WHO recommendation on routine antibiotic prophylaxis for women undergoing elective or emergency caesarean section

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Recommendation

Routine antibiotic prophylaxis is recommended for women undergoing elective or emergency caesarean section.

(Moderate - quality evidence, strong recommendation)

Publication history

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Remarks

- Antibiotic prophylaxis in this context refers to antibiotic use prior to the initiation of/or during caesarean section in the absence of clinical signs of infection. The GDG noted that it is essential for clinicians to be clear about this description to avoid using antibiotic regimens that are most applicable for treating confirmed infection – i.e. therapeutic antibiotic use.
- The intravenous route should be used for antibiotic administration given that the evidence underpinning this recommendation was based on findings from trials where the majority used this route.
- The GDG emphasized the importance of using the simplest and shortest antibiotic regimen for prophylaxis. As the evidence suggests that single-dose regimens are as effective as multiple-dose regimens, the GDG favoured single-dose antibiotic regimens which can easily be given prior to/during caesarean section, rather than multiple-dose regimens which sometimes extend to the postoperative period. Clinical judgement is needed to evaluate other factors that might increase the risk of developing post-caesarean infections and are, therefore, more likely to benefit from multiple antibiotic doses (e.g. prolonged duration of surgery (long “skin-to-skin” interval), difficult surgical manipulation or massive blood loss)

Background

Bacterial infections during labour and the puerperium are among the leading causes of maternal mortality worldwide, accounting for about one tenth of the global burden of maternal deaths.\(^1\) While the number of deaths arising from these infections has decreased considerably in high-income settings, the situation has not improved in resource-limited settings. Most of the estimated 75,000 maternal deaths occurring worldwide yearly as a result of infections are recorded in low-income countries.\(^3\) Although the reported
incidence in high-income countries is relatively low (between 0.1 and 0.6 per 1000 births), it is nonetheless an important direct cause of maternal mortality.(3, 4)

Apart from deaths and acute morbidities associated with infections during or following childbirth, long-term disabilities such as chronic pelvic pain, fallopian tube blockage and secondary infertility can also occur. Maternal infections around childbirth also have a considerable impact on newborn mortality, and an estimated 1 million newborn deaths are associated with such infections annually.(5, 6) In addition, infection-related morbidities and prolonged hospitalization can interfere with mother–infant bonding in the first days after birth.

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(7) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of maternal peripartum infections (2015).(8)

A Cochrane review was conducted on the routine use of prophylactic antibiotics for preventing infection and improving outcomes in women undergoing caesarean sections.(9) In the review, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting on recommendations on prevention and treatment of maternal peripartum infections in September 2015, where this recommendation was developed. The GDG comprised of a group of independent experts, who used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Recommendation question

For this recommendation, we aimed to answer the following question:

- Among women undergoing caesarean section (P), does routine antibiotic prophylaxis (I), compared with no antibiotic prophylaxis (C), prevent infectious morbidities and improve outcomes (O)?

Evidence Summary

Evidence for the routine use of prophylactic antibiotics for preventing infection and improving outcomes in women undergoing caesarean sections was extracted from a Cochrane systematic review of 95 trials including over 15 000 women.(9)

Trials were conducted in low-, middle- and high-income countries: 39 in the USA, six in Germany, four in Mexico, three studies each in Canada, Finland, Israel, Italy, South Africa and the UK; two studies each in Austria, France, Greece, Hong Kong, Malaysia, Nigeria, Sweden and the United Arab Emirates; and one study each in China, Denmark, Hungary, Kenya, the Netherlands, New Zealand, Saudi Arabia, Spain, Sudan, Tunisia, Turkey and Zimbabwe.

The antimicrobial agents most often used in the trials included ampicillin, first-generation cephalosporin (usually cefazolin), second-generation cephalosporin (ceftamandole or cefuroxime), cefamycin (cefoxitin, cefotetan), metronidazole, penicillins with an extended spectrum of activity (e.g. ticarcillin, mezlocillin or pipericillin), beta-lactam/beta-lactamase inhibitor combination and aminoglycoside containing combination. Antibiotics were in a majority of cases delivered intravenously. In one study, antimicrobial prophylaxis was
administered by rectal suppository. In four studies, follow-up doses were administered by rectal suppository or vaginal tablet. The duration of the postoperative treatment course varied from a single intravenous dose to as long as a week.

A large proportion of the studies (n = 59, 8500 women) gave no information on the type of surgery performed. Clinical definitions for evaluated outcomes were broadly consistent across trials, except for febrile morbidity and serious infectious morbidity. No study reported on baseline risk of infection before the intervention.

**Any antibiotic prophylaxis versus no antibiotic prophylaxis (EB Table 16a)**

- There was a reduction in cases of serious infectious complications (RR 0.31, 95% CI 0.20 to 0.49; 32 trials, 6159 women), maternal febrile morbidity (RR 0.45, 95% CI 0.40 to 0.51; 56 trials, 9046 women), endometritis (RR 0.38, 95% CI 0.34 to 0.42; 83 trials, 13 548 women), wound infections (RR 0.40, 95% CI 0.35 to 0.46; 82 trials, 14 407 women) and maternal urinary tract infections (RR 0.56, 95% CI 0.49 to 0.65; 66 trials, 10 928 women). Adverse events (rash, phlebitis at the site of the intravenous infusion) were more frequent in the treated group (RR 2.43; 95% CI 1.00 to 5.90; 13 trials, 2131 women). There were no serious drug-related adverse events reported. Maternal length of hospital stay was shorter in the treated group (MD -0.46, 95% CI -0.65 to -0.28; 19 trials, 3168 women) compared with controls.

