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REVIEW

PREVENTIVE EFFECTS OF ANTIBIOTICS IN SURGICAL SITE INFECTIONS AFTER CAESAREAN SECTION: A META-ANALYSIS

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Abstract

This research aimed to systematically assess the preventive effects of antibiotic use on surgical site infections and other complications following caesarean section using meta-analysis. Controlled studies on surgical site infections following caesarean section with antibiotic use published from January 1970 to December 2023 were retrieved from PubMed, Embase and Web of Science. Literature screening was conducted based on inclusion and exclusion criteria, and the quality of included studies was assessed. Meta-analysis was performed using Review Manager 5.3. Twelve studies involving 5,556 participants were included, with NOS scores ranging from 6 to 8, and most Cochrane risk of bias assessments were categorised as "Unclear risk" or "Low risk". Meta-analysis revealed that the incidence of surgical site infections (Odds ratio [OR] = 0.40, 95% confidence interval [CI] = 0.310.51, Z = 7.30, p < 0.00001) and endometritis (OR = 0.55, 95% CI = 0.410.73, Z = 4.09, p < 0.0001) was markedly lower in the antibiotic group *versus* the non-antibiotic group. Nevertheless, the incidence of urinary tract infections differed inconsiderably between the antibiotic and non-antibiotic groups (OR = 0.59, 95% CI = 0.29 ~ 1.18, Z = 1.49, p = 0.14). The findings suggest that antibiotic prophylaxis after caesarean section effectively prevents the occurrence of surgical site infections and endometritis postoperatively.

Rezumat

Studiul a avut ca scop evaluarea sistematică a efectelor preventive ale utilizării antibioticelor asupra infecțiilor și a altor complicații după cezariană. Au fost evaluate studiile publicate între ianuarie 1970 și decembrie 2023, preluate din PubMed, Embase și Web of Science. Meta-analiza a fost efectuată utilizând Review Manager 5.3. Au fost incluse douăsprezece studii care au implicat 5.556 de participanți, cu scoruri NOS cuprinse între 6 și 8, iar majoritatea evaluărilor Cochrane privind riscul de bias au fost clasificate ca „risc neclar" sau „risc scăzut". Meta-analiza a relevat că incidența infecțiilor la locul intervenției chirurgicale (raportul de șanse [OR] = 0,40, interval de încredere [CI] de 95% = 0,310,51, Z = 7,30, p < 0,00001) și endometritei (OR = 0,55, IC 95% = 0,410,73, Z = 4,09, p < 0,0001) a fost semnificativ mai mică în grupul tratat cu antibiotice comparativ cu grupul netratat cu antibiotice. Cu toate acestea, incidența infecțiilor tractului urinar a diferit nesemnificativ între grupul tratat cu antibiotice și grupul netratat cu antibiotice (OR = 0,59, IC 95% = 0,29 ~ 1,18, Z = 1,49, p = 0,14). Rezultatele sugerează că profilaxia cu antibiotice după cezariană previne în mod eficient apariția infecțiilor la locul intervenției chirurgicale și a endometritei postoperatorii.

Keywords: caesarean section, antibiotics, surgical site infection, endometritis, meta-analysis

Introduction

Caesarean section, performed on pregnancies of at least 28 weeks gestation by surgically opening the abdominal wall and uterine wall to deliver the foetus and its appendages, reduces mortality rates for high-risk pregnancies and obstructed labour in both mothers and newborns [1]. Recently, the rate of caesarean sections has been steadily increasing. Nevertheless, being a surgical procedure adjacent to the uterine cavity and communicating with the vagina, caesarean sections are prone to complications such as infections, with surgical site infections being the most common type [2]. Surgical site infection after caesarean section refers to infections occurring at the surgical site within 30 days post-operation, with an incidence rate ranging from 3% to 15% [3]. Surgical site infection can lead to postoperative pain, delayed recovery, and in severe cases, sepsis and even death [4]. Prophylactic antibiotic use is believed to effectively prevent complications following caesarean section. Nevertheless, there is still a risk of postoperative infections despite prophylactic antibiotic administration. Kuhr *et al*. demonstrated that among 2725 women undergoing caesarean section and receiving antibiotics intraoperatively, 88 cases (3.2%) experienced postoperative complications, including surgical site infections, endometritis and sepsis, with an overall low infection rate [5]. Nabhan *et al*. conducted a study involving 1,354 women who underwent caesarean section and found that prophylactic antibiotic administration *via* intravenous injection or oral intake significantly reduced the incidence of surgical site infections and endometritis complications [6]. Ben Shoham *et al*. demonstrated that the coverage rate of prophylactic

