

Title

Operative vaginal delivery and postpartum infection

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Abstract

Over the past decade, there has been an increase in awareness of infections associated with pregnancy and delivery. The most significant cause of postpartum infection is caesarean section, with 20-25% of operations followed by wound infections, endometritis or urinary tract infections. Around 13% of women in the UK undergo operative vaginal delivery (OVD) with forceps or vacuum, which is also associated with an increased risk of infection, estimated at 0.7% to 16% of these deliveries. Despite this, previous reviews have identified only one small trial of antibiotic prophylaxis in 393 women, and concluded that there was insufficient evidence to support the routine use of prophylactic antibiotics after operative vaginal delivery. The ANODE trial, a multi-centre, blinded, placebo-controlled trial from the UK, is due to report findings from more than 3,400 women in 2019, and will be the largest study to date of antibiotic prophylaxis following operative vaginal delivery.

Keywords

operative vaginal delivery, infection, sepsis, fever, postpartum, pregnancy

Background

Over the past decade, there has been an increase in awareness of infections associated with pregnancy and delivery [1]. Each of these infections has the potential to progress to severe sepsis and septic shock [2-4], highlighting the need for adequate measures to prevent and treat pregnancy-associated and postpartum infections.

The most significant risk factor for postpartum infection is caesarean section, which is frequently associated with wound infection, endometritis or urinary tract infection [5]; post-operative incidence of infection is estimated at 20-25% [6]. For this reason evidence reviews and guidelines recommend the routine administration of prophylactic antibiotics to women undergoing caesarean birth [6, 7]. Based on a meta-analysis of 95 randomised controlled trials, enrolling over 15,000 women, the administration of prophylactic antibiotics has been estimated to reduce the risk of infectious complications after caesarean section by 60-70% [6].

Forceps or vacuum for operative vaginal delivery (OVD) are used in 12.6-13.1% of deliveries in the United Kingdom [8], and are also associated with an increased risk of infection. The use of instruments can introduce micro-organisms into the genital tract, leading to endometritis and more severe ascending infection. Furthermore, OVD often follows a longer labour, and is also associated with multiple vaginal examinations and bladder catheterisation which provide additional routes for infection [9]. The increased risk of vaginal lacerations, and the use of episiotomy during delivery, alongside the challenge of maintaining a clean environment with perineal wounds can create further potential entry routes for micro-organisms.

Despite this increased risk of infectious morbidity, few studies have assessed the role of antibiotic prophylaxis after OVD. A Cochrane review [9] identified one small trial [10], including a total of 393 women, and concluded that there was insufficient evidence to support the routine use of prophylactic antibiotics after operative vaginal delivery, but recognised the dearth of evidence on the topic. In the context of increasing concerns around the unnecessary use of antibiotics, and their implications for

antimicrobial resistance [11] and allergic conditions [12], it is vital that these decisions are evidence-based. The ANODE trial, a multi-centre, blinded, placebo-controlled trial from the UK, is due to report findings from 3,424 women in 2019, and will be the largest study to date of antibiotic prophylaxis following OVD [13].

This review will cover:

1. The epidemiology of postpartum infection after operative vaginal delivery, including the incidence, the type of infection and risk factors for infection
2. The current evidence on the use of prophylactic antibiotics, including an outline of the ANODE trial

Epidemiology of postpartum infection after operative vaginal delivery

Terminology, definitions and pathophysiology

Postpartum infections after vaginal and caesarean delivery or during breastfeeding can involve several sites. Postpartum infection is diagnosed when a woman has a temperature greater than 38°C and other signs of infection such as abdominal pain, uterine, flank or breast tenderness, rigors, or offensive vaginal discharge. As it is common for women to have a low-grade fever in the first 24 hours after birth, the diagnosis is usually made after repeated or high-grade fever, or if there are other developing signs and symptoms of infection, noting that when infection is severe, the temperature may be paradoxically low.

The most common postpartum infections associated with OVD include genital tract infections (endometritis), perineal or wound infections and urinary tract infections (cystitis or pyelonephritis). Other infections that can occur in the puerperium include breast infections (mastitis) and respiratory tract infections.

