✓
Erythromycin	✓✓	X/✓	✓	✓	X/✓	✓	✓✓✓	✓	✓	✓	✓	✓
Solithromycin	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓	✓✓✓	✓✓

Table 1: Comparison of pharmacokinetic and pharmacodynamics properties of solithromycin and four antibiotics currently administered in pregnancy for prevention of preterm birth. Key: X/• none or minimal; •low or weak; •• modest or good; ••• high or excellent.

The bacterial culprits that commonly cause infection-driven preterm birth have been identified – some are common bacteria found in the reproductive tract of most pregnant women, some are more commonly associated with the oral microbiota, while others are often found in women with abnormal vaginal flora (e.g. bacterial vaginosis).

However, the bacteria most commonly isolated from the amniotic cavity with preterm birth are the Ureaplasma species, tiny microorganisms present in the reproductive tracts of around 50 per cent of pregnant Australian women. A related bacterium, Mycoplasma hominis, is also a relatively common isolate. Collectively, these so-called 'genital mycoplasmas' are a major cause of preterm birth and are a focus of our current research efforts.

Most studies that have attempted to administer antibiotics to women to prevent preterm birth or treat preterm labour have been unsuccessful and have neither reduced the rate of preterm birth nor improved neonatal outcomes.
Meta-analyses have concluded that antibiotics administered in pregnancy for treatment and prevention of preterm labour are ineffective and not justified.

However, the majority of trials have suffered from several design flaws. Firstly, most trials included women without a proven risk of bacterial infection-driven preterm birth, who were therefore unlikely to benefit from antibiotic therapy. Secondly, antibiotics were often administered too late in pregnancy to prevent the consequences of mid-pregnancy intraamniotic infection. Thirdly, the antibiotics used were often ineffective against the organisms most commonly associated with intrauterine infection (such as genital mycoplasmas). Fourthly, even if intrinsically effective antibiotics were employed (e.g. macrolides), they did not readily cross the placenta or fetal membranes and so did not effectively treat fetal or amniotic infection. Finally, no attempts were made to mitigate the effects of inflammation in the fetus or amniotic cavity, which is actually the main mediator of neonatal morbidity and mortality.

Our research, therefore, is focused on identifying women at high risk of delivery preterm as a result of intrauterine infection so that they can receive appropriate and effective antimicrobial therapy in mid-pregnancy, before the onset of symptoms.

A large NHMRC-funded study is currently underway aimed at using microbiological, biochemical and metagenomic approaches to identify asymptomatic women who are at high risk of preterm birth arising from intrauterine infection.

Importantly, we believe we may already have identified the ideal treatment. Using our pregnant sheep model we have discovered that a new, as-yet unapproved fluoroketolide antibiotic called solithromycin, is capable of crossing the placenta and reaching effective concentrations in the fetal circulation and amniotic fluid within four hours of a single maternal dose. Solithromycin, a fourth generation macrolide, is the first 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. Its high oral bioavailability (~70 per cent), ease of administration (400 mg once per day), excellent potency and ability to overcome resistance, combined with a favourable tolerability/side-effect profile, make it a convenient and extremely attractive therapeutic option (*Table 1 above*).

Importantly, it is highly effective against a wide variety of antibiotic-resistant bacteria and is particularly potent against genital mycoplasmas. In this regard, its pharmacodynamic profile is markedly superior to other antibiotics such as azithromycin, erythromycin, clindamycin and metronidazole that have typically been used for this indication in pregnancy (*Table 1 above*).

As if its potency, spectrum of activity and pharmacokinetic properties weren't attractive enough, solithromycin (like other macrolides) also has considerable anti-inflammatory properties. In fact, recent studies have shown that solithromycin is significantly more potent than existing macrolides in terms of suppressing macrophage/monocyte activation and MMP9 release. This additional benefit may prove to be particularly important, as it is now widely accepted that it is critical to prevent and resolve fetal inflammation which occurs as a consequence of intrauterine infection in order to protect the fetus and maximise the benefits of antenatal/perinatal antimicrobial treatment.

A series of clinical trials to evaluate the benefits and consequences of solithromycin administration in pregnancy have been designed and will hopefully commence later this year. This is an exciting time in perinatal research, and WA is at the forefront of advances that have the potential to alter clinical practice and reduce the numbers of early preterm births in Australia and around the world.

Jefffrey Keelan is Professor of Obstetrics, The University of Western Australia at King Edward Memorial Hospital, Perth. He is Scientific Director of the WA Preterm Birth Prevention Initiative and Deputy Director of the Women and Infants Research Foundation of WA. He has no conflicts to declare. ■