antibiotics during caesarean section exceeded 99%, with a postoperative surgical site infection probability of around 2%, and the timing of prophylactic antibiotic administration did not affect the occurrence rate of postoperative surgical site infections [7].

To better understand the impact of prophylactic antibiotic use during caesarean section on complications such as postoperative surgical site infections in women, this study systematically assessed the preventive effects of antibiotics on post-caesarean section surgical site infections, endometritis, urinary tract infections and other complications using meta-analysis. The aim is to provide evidence-based guidance and clinical reference for post-caesarean section incision management and the prevention of surgical site infections.

Materials and Methods

Literature search

PubMed, Embase, Web of Science and other English databases were chosen for literature retrieval, covering the period from January 1970 to December 2023. Advanced search methods were utilised to extract records, employing a blend of subject terms and free-text terms, encompassing keywords like "caesarean delivery," "caesarean," "antibiotic," "β-lactamides," "macrolides," "surgical site infection," "wound infection," "complications," and "infection". Additionally, citation tracking was performed to ensure the comprehensive literature collection.

Criteria for inclusion

Inclusion criteria: (i) English-language literature published domestically and internationally on antibiotic prophylaxis for preventing surgical site infections after caesarean section; (ii) Types of literature included case-control studies, randomised controlled trials and prospective cohort studies; (iii) Study subjects were women under-going caesarean section; (iv) Outcome measures included surgical site infection/wound infection according to hospital infection diagnostic criteria.

Exclusion criteria: (i) Duplicate publications; (ii) Unclear outcome indicators or incomplete data; (iii) Basic research, literature reviews, conference papers, case reports, *etc.*; (iv) Full-text unavailable.

Data extraction

An Excel® spreadsheet was employed for the data collection, with literature screening and data extraction conducted independently by two pertinent researchers. Extracted data encompassed details including first author, publication year, study population, sample size, grouping, treatment methods, outcome measures and more. Following data extraction, results were cross-validated by the two researchers. Should disparities arise, discussion ensues to achieve consensus, or if required, arbitration and conclusive decision-making are facilitated by a third researcher.

Literature quality evaluation

Literature quality evaluation utilised the Newcastle-Ottawa Scale (NOS), as per recommendations from the Agency for Healthcare Research and Quality [8]. NOS comprises four criteria for participant selection, one criterion for study comparability and three criteria for exposure or outcome assessment, yielding a total score of 9 points. Scores between 0 to 3 denote low quality, 4 to 6 points indicate moderate quality and 7 to 9 points signify high quality. Moreover, the Cochrane Risk of Bias assessment tool was applied to assess study quality. This tool covers various domains including the selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting of outcomes) and other biases. Two independent researchers conducted the quality assessment of the literature and cross-validated the outcomes. Any discrepancies were resolved through discussion.

Statistical analysis

Meta-analysis was conducted using Review Manager 5.3 (Cochrane Collaboration, UK) to analyse outcome measures from the included studies. Initially, data heterogeneity was assessed. Heterogeneity was considered insignificant when I^2 was below 50% and P was above 0.1, warranting the use of a fixed-effects model. Conversely, significant heterogeneity was indicated by I^2 values of 50% or higher and P values of 0.1 or lower, prompting the adoption of a random-effects model. Outcome measures encompassed rates of surgical site infection, urinary tract infection and endometritis occurrence, all treated as count data. Thus, odds ratios (ORs) were employed as the summary effect measure, accompanied by a combined 95% confidence interval (CI) to indicate the meta-analysis results. A funnel plot was utilised to evaluate potential publication bias.