The use of vacuum or forceps can lead to ascending infection with micro-organisms found in the cervicovaginal flora or the gastrointestinal tract and clinical endometritis particularly because of the increased number of assessments and interventions mentioned above, alongside challenges in maintaining a clean perineal/vaginal environment.

In some cases, the infection can progress to severe sepsis or septic shock, which has become a recognised cause of significant maternal morbidity and mortality in recent years [1, 4]. The presence of two or more of the following criteria have been used to indicate severe sepsis [4]:

- Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$ measured on two occasions, at least 4 hours apart
- Heart rate >100 beats/minute measured on two occasions, at least 4 hours apart
- Respiratory rate >20 /minute measured on two occasions, at least 4 hours apart
- White cell count $>17 \times 10^9/\text{l}$ or $<4 \times 10^9/\text{l}$ or with $>10\%$ immature band forms, measured on two occasions

However, these criteria were empirically adapted from criteria used in the non-pregnant population, and in recognition of this, and the importance of maternal sepsis as a cause of death and morbidity globally, the World Health Organisation has recently developed a new definition of maternal sepsis [14], and is currently undertaking work to develop robust diagnostic criteria [15].

Risk of postpartum infection after operative vaginal delivery

Few studies have specifically investigated postpartum infection in women who have had operative vaginal deliveries (OVD). Many large studies and reviews of outcomes after OVD have not considered infection while documenting other important causes of morbidity and mortality [16-19].

Table 1 Studies examining risk of postpartum infection in women who underwent operative vaginal delivery

Authors	Year	Study details	Incidence of infectious morbidity	Study size
Greis et al [20]	1981	1 hospital, USA Matched case-control No follow-up beyond discharge 1977-1978	Febrile morbidity 6% after vacuum extraction vs 9% after forceps and 48% after Caesarean	90 vacuum extraction deliveries 100 forceps deliveries
Heitmann and Benrubi [10]	1989	Randomised controlled trial of antibiotics vs no treatment after OVD 1986-1989	Endomyometritis 3.5% in control group	201 women in control group (no treatment)
Hagadorn-Freathy [21]	1991	1 hospital, USA 1988	Infection 7% (n=25)	357 forceps deliveries
Williams [22]	1991	1 hospital, USA Randomised trial of forceps vs. vacuum No follow-up beyond discharge 1989	Endometritis 16% in forceps delivery, 8% in vacuum delivery	40 forceps deliveries 41 vacuum deliveries
Kabiru [23]	2001	1 hospital, USA Facility-based data, no active follow-up 1980-1996	Postpartum infection 2.9% (n=202) Fever 2.0% (n=138)	6,882 operative vaginal deliveries
Burrows [24]	2004	1 hospital, USA Facility-based data, no active follow-up ICD-9 coded 1995 – 2000	Endometritis 0.7% (n=33) Pneumonia 0.2% (n=9)	4,908 operative vaginal deliveries
Macleod [25]	2008	2 hospitals, UK Facility-based data, no active follow-up 2004-2006	Perineal infection 4.2% (n=58); 3.1% in vacuum (n=14) vs 4.9% in forceps (n=44)	1,360 operative vaginal deliveries (456 vacuum and 904 forceps)
Lawani [26]	2014	1 hospital, Nigeria Facility-based data, no active follow-up 2002-2011	Genital sepsis 0.7% (n=4)	461 operative vaginal deliveries
Bailit [27]	2016	25 hospitals, USA Facility-based data, no active follow-up after discharge 2008-2011	Postpartum infection 0.2% in vacuum (n=3), 0.9% in forceps (n=9)	2,400 attempted operative vaginal deliveries
Son [28]	2017	Registry data, USA Facility-based data, no active follow-up 2008-2011	Endometritis 2.5% (n=24) vs 9.1% (n=26) after Caesarean section	945 operative vaginal deliveries

Incidence and onset of infection

Existing studies (Table 1) clearly vary in their definitions of “postpartum infection”, also referred to as “puerperal sepsis”, “puerperal fever”, “genital tract sepsis” as well as other terms. The postpartum period is usually defined as up to six weeks after delivery, although some studies consider only the first ten days after delivery or diagnoses made prior to discharge. The reported incidence ranges from 0.7% to 16%, which is likely to relate to a number of factors, including the varying definitions used, the size of the studies and the lack of active follow-up to identify cases. Estimates of the incidence after Caesarean birth range from 1.1% to 25%, and for unassisted vaginal birth from 0.2 – 5.5% [29].

