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EXPERT OPINION

Macrolides and the placenta

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To the Editor,

In the recent review of antimicrobial treatment during pregnancy, Lamont and colleagues [1] state that "They [macrolides] freely cross the placenta…" The reference [2] cited by the authors only states that macrolides cross the placenta and then begins a chain of referencing earlier sources which demonstrate that fetal blood levels of macrolides are quite lower than maternal blood levels after administration of macrolides in pregnancy [3,4].

The *in vitro* placental cotyledon perfusion model used by Heikkinen *et al.* [3] showed limited transplacental transfer of macrolides, including azithromycin. Ramsey's group also demonstrated low fetal serum and amniotic fluid levels of azithromycin in a study of term gravid women [4].

International guidelines continue to recommend against the use of macrolides for treatment of syphilis in pregnancy due to the long-recognized lack of placental penetration clinically. Until and unless additional data become available, clinicians should not use macrolides to treat infections in pregnancy if there is a concern for transplacental passage of the infection.

Declaration of interest

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•• **References earlier sources that clearly state that the transplacental transfer of macrolides is low and cites earlier sources that show fetal blood levels of erythromycin reaching only 2 – 10% of that shown in maternal blood.**

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Author's response

To the Editor,

We are grateful to Drs Gelfand & Cleveland for their comments that are a valued contribution to the peer review process.

We qualified our statement that 'macrolides freely cross the placenta' by stating that there may be gestational age-related pharmacokinetic variation [1]. The clinical study cited by Drs Gelfand & Cleveland [2] was specific to azithromycin used in 20 women undergoing elective cesarean section at term who were given 1 g of oral azithromycin 6, 12, 24, 72, or 168 h before the operation. Azithromycin levels in placental tissue were higher than in maternal serum and sustained for up to 72 h after administration. Amniotic fluid levels of azithromycin were highest at 6 h and declined rapidly. The authors concluded, "azithromycin may have potential use for the treatment of perinatal infections".

We made no specific mention of treatment of syphilis in pregnancy and without knowing to which international guidelines they are referring to, we are unable to comment. However, guidelines are educational aids to good clinical practice and are not intended to be prescriptive directions defining a single course of management. In addition, guidelines based on retrospective analyses of pooled data are only as good as the quality of studies included [3]. We cited a number of macrolide studies in which no meaningful association between their use and congenital malformations were found. This included one large study involving over 100,000 pregnancies, of which ~ 1000 were exposed to macrolides in which no association was found between macrolides and congenital malformations, perinatal mortality, low birth weight, low Apgar score or preterm birth [2]. If these studies were not included in the guidelines to which Drs Gelfand & Cleveland refer, perhaps they should be. Finally, we did state in our conclusion of the macrolide section that, as there is relatively little or mixed data on macrolides such as clarithromycin, azithromycin and roxithromycin, these should be used with more caution until larger studies are available.

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