Results and Discussion

Search results for included literature

A total of 421 pertinent articles were sourced from PubMed, Embase and Web of Science. Post initial screening, 196 duplicate articles were eradicated. Subsequent scrutiny of titles and abstracts led to the selection of 69 articles for further evaluation. Upon acquiring full-text articles, 57 articles not meeting the inclusion criteria were omitted. Eventually, 12 articles were deemed suitable for meta-analysis. The depiction of the literature search process is delineated in Figure 1.

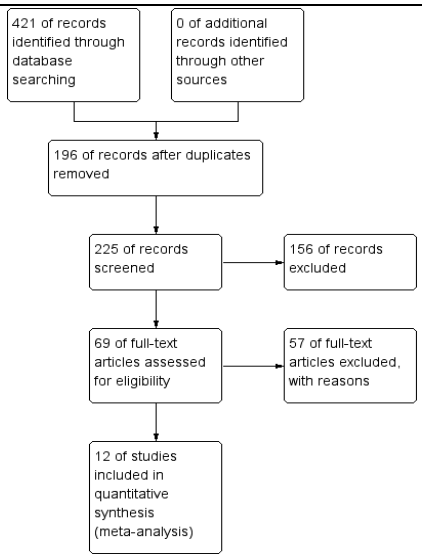

Figure 1.
Literature screening process

Basic characteristics of literature

The study encompassed a total of 12 pertinent articles, involving 5,556 patients. Of these, 3,152 patients belonged to the antibiotic group, while 2,404 patients were part of the non-antibiotic group. Patients in the antibiotic group predominantly received intravenous infusion of cephalosporins such as cefazolin, cefotaxime, cefuroxime, azithromycin, or metronidazole, or oral administration of metronidazole or erythromycin, among other treatment modalities. Conversely, patients in the non-antibiotic group were administered placebo treatment at commensurate doses. The fundamental characteristics of the included studies are delineated in Table I.

Quality evaluation of literature

It was found that the scores for selection of study participants ranged from 2 to 3 points, comparability ranged from 1 to 2 points and exposure or outcome ranged from 2 to 3 points, with a total score ranging from 6 to 8 points (Table II). This indicates that the overall quality of the included literature was moderate to high, meeting the requirements. Subsequently, the quality assessment was conducted. It was observed that only one article had a "High risk" of incomplete outcome data (attrition bias), while the other literature had "Unclear risk" or "High risk" in domains such as random sequence generation (selection bias), allocation concealment (selection bias), participants and personnel blinding (performance bias), outcome assessment blinding (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias, indicating relatively high quality of the included literature and meeting the requirements (Figure 2 and Figure 3).

Table I
Basic characteristics of literature

First author	Year	Sample size		Therapeutic methods	Outcome indicators
		Antibiotic group	Non-antibiotic group		
Harris [9]	2019	826	103	Intravenous injection of 2 - 3 g cefazolin or 900 mg clindamycin and 80 g gentamicin.	Surgical site infection, endometritis
Hong [10]	2016	202	212	At cord clamping, a single intravenous infusion of 2 g cefazolin diluted in 100 mL of 0.9% saline solution.	Surgical site infection, urinary tract infection, endometritis
Jawad [11]	2022	50	50	12 hours postoperatively, intravenous injection of a single dose of 1 g cefotaxime.	Surgical site infection, urinary tract infection, endometritis
Phelan [12]	1979	61	61	Intravenous infusion of 500 mg cefazolin.	Surgical site infection, urinary tract infection, endometritis
Polk [13]	1982	138	128	Intravenous infusion of 2 g ceftriaxone three times.	Surgical site infection, urinary tract infection, endometritis
Rizk [14]	1998	59	61	At cord clamping, intravenous infusion of 1.5 g cefuroxime.	Surgical site infection, endometritis
Rudge [15]	2006	200	200	At cord clamping, a single intravenous infusion of 2 g cefoperazone diluted in 100 mL of 0.9% saline solution.	Surgical site infection, endometritis
Ruiz-Moreno [16]	1991	50	50	At cord clamping, intravenous infusion of 1 g metronidazole.	Surgical site infection, endometritis
Sanusi [17]	2022	135	134	After skin incision, intravenous infusion of 500 mg azithromycin diluted in 250 mL of 0.9% saline solution.	Surgical site infection, endometritis
Tara [18]	2022	210	210	Oral administration of 500 mg cefaclor and 500 mg metronidazole.	Surgical site infection
Tita [19]	2016	1019	994	Intravenous infusion of 500 mg azithromycin.	Surgical site infection, endometritis
Valent [20]	2017	202	201	Oral administration of 500 mg cefaclor and 500 mg metronidazole.	Surgical site infection, endometritis