- The majority of the trials did not report on neonatal outcomes. Those trials reporting them declared few neonatal deaths but no relationship to the use of antibiotics (two trials), no complications related to drug administration (two trials) or any neonatal morbidity (five trials).

- Subgroup analyses based on whether single dose only or multiple dose or either antibiotic regimens were used showed similarity in terms of effect size and direction for all maternal critical outcomes (as shown by the interaction tests) except for endometritis:
  - Febrile morbidity: single dose (RR 0.50, 95% CI 0.42 to 0.60, 27 trials, 5410 women); multiple doses (RR 0.41, 95% CI 0.35 to 0.49, 26 trials, 3192 women); both (RR 0.33, 95% CI 0.21 to 0.53, 3 trials, 444 women); P = 0.13.
  - Wound infection: single dose (RR 0.45, 95% CI 0.38 to 0.54, 27 trials, 7937 women); multiple doses (RR 0.35, 95% CI 0.28 to 0.43, 42 trials, 6208 women); both (RR 0.27, 95% CI 0.07 to 0.98, 2 trials, 262 women); P = 0.15, I² = 47.6%; serious infectious complications: single dose (RR 0.50, 0.25 to 1.0, 15 trials, 3819 women); multiple doses (RR 0.24, 0.13 to 0.43, 17 trials, 2340 women); P = 0.11.
  - Urinary tract infection: single dose (RR 0.60, 95% CI 0.49 to 0.72, 33 trials, 6941 women); multiple doses (RR 0.51, 95% CI 0.41 to 0.64, 32 trials, 3805 women); both (RR 0.70, 95% CI 0.21 to 2.39, 1 trial, 282 women); P = 0.58.
  - Maternal hospital stay: single dose (MD -0.39 days, 95% CI -0.60 to -0.19, 12 trials, 2369 women); multiple doses (MD -0.65 days, 95% CI -1.01 to -0.30, 7 trials, 799 women); P = 0.21.
  - Adverse effects: single dose (RR 2.12, 95% CI 0.66 to 6.75, 7 trials, 1329 women); multiple doses (RR 2.94, 95% CI 0.73 to 11.76, 6 trials, 802 women); P = 0.72.
  - Endometritis: A significant reduction in endometritis was observed for both dosing types; however, the interaction tests showed a significant difference between subgroups: single dose (RR 0.43, 95% CI 0.38 to 0.50, 41 trials, 8487 women); multiple dose (RR 0.32, 0.27 to 0.37, 40 trials, 4799 women); both (RR 0.36, 95% CI 0.17 to 0.73, 2 trials, 262 women); P = 0.02, I² = 75.3% – although in the same direction. Multiple-dose antibiotic prophylaxis significantly was associated with a 68% reduction in the risk of endometritis compared to a 57% reduction for single-dose antibiotics.

**Antibiotic prophylaxis versus no antibiotic prophylaxis: by antibiotic class (EB Table 16b)**

- Approximately two thirds of studies evaluated treatment with a first- or second-generation
cephalosporin, including cefamycins, or ampicillin. No study reported on monotherapy with a penicillinase-resistant penicillin, fourth-generation cephalosporin, carbapenem, tetracycline, macrolide and aminoglycosides.

- There were reductions in maternal outcomes for all antibiotics subgroups, without differences between subgroups for serious infection outcomes ($P = 0.93$; $\text{I}^2 = 0\%$) and wound infection ($P = 0.17$; $\text{I}^2 = 26.8\%$). Interaction tests indicated potentially significant differences among subgroups for febrile morbidity ($P < 0.001$; $\text{I}^2 = 73.8\%$) and endometritis ($P = 0.07$; $\text{I}^2 = 38.6\%$). The smallest reduction in febrile morbidity was seen for cefamycins (RR $0.73$, $95\%$ CI $0.61$ to $0.88$; 9 trials, 1894 women), and the largest for other regimens (RR $0.23$, $95\%$ CI $0.07$ to $0.76$; 1 trial, 118 women). The smallest reduction in endometritis was seen for beta-lactamase inhibitor combinations (RR $0.67$, $95\%$ CI $0.27$ to $1.66$; 5 trials, 788 women), though this was insignificant, and the largest reduction for natural penicillins (RR $0.19$, $95\%$ CI $0.05$ to $0.65$; 1 trial, 66 women).

**Antibiotic prophylaxis versus no antibiotics: by type of caesarean section (EB Table 16c)**

- Seventeen studies (3500 women) included data on women undergoing elective caesarean sections, according to the review definition, while 22 studies (2500 women) included non-elective procedures. Two studies included both. Three subgroups were compared: elective, non-elective and both elective and non-elective or undefined caesarean section.

- Interaction tests showed a significant difference ($P = 0.001$; $\text{I}^2 = 85.2\%$) between subgroups for wound infection (elective CS: RR $0.62$, $95\%$ CI $0.47$ to $0.82$; non-elective CS: RR $0.39$, $95\%$ CI $0.27$ to $0.58$; undefined caesarean section: RR $0.34$ $95\%$ CI $0.28$ to $0.40$) and maternal urinary tract infection (elective CS: RR $0.92$, $95\%$ CI $0.57$ to $1.50$; non-elective CS: RR $0.44$ $95\%$ CI $0.31$ to $0.60$; undefined caesarean section: RR $0.59$ $95\%$ CI $0.49$ to $0.70$). There were no differences between subgroups for febrile morbidity ($P = 0.79$; $\text{I}^2 = 0\%$), endometritis ($P = 0.84$; $\text{I}^2 = 0\%$), febrile morbidity ($P = 0.79$; $\text{I}^2 = 0\%$) or serious infectious maternal outcomes ($P = 0.73$; $\text{I}^2 = 0\%$).
Supporting systematic review:


References


Citation


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