Notably the study documenting a 16% incidence of endometritis included only 40 women; reported incidence rates for the larger studies (>1000 women) ranged from 0.2% to 2.9% [22]. However, the lack of active follow-up beyond discharge is likely to mean that the incidence has been underestimated in these larger studies. A Swedish registry study of 795,000 women giving birth found that the peak occurrence of urinary tract infections is 6 days postpartum, and the peak occurrence of endometritis and wound infections is 7 days postpartum [30]. Thus most infections occur after discharge from hospital, estimated by one review to be up to 80% of postpartum infections [29]. Hence, without active follow-up or surveillance, the true incidence of postpartum infectious morbidity after OVD is likely to be underestimated since most infections will present in the community to other healthcare providers. Therefore, all incidence rates reported in

Table 1 should be interpreted with caution.

Nonetheless, it is clear that OVD is an independent risk factor for infection, when compared to unassisted vaginal birth, as evidenced by several recent studies of maternal infection or maternal sepsis.

A Swedish population-based study comparing 16,976 women with postpartum infection (endometritis, wound infection or urinary tract infection) to 702,435 women without infection (2005-2012), showed that women with a wound infection were 7.0 times more likely to have had an OVD, women with endometritis 1.6 times more likely and women with a urinary tract infection (UTI) 3.7 times more likely, compared with women without infection [30]. For comparison, women with wound infection, endometritis and UTI were 17.2, 2.2 and 3.1 times more likely respectively to have a caesarean birth.

In a UK population-based study of 365 cases of severe maternal sepsis, compared to 757 controls without sepsis (2011-2012), women with severe sepsis were 2.5 times more likely to have had an OVD (after adjustment for socio-demographic characteristics and medical history) [4]. Women who had severe sepsis were 8 times more likely to have had a Caesarean section after onset of labour. Similarly, a Scottish population-based study of 103 women with maternal sepsis compared to 412 controls without sepsis (1986-2009), found that women with sepsis had double the odds of having had an OVD (adjusted OR 2.2, 95% CI 1.0-4.9) [31]. The observed risk was almost identical in a cross-sectional facility-based study of over 75,000 births in one hospital in Israel (1989-1997) [31], which reported that women who had postpartum endometritis had double the odds of having had an instrumental delivery (unadjusted OR 2.3), compared to those without infection [32].

Infection risk and type of instrument

All studies in

Table 1 which reported the incidence by type of instrument, showed a higher incidence of infection in women undergoing forceps delivery when compared to vacuum extraction:

- Greis et al 1981: 9% of women had febrile morbidity after forceps, compared to 6% after vacuum extraction [20]
- Williams et al 1991: 16% of women had endometritis after forceps delivery, compared to 8% after vacuum delivery [22]
- Macleod et al. 2008: 3.1% had a perineal infection after vacuum delivery, compared to 4.9% after forceps [25]
- Bailit et al 2016: 0.9% had postpartum infection after forceps delivery, compared to 0.2% after vacuum delivery [27]

It is important to note, that while there appears to be a difference in incidence rates between forceps and vacuum deliveries, most of the studies did not report whether this was statistically significantly different after adjustment for confounding variables. Bailit et al 2016 [27] did report a statistically significant relative risk with forceps 2.7 times more likely to be associated with postpartum infection compared to ventouse (95% CI 1.6-4.3). Noting that the level of evidence is weak as these are small observational studies, this difference merits further investigation.

Perineal infection and operative technique

Operative vaginal delivery is often associated with either a perineal tear or episiotomy and an increased risk of obstetric anal sphincter injury (OASI). At present, the evidence does not support routine use of episiotomy, but episiotomy is used based on clinical judgement [33]. Unlike abdominal incisions, perineal tears or episiotomies cannot be covered and are subject to ongoing contamination during the healing process.

“Fear of perineal infection” has been rated as the most important outcome women are concerned about in the puerperium when asked to prioritise childbirth-related outcomes [34]. Perineal infections

in particular are associated with perineal pain, wound dehiscence and purulent discharge, which can have a significant impact on women's quality of life and sexual function.