Table II

NOS evaluation of literature

First author	Year	Research subject selection	Comparability	Exposure or outcome	Score
Harris [9]	2019	3	2	2	7
Hong [10]	2016	3	2	2	7
Jawad [11]	2022	3	2	3	6
Phelan [12]	1979	3	2	2	7
Polk [13]	1982	3	1	2	6
Rizk [14]	1998	3	2	2	7
Rudge [15]	2006	3	2	3	8
Ruiz-Moreno [16]	1991	2	2	2	6
Sanusi [17]	2022	3	1	3	7
Tara [18]	2022	3	2	3	8
Tita [19]	2016	3	2	3	8
Valent [20]	2017	3	2	3	8

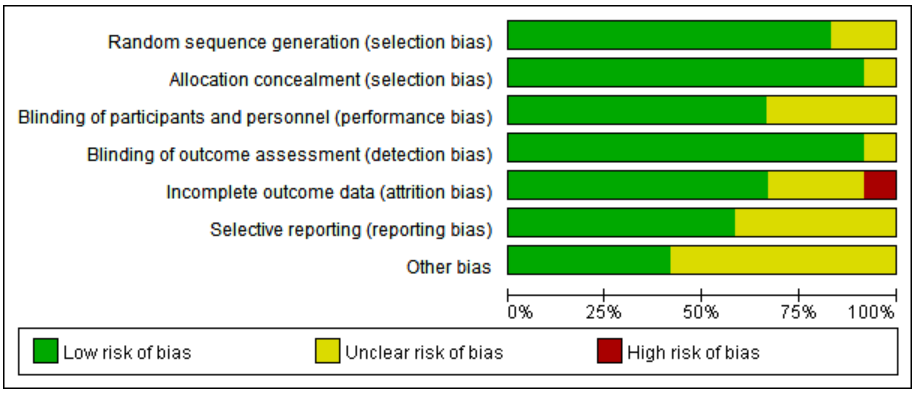

Figure 2.
Risk of literature bias

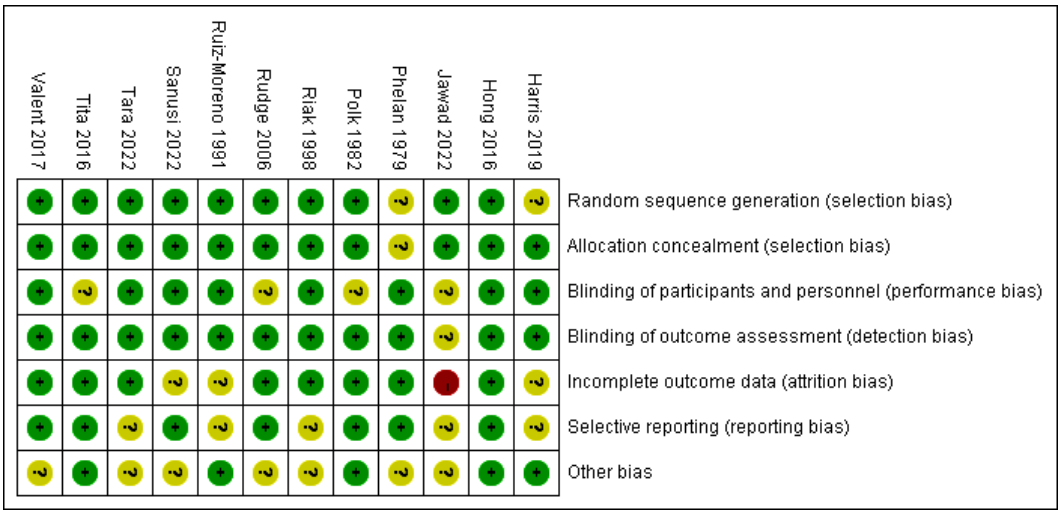

Figure 3.
Summary of bias risks

Meta-analysis results of included literature

Surgical site infection. A comprehensive review of 12 articles explored the efficacy of antibiotics in preventing surgical site infections post-caesarean section [9-20]. Heterogeneity testing revealed an I^2 value of 0% and a *P*-value of 0.65, suggesting no notable heterogeneity across the studies. Consequently, a fixed-effects model was applied for analysis. Meta-analysis unveiled a notable reduction in the likelihood of surgical site infection post-antibiotic treatment in the antibiotic