Antibiotic prophylaxis for women undergoing Caesarean section and infant health: a commentary

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In 2011, the National Institute for Health and Care Excellence (NICE) revised their guidance on the timing of intravenous prophylactic antibiotic administration for Caesarean section, advising that antibiotics should be given prior to skin incision[1]. This change has recently been supported by a Cochrane review which advises administration of antibiotics 60 minutes prior to incision to prevent maternal postpartum infectious morbidity[2]. While it is clearly important that women giving birth are protected from infection-related complications of Caesarean section, it is also of concern that nearly 25% of births in the United Kingdom (UK) delivered by Caesarean section will be affected by this recommendation, which will lead to some 175,000 infants[3] annually being exposed to broad spectrum antibiotics around the time of birth. NICE recommends the use of prophylactic broad spectrum antibiotics for women undergoing Caesarean section which are effective against the microorganisms associated with endometritis, urinary tract and wound infections[1]. These antibiotics rapidly cross the placenta and will reach the baby's circulation before birth, with an inevitable but not yet fully characterised influence on newborn microbial colonisation. Previous NICE guidance advised cord clamping prior to giving mothers antibiotics to prevent such collateral neonatal antibiotic exposure[4].

There is increasing evidence for a functional role of gut microbiota in driving immune development in the newborn and the development of chronic conditions later in life[5]. We know that the immune system both modifies and is modified by our response to pathogens according to the composition of early microbial colonisation[6], and that the pattern of gut colonisation by microorganisms is associated with mode of delivery[7]. There is also evidence that infants with abnormal microbiota are at increased risk of diseases such as atopic dermatitis, inflammatory bowel disease and Type 1 diabetes[8, 9]. As such, there is growing awareness of the importance of microbes and the immune system as aetiological agents in human disease[5, 10].

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The recommendation in the Cochrane review draws on data from 12 high quality trial reports showing an absolute risk reduction of 2.8% in maternal infectious morbidity (from 8.5% to 5.7%, relative risk (RR) 0.57, 95% CI 0.45-0.72) when comparing those receiving antibiotics preoperatively with those receiving antibiotics after cord clamping. This was due to reductions in clinically diagnosed endometritis (from 28 to 15 per 1000, RR 0.54, 95% CI 0.54-0.82) and wound infection (from 41 to 24 per 1000, RR 0.59, 95% CI 0.44-0.81), both of which can be associated with sepsis and maternal mortality[11], although the vast majority of these infections are mild and respond promptly to treatment. However, the review fails to consider the effects of broad spectrum antibiotics on the neonatal microbiota and the potential long-term health sequelae of disrupted microbial colonisation in the infant.

Ideally, high quality evidence of immediate benefits to the mother should be weighed against equally good evidence about any potential risks of long-term harm to the infant. However, to date, no randomised controlled trials (RCTs) have measured the long-term effects on infants of receiving intrapartum antibiotics. Such studies are unlikely to be undertaken because of the long duration of follow up required to measure health outcomes that might not present until years later. Evidence suggesting an adverse effect of early antibiotic exposure on the infant gut currently comes from observational studies[5], but the limitations in such studies mean they are less likely to be included in systematic reviews, upon which NICE guidance is primarily based. The focus on RCTs risks potentially important long-term infant health outcomes being ignored.

It is possible to test whether early life exposure to antibiotics affects microbial colonisation of the gut and other mucosal surfaces in the neonate, and to explore whether antibiotics exposure might lead to selective survival of microbes with genes conferring antimicrobial resistance, without RCT-level evidence[10]. Given that the new guidance will affect such large numbers of infants, we feel it is important to consider the emerging literature on the role of the microbiota in determining long-term

infant health. This is part of a wider issue for evidence-based practice whereby high-quality reviews currently prioritise evidence from studies with strong epidemiological designs, which may only measure short-term outcomes, over weaker evidence of health consequences that may occur in the longer term. We acknowledge that there is not yet clear evidence on which to base immediate changes to clinical practice. Instead, we suggest a more nuanced weighing of evidence is needed, which gives consideration to study designs capable of assessing long-term outcomes. It might also be time to update how these reviews are communicated to patients, making clear where certain short-term gains are given precedence in structured reviews over uncertain long-term, and potentially adverse, health outcomes.

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Peter Brocklehurst, Nigel Field and Sarah R Bailey conceived this article. Sarah R Bailey and Nigel Field wrote the first draft, with further contributions from Peter Brocklehurst, Alison J Rodger, and Claire L Townsend. All authors reviewed successive drafts and approved the final version of the article.

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