Only one study included in this review [25] gave a breakdown of the risk of perineal infection as a result of perineal tears or episiotomy associated with operative vaginal delivery. This study of 1,360 women who had an operative vaginal delivery in two maternity units in the UK, found that 4.2% had a perineal infection. This was strongly associated with whether or not they had an episiotomy, with adjusted risk of perineal infection being 4.0 times greater in women who had an episiotomy (95% CI 1.44-11.37). The incidence is likely to be higher as there was no active follow-up of these women beyond discharge and records were not linked. This study also reported non-significantly raised odds of OASI in association with episiotomy use, and it is likely that the studies of postpartum infection after OVD are further confounded by differing rates of OASI. In a study of 341 postpartum women with sutured episiotomies or tears, where women were contacted 21 days after delivery, 11% were found to have signs and symptoms of a wound infection [35].

It is likely that the use of episiotomy has a role in the observed association between operative vaginal delivery and perineal infections. In the large Swedish study on postpartum infections (described above), there was a strong association between instrumental delivery and wound infections (including perineal and surgical site infections) with odds ratio (OR) of 6.9 (95% CI 6.3-7.6), but an even stronger association with episiotomy (OR 10.2, 95% CI 8.9-11.5) and Caesarean birth (OR 17.2, 95% CI 16.1-18.3).

Risk factors for infection

It is challenging to identify risk factors that make women more susceptible to postpartum infection after operative vaginal delivery as none of the identified studies in

Table 1 address this question solely in this population. However, several studies, summarised in Table 2, have identified risk factors more broadly for maternal infection or maternal sepsis, and adverse outcomes after these infections.

Each of the studies identified an increased risk relating to socio-demographic, medical and pregnancy-related factors. Socio-demographic factors such as age, ethnicity and weight, were found to be risk factors for adverse outcomes from pregnancy-related sepsis (see Table 2). While most socio-demographic factors are not modifiable, it is important for both women and clinicians to be aware of these increased risks. Similarly, many medical conditions such as diabetes, cardiovascular disease, anaemia and immunosuppression were found to be associated with risk of infection [2, 31, 36, 37]. This finding highlights the need for a higher index of suspicion for the potential for complications in women with medical conditions.

Several studies identified obstetric or pregnancy-related factors associated with infection such as caesarean section, operative vaginal birth or induction of labour [31, 38, 39]. However, obstetric interventions can be both a cause and consequence of maternal infection and this is particularly difficult to differentiate in analyses which analyse women with antenatal, intrapartum and postpartum infections as a single group, or use routine data where temporality is unclear. In the studies which are able to examine solely postpartum infection, the association with operative vaginal delivery remains, suggesting that it is potentially causal.

Table 2 Risk factors identified from population-based studies on maternal sepsis

Authors	Year	Study details	Comparison groups	Risk factors identified
Acosta et al. [4]	2014	National, prospective case-control study, UK 2011-2012 antepartum, intrapartum and postpartum women	(1) severe sepsis vs. uncomplicated pregnancies (2) septic shock vs severe sepsis without septic shock	Black or other ethnic minority Major pre-existing medical problem Primiparity Febrile illness or recent antibiotics Operative vaginal delivery Caesarean section
Acosta et al. [37]	2013	Retrospective cohort study using linked hospital and vital statistics data, using ICD-9-CM coding, California, USA 2005-2007 All live births	(1) severe sepsis or septic shock vs. uncomplicated sepsis (2) uncomplicated sepsis vs. no sepsis	Black, Asian, Hispanic Public or no insurance Diabetes Chronic hypertension Primiparity Multiple pregnancy Pre-eclampsia Post-partum haemorrhage
Acosta et al. [31]	2012	Population-based, case-control study, using ICD-9 coding 1986–2009 Scotland antepartum, intrapartum and postpartum women	severe sepsis, uncomplicated sepsis and uncomplicated pregnancies	Age < 25 years Obesity Anaemia Multiparity Induced labour Operative vaginal delivery
Al-Ostad et al. [36]	2015	Population-based, cohort study using routine data, USA 1998-2008	sepsis vs uncomplicated pregnancies	Black ethnicity Age > 35 years Smoking Medical co-morbidities (diabetes, cardiovascular disease) Preterm birth Postpartum haemorrhage
Axelsson and Blomberg [38]	2017	Population-based, retrospective cohort study using registry data, Sweden 1997-2012	postpartum sepsis vs. no sepsis	Obesity Obstetric interventions (induction of labour, Caesarean section) Post-partum anaemia
Bauer et al. [39]	2013	Population-based, retrospective study using routine hospital data, USA 1998-2008 Women hospitalised for delivery	sepsis plus organ dysfunction code vs. no sepsis	Age > 35 years African-American race Medicaid insurance Heart failure Chronic liver or renal failure Systemic lupus erythematosus HIV infection Multiple pregnancy Cervical cerclage Preterm premature rupture of membranes or preterm delivery Emergency Caesarean
Mohamed-Ahmed et al [2]	2015	Population-based case-control study, UK 2009-2012 antepartum, intrapartum and postpartum women	sepsis deaths vs. severe sepsis morbidity	Delay in antibiotics or no treatment Employment status Medical co-morbidities (anaemia and immunosuppression) Multiparity