group relative to the non-antibiotic group, with a considerable disparity (OR = 0.40, 95% CI = 0.31 ~ 0.51, Z = 7.30, $p < 0.00001$). The forest plot delineating the outcomes for surgical site infection occurrences post-treatment is depicted in Figure 4.

Urinary tract infection. Four articles were identified [10-13], reporting on the efficacy of antibiotics in preventing urinary tract infections following caesarean

section. Heterogeneity testing across the studies yielded an I^2 value of 0% and a *P*-value of 0.90, indicating minimal heterogeneity. Consequently, a fixed-effects model was employed for analysis. Meta-analysis findings indicated neglectable difference in the likelihood of urinary tract infection occurrence post-antibiotic treatment *versus* the non-antibiotic group (OR = 0.59, 95% CI = 0.29 ~ 1.18, Z = 1.49, p = 0.14). The forest plot illustrating the meta-analysis results for urinary tract infection occurrences post-treatment is depicted in Figure 5.

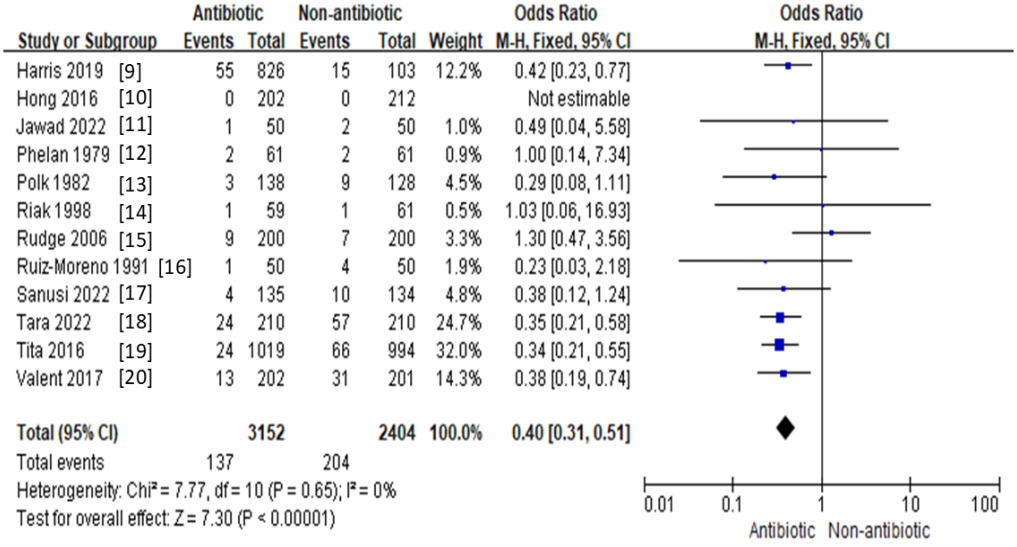

Figure 4.
Forest plot of the incidence of surgical site infections after caesarean section

