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## Antibiotics for operative vaginal delivery: practice-changing data.

Vincenzo Berghella  
*Thomas Jefferson University*

Federica Bellussi  
*University of Bologna*

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# Antibiotics for operative vaginal delivery: practice-changing data



The large randomised controlled trial on the effect of antibiotics to prevent infection after operative vaginal delivery by Marian Knight and colleagues<sup>1</sup> in *The Lancet* is practice changing. Operative vaginal deliveries include either vacuum or forceps, and are used in about 2–15% of births.<sup>2</sup> Even if one conservatively estimates 2% of babies are born by operative vaginal delivery globally, about 2 700 000 of the world's 135 million annual births are operative vaginal deliveries. Up to 16% of these births can be associated with infection without antibiotics prophylaxis,<sup>3</sup> representing about 432 000 annual infections associated with operative vaginal delivery worldwide.

The most common infections increased with operative vaginal delivery compared with spontaneous vaginal delivery, include endometritis, perineal wound, and urinary tract infections—all of which, in rare cases, can lead to sepsis.<sup>3</sup> Compared with spontaneous vaginal delivery, operative vaginal delivery can introduce microorganisms into the genital tract, is associated with longer labour, more vaginal examinations, with bladder catheterisation before the procedure, and with more perineal lacerations and use of episiotomy, all of which can increase the risk of infections. These infections can occur even after discharge, and the risk peaks at about 6–7 days post partum.<sup>3</sup> The incidence of infections is higher with forceps than with vacuum. Episiotomy also increases the risk of perineal infections compared with no episiotomy,<sup>4</sup> possibly also because of the association with more and worse perineal lacerations.<sup>5</sup> Unfortunately, the evidence on the effect of technical characteristics of the repair of perineal lacerations or episiotomies, or both, on perineal infections is scarce.<sup>6,7</sup> Perineal infections are associated with wound dehiscence, need for repair, and perineal pain, and influence women's quality of life and sexual wellbeing.<sup>3</sup>

In Knight and colleagues' study,<sup>1</sup> 3427 women with mostly singleton gestations at 36 weeks or later were randomly assigned to receive either amoxicillin 1 g and clavulanic acid 200 mg or placebo within 6 h of operative vaginal delivery. The primary outcome, confirmed or suspected maternal infection within 6 weeks of delivery, was defined by one of the following: a new prescription of antibiotics for presumed perineal

wound-related infection, endometritis or uterine infection, urinary tract infection with systemic features (pyelonephritis or sepsis), or other systemic infection (clinical sepsis); confirmed systemic infection on culture; or endometritis. This primary outcome was significantly less common in the antibiotic (11%) versus the placebo (19%) group (risk ratio [RR] 0.58, 95% CI 0.49–0.69). The incidences of perineal infection, perineal pain, use of pain relief for perineal pain, need for additional perineal care, wound breakdown, perineum ever too uncomfortable to feed the baby, and any visits in relation to perineal concerns were all each statistically significantly decreased in the antibiotics group compared with placebo. The primary outcome was more common in forceps versus vacuum deliveries, but the magnitude of the beneficial effect of the antibiotic versus placebo was similar (forceps 13% vs 22%, RR 0.62, 95% CI 0.45–0.86, respectively; vacuum 8% vs 14%, RR 0.56, 95% CI 0.39–0.80, respectively).

The main strengths of this study are that it is large, methodologically well done, covers an important clinical issue, and is practice changing. Only one small study<sup>8</sup> had been previously done on this issue. Other strengths are the use of only one dose of antibiotics, limiting the effect on microbiota of both mother and baby (effect through breastfeeding). Risks of negative effects on the baby, such as necrotising enterocolitis or asthma,<sup>3</sup> can be minimised if the antibiotic is given after delivery, and this antibiotic has been shown to be safe for infant breastfeeding.<sup>9</sup>

The main limitation of the study is the primary outcome, which was driven mostly by a new prescription for antibiotics for presumed perineal infection. Although the trial was blinded, the prescribing of antibiotics is more subjective than culture-proven infection. The study shows that the results for the cumulative primary outcome are the same as those for new prescription for antibiotics for presumed perineal infection. The criteria used by practitioners to decide to whom to give antibiotics was unclear. Nonetheless, confirmed culture-proven sepsis was significantly less in the amoxicillin and clavulanic acid group than in the placebo group (0.6% vs 1.5%, respectively; RR 0.44, 95% CI 0.22–0.89). The timing of antibiotics was 3.2 h after delivery, which is



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late; in practice, administration of the antibiotic intravenously right after delivery would be feasible. Indeed, prophylaxis for caesarean section is more effective when given before skin incision than after cord clamping. The choice of antibiotics is debatable, but Knight and colleagues have made a good case for their choice of amoxicillin and clavulanic acid.<sup>3</sup> Another limitation of the study is that women with third-degree and fourth-degree lacerations were excluded because they get antibiotics anyway.<sup>10</sup> The majority (89%) of women enrolled had an episiotomy—a proportion that is too high, even for operative vaginal delivery, as admitted by authors. Unfortunately, a subgroup analysis for just those women without an episiotomy is not available. Moreover, neonatal outcomes are not reported; although the antibiotic was given after birth, it is secreted in breastmilk, and could affect neonates. Another potential issue is the development of antibiotic resistance.

More emphasis should be placed on prevention of perineal trauma, and therefore perineal infection, in future research. The use of perineal massage<sup>11</sup> and warm compresses to the perineum<sup>12</sup> in the second stage of labour have each been associated with a significant decrease in perineal trauma. Clinical guidelines should be updated to reflect the new recommendation of giving a single dose of intravenous amoxicillin and clavulanic acid within 6 h after operative vaginal delivery, in particular to women who also have an episiotomy. More research is needed for operative vaginal deliveries not necessitating an episiotomy.

\*Vincenzo Berghella, Federica Bellussi

Department of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia, PA 19107, USA (VB); and Department of Obstetrics and Gynecology, University of Bologna, Bologna, Italy (FB)

vincenzo.berghella@jefferson.edu

We declare no competing interests.

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## Durable complete response in renal cell carcinoma clinical trials



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Renal cell carcinoma is one of the most common urological cancers and its incidence is on the rise.<sup>1</sup> Outcomes for patients with advanced renal cell carcinoma have improved substantially with the advent of vascular endothelial growth factor (VEGF)-targeted drugs, and with the approval of immune checkpoint blocking antibodies in the past 4 years.<sup>2</sup> Although each of these drug classes has shown single drug efficacy, responses remain transient for most patients, culminating in a high proportion of patients eventually having disease progression or death.<sup>2</sup>

Angiogenesis and immunosuppression are hallmarks of cancer that allow for tumour cell growth and

survival, and preclinical and early phase clinical data have shown these two pathways to be linked.<sup>3–5</sup> Targeting VEGF and its receptors results in increased T-cell priming and infiltration; however, targeting also induces interferon gamma-mediated counter-regulatory programmed death-ligand 1 (PD-L1) upregulation, and T-cell exhaustion.<sup>3,5</sup> Furthermore, PD-L1 expression predicts for worse outcomes after treatment with antiangiogenic drugs in patients with renal cell carcinoma.<sup>6,7</sup> Thus, the combination of antiangiogenic and immune checkpoint blocking drugs, which allows a newly inflamed tumour microenvironment to effectively eradicate