Causative organisms

The most frequently encountered causative organisms in postpartum infection are [40]:

- *Escherichia coli* (*E. coli*)
- Group A streptococcus (e.g. *Streptococcus pyogenes*)
- Group B streptococcus (e.g. *Streptococcus agalactiae*)
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

Other important bacteria include methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium septicum*, *Clostridium perfringens*, *Clostridium sordellii* and *Morganella morganii*.

In a study of maternal bacteraemia in women delivering in two hospitals in Ireland, of the 130 cases that occurred postpartum, 55 were due to *E. coli* (42.3%), 12 were Group B streptococcus (9.2%), 12 were *Staphylococcus aureus* (9.2%), 11 were anaerobes (8.4%) and 10 were Group A streptococcus (7.7%).[41] Similarly, a study of 135 cases of maternal bacteraemia in five hospitals in France, showed that *E. coli* was the most commonly isolated pathogen (45%), though this included women with infections during pregnancy. [42]

In a prospective UK population-based case-control study, of the 231 postpartum cases of severe sepsis, no causative organism was identified in 32.9% of postpartum infections (n=76), but where an organism was identified: *E. coli* was the most common infection (19.1%), followed by Group A streptococcus (13.0%), *Staphylococcus* (9.1%), Group B streptococcus (7.4%), other streptococcal infection (6.5%) and mixed organisms (6.1%). [4]

E. coli

E. coli is the most frequently isolated bacterium in urinary tract infections in pregnancy, and is associated with asymptomatic bacteriuria, cystitis and pyelonephritis. However, *E. coli* can also cause genital tract infections (chorioamnionitis and endometritis) and bacteraemia. The latter route, in

particular, has been associated with poor maternal and fetal outcomes [41, 43], when compared to bacteraemia secondary to urinary tract infection. Fetal mortality was estimated at 27% [43], though most infections occurred during the third trimester, rather than postpartum. *E. coli* has been noted to be an important cause of maternal death from sepsis in the UK and Ireland Confidential Enquiries, most notably after second trimester miscarriage, but also following term delivery [44, 45]. For the clinician, it is important to be aware of the risk of *E. coli* as a contaminant, at the point of bladder catheterisation and/or instrumental delivery, and that infection via the genital route is associated with the worst outcomes. Antibiotic choice should be guided by local prescribing policies and resistance patterns [44], but ampicillin, amoxycillin, trimethoprim and cephalosporins are frequently used as first-line [46].

Group A streptococcus

Group A streptococcal (GAS) infection, also known as *Streptococcus pyogenes*, has long been recognised as a cause of postpartum infection. In recent years, there has been a resurgence of GAS infections in both pregnant and general populations, where it is known for causing invasive disease, severe sepsis and death. In pregnancy, apart from endometritis, it can cause necrotising fasciitis and toxic shock syndrome [47]. It arises particularly following vaginal birth and has a high mortality [37]. GAS infections continue to cause maternal death in the UK and Ireland [44, 45] and similarly, in the Netherlands, 42% of direct maternal deaths from sepsis are the result of GAS [48].

The exact reasons for this resurgence are not known. GAS is carried asymptomatically on the skin or throat by 5-30% of the population [49], and can also be found in the flora of the female reproductive tract. However, unlike Group B streptococcus (GBS) colonisation, GAS colonisation is rare, estimated to be around 0.03% [50]. Thus, potential entry routes for infection can be ascending e.g. from vaginal colonisation or nosocomial exposure from GAS carriers in a hospital setting) or descending (e.g. originating in the respiratory tract and disseminating through the bloodstream).

As GAS has increased in the general population, this could mean that postpartum women are more likely to be exposed to carriers and infected persons. A review of maternal deaths secondary to GAS infection found that all women who died had either worked with, or had, young children, and several of the women had a recent history of sore throat or respiratory infection [51]. Children are known carriers of GAS, with childcare settings associated with outbreaks of scarlet fever. This is likely to represent a greater source of infection than nosocomial transmission, which has been estimated to be responsible for only 13.9% of postpartum GAS infections [52].

The reasons why GAS causes severe infection and outcomes in postpartum women remain unclear but likely include the altered immune status associated with pregnancy, disrupted mucosal barriers, virulence of the micro-organism and host susceptibility [53]. It is recognised that GAS is the most serious infection in the postpartum period, and women with GAS infection are 3.3 times more likely to progress from severe sepsis to septic shock compared to women with *E. coli* infection (95% CI 1.4-7.8) [4].

Presentation and progress of GAS infection can vary [53]:

- Clinical features can be non-specific, but will often include fever, abdominal pain and hypotension, which can be difficult to identify in the immediate postpartum period. Less frequently, there may be raised white cell count and/or tachycardia.
- GAS infection can present rapidly, within 2 to 48 hours postpartum, and timely diagnosis is vital [54]. GAS infection should be considered in women presenting with sepsis within 12 hours of delivery, and treated aggressively.
- Streptococcal toxic shock syndrome can occur in 20% of cases [55], and features include hypotension and organ dysfunction, e.g. renal failure, acute respiratory distress, coagulopathy, soft tissue necrosis, macular rash and desquamation.
- Maternal mortality is high in GAS infection, reported as up to 30-50%. With signs of septic shock, maternal mortality is 60%. Maternal mortality is highest when infection develops

within close proximity to delivery, with women at highest risk of death in the first 4 days after delivery.

- The majority of GAS infections occur postpartum (80-90%). The incidence of vertical transmission and infant mortality is low.
- Blood, urine and endometrial aspirates should be sent for microscopy, Gram stain and culture.
- Treatment should include timely administration of antibiotics, usually a penicillin [46], aggressive fluid resuscitation and may require source control - debridement or hysterectomy if there is evidence of necrosis.
- Computed tomography (CT) and magnetic resonance imaging (MRI) can be useful in determining the extent of necrosis and planning surgical treatment, though it should not delay management. It can also show any gas in the tissues or abscesses, which would suggest other types of infection such as *Clostridium perfringens*.

Group B streptococcus

Group B streptococcus (GBS) is more prevalent than GAS, but is associated with less severe maternal disease. GBS colonises the genital tract and gastrointestinal tract of around 20-40% of adults, and the upper respiratory tract of infants [56]. In women, GBS can cause urinary tract infection (cystitis, pyelonephritis), asymptomatic bacteriuria, endometritis and chorioamnionitis. GBS is found in around 30% of cases of asymptomatic bacteriuria [57], and this is associated with heavy colonisation of the genital tract.

GBS is most well-known as a cause of severe early-onset infection in newborn infants, accounting for 50% of laboratory-confirmed cases of neonatal sepsis. However, it is estimated that only 0.3% of infants born to mothers colonised with GBS will develop GBS sepsis [58]. Universal screening during pregnancy is not recommended in the United Kingdom [59]. Intrapartum prophylaxis is recommended for women with asymptomatic bacteriuria and those with a previous baby with GBS disease and should be considered for those with a history of GBS carriage in a prior pregnancy [59].

Unlike GAS infection, severe sepsis from GBS is a rare occurrence. In a UK population-based study of confirmed or suspected severe sepsis secondary to GBS, the incidence was found to be 1 per 100,000 maternities for confirmed cases and 2.8 per 100,000 for presumed cases [60]. Approximately half were antenatal (46.4%, n=13) and half were postpartum cases (53.6%, n=15), and none of the women died. Importantly, women with severe GBS sepsis in the postpartum period were 4.4 times more likely to have had an operative vaginal delivery when compared to controls (95% CI 1.3-14.2). Usual treatment is with penicillin [46].

Prevention of infection after operative vaginal delivery

Basic sterile technique is routine at operative vaginal delivery, but as noted above, any vaginal/perineal wounds will still become contaminated and there is potentially a role for preventative management using prophylactic antibiotics. Whilst the evidence for antibiotic prophylaxis at caesarean section is clear, with a meta-analysis of 95 randomised controlled trials, enrolling over 15,000 women, finding that the administration of prophylactic antibiotics reduced the risk of infection after caesarean section by 60-70% [6], few studies have assessed the role of antibiotic prophylaxis after operative vaginal delivery. A Cochrane review [9] identified one single-centre, randomised controlled trial conducted from 1986 to 1989 and reporting findings from 192 women who received 2gm of intravenous cefotetan (a cephamycin, similar to second generation cephalosporins but with additional coverage against anaerobes) compared to 201 women who received no treatment [10]. The antibiotic was administered after cord clamping. There were 7 cases of endometritis in the control group, and 0 cases in the treatment group, with risk reduction of 93% (RR 0.07). Guidelines either fail completely to mention infection as a complication of operative vaginal delivery, or recognise the lack of evidence about antibiotic prophylaxis, hence practice is inconsistent [61-64].

The ANODE trial

The ANODE trial is a multi-centre, blinded, placebo-controlled trial which has recruited 3,424 women across 27 centres in the UK and is due to report in 2019 [65]. It aims to compare the incidence of confirmed or suspected maternal infection in the first six weeks after operative vaginal delivery amongst women who have been randomised to receive a prophylactic antibiotic versus those who received a placebo. Recruitment of 3,424 has 80% power to detect a 50% reduction in the rate of postpartum infection from a conservative estimate of 4% [9] to 2%.

The study characteristics of the existing trial and the ANODE trial of antibiotic prophylaxis after OVD are summarised in Table 3.

Table 3 Study characteristics of RCTs on antibiotic prophylaxis after operative vaginal delivery

	Heitmann and Benrubi 1989 [10]	Knight et al. 2016 ANODE Trial [65]
Study design	Randomised controlled trial	Randomised controlled trial
Population	1 hospital in USA 393 women Forceps delivery only 1986-1989	27 hospitals in UK 3,424 women aged > 16 years and ≥ 36 weeks gestation who have undergone operative vaginal delivery 2016-2018
Intervention	One dose 2g of IV cefotetan after cord clamping	One dose 1.2g of IV co-amoxiclav after delivery of the baby
Comparison	No treatment	Placebo (20ml saline)
Outcomes	Endomyometritis	Primary outcome: Suspected maternal infection within 6 weeks of delivery, as defined by: (1) a new prescription of antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection with systemic features or other systemic infection (2) confirmed systemic infection on culture (3) endometritis Secondary outcomes: systemic sepsis, perineal wound infection, surgical site infection, perineal pain /

		dyspareunia, hospital admissions and GP visits, antibiotic side effects
Study features	Not blinded, not placebo-controlled Randomisation table used	Blinded Placebo-controlled Randomisation list using permuted blocks of variable size

ANODE intervention

Recent recommendations suggest that antibiotic prophylaxis for caesarean section should be given prior to delivery. The ANODE trial [13] specifically investigates the use of antibiotic prophylaxis after operative vaginal delivery of the infant for the following reasons:

- There are increasing concerns about the risks of prenatal exposure to antibiotics, with known associations with necrotising enterocolitis [66] and cerebral palsy [67] amongst the children of women managed with antibiotics for suspected preterm labour. Use of antibiotics in the third trimester has also been associated with an increased risk of asthma in early childhood [68], and the potential for antibiotics to alter the infant microbiome and thus have long term impacts on other disease states is also increasingly being recognised [69].
- The major difference between an episiotomy wound and a caesarean section wound is the fact that there is ongoing contamination of the surgical field and the rationale is to actually increase the length of time that there would be therapeutic levels of antibiotic by giving the single dose *post-delivery*.
- There have been several cases of anaphylaxis relating to antibiotics given prophylactically for caesarean delivery identified in a national UK study [70]. Although the incidence is extremely low, this is of concern particularly with antenatal administration when there is also the potential for fetal compromise.

Because of concerns over prenatal exposure to co-amoxiclav, prophylaxis at caesarean delivery has moved towards the use of cephalosporins. Co-amoxiclav has a wider spectrum of activity (encompassing anaerobes and enterococci), which is important in view of the likelihood of perineal contamination with bowel flora and the association of anaerobic bacteria with perineal wound breakdown. Additionally, amoxicillin is up to 10-fold more active than cefuroxime against group A streptococci (GAS). Because of the association of GAS with very severe, rapidly progressive postnatal infection, adequate coverage against this organism is essential. Furthermore, national guidance advises avoidance of use of cephalosporins because of concerns over *Clostridium difficile* [71]. Many hospitals have thus relegated cephalosporins from first-line use on the basis of this guidance. Finally, co-amoxiclav is less likely to select for antibiotic resistances (e.g. MRSA, ESBL- and AmpC-producing Gram-negative bacteria) [72]. Cephalosporins are associated with selection of a number of antibiotic resistances (as well as *C. Difficile*), most notoriously MRSA and ESBL-producing Gram-negative bacteria. In neonates, cephalosporins have been associated with an increased risk of candidiasis and there is a theoretical risk of the same in women.

Although a single dose of prophylactic antibiotic at caesarean delivery reduced the risk of infection [6], it could be argued that the continued contamination of the perineal area necessitates a longer duration of prophylaxis. However, increasing awareness of the need for antimicrobial stewardship and considerations around the indiscriminate use of antibiotics promoting antimicrobial resistance have led to multiple studies investigating shorter durations of antibiotic treatment for infections. The authors of a Cochrane review caution that antibiotics are not a substitute for infection prevention and control measures around the time of childbirth and the postpartum period [73]. It follows that awareness that a repaired episiotomy is a surgical wound and vigilance for surgical site infection remains important.

For these reasons ANODE will investigate the administration of a single intravenous dose of 1.2g co-amoxiclav (1g amoxicillin/200mg clavulanic acid) given in the immediate postpartum period (up to 6 hours).

Summary (250 words)

It is increasingly recognised that infection after OVD may be as important as infection after caesarean birth. The incidence of infection after OVD is estimated as 0.7 to 16% and is higher than after normal vaginal birth. The incidence after forceps delivery appears higher than after vacuum. However, few studies have established the incidence in postpartum women after they are discharged from hospital, and the studies are very variable in quality. None fully take into account potential confounders such as obstetric anal sphincter injury. It is also clear that sepsis is re-emerging as a significant cause of maternal morbidity and mortality, emphasising the need for preventative measures and the prompt recognition and treatment of infections.

Endometritis, perineal infections and urinary tract infections remain the most common postpartum infections, and are most often caused by *E. coli*, Group A streptococcus (GAS) and Group B streptococcus. *E. coli* is the most common, frequently associated with UTI, but can be associated with severe outcomes after genital tract infection. GAS leading to endometritis, necrotising fasciitis and toxic shock syndrome, has a mortality of 30-50% and is most common after vaginal deliveries.

The ANODE trial is a multi-centre, blinded, placebo-controlled trial which has recently completed recruiting 3,424 in the UK and is due to report in 2019. It aims to compare the incidence of confirmed or suspected maternal infection in the first six weeks after operative vaginal delivery amongst women who have been randomised to receive a prophylactic antibiotic versus those who receive a placebo.

Practice Points

- OVD is associated with an increased risk of postpartum infection compared with unassisted vaginal delivery, principally due to wound infections, endometritis and urinary tract infections.
- Basic sterile technique together with awareness of the symptoms and routes of infection remain important.
- There is no current evidence to support routine use of antibiotic prophylaxis either before or after OVD.

Research agenda

- The incidence of all postpartum infections (including endometritis, UTI and perineal infections) after operative vaginal delivery, using observational studies with active follow-up of women beyond discharge.
- The role of different instruments (vacuum and forceps) in the incidence of infection, taking into account confounding such as use of episiotomy and OASI.
- The value of antibiotic prophylaxis in preventing postpartum infection and associated outcomes.

Conflict of interest:

MK and KH are both co-investigators on the ANODE trial, funded by a grant from the National Institute for Health Research. The authors have no other conflicts to declare.

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