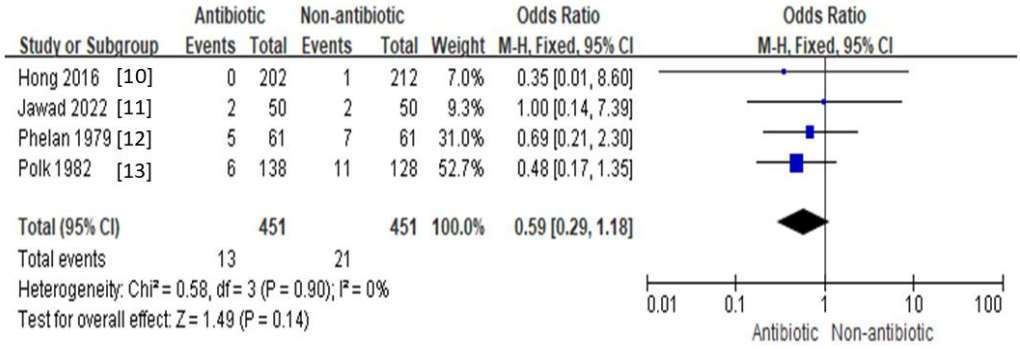

Figure 5.
Forest plot of the incidence of urinary tract infections after caesarean section

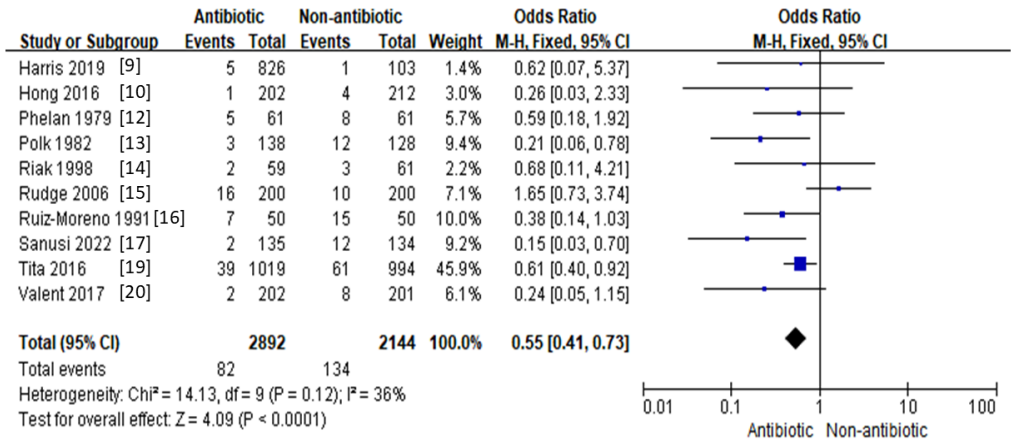

Figure 6.
Forest plot of the incidence of endometritis after caesarean section

Endometritis. Ten articles [9, 10, 12-17, 19, 20] were included, reporting on the efficacy of antibiotics in preventing endometritis following caesarean section. Heterogeneity testing across the studies yielded an I^2 value of 36% and a *P*-value of 0.12, indicating minimal heterogeneity. Consequently, a fixed-effects model was employed for analysis. Meta-analysis findings indicated a drastic reduction in the likelihood of endometritis occurrence post-antibiotic treatment in the antibiotic group *versus* the non-antibiotic group (OR = 0.55, 95% CI = 0.41 ~ 0.73, Z = 4.09, p < 0.0001). The forest plot illustrating the meta-analysis results for endometritis occurrences post-treatment is depicted in Figure 6.

Publication bias. A funnel plot analysis was performed to assess the outcome measures of the antibiotics in preventing surgical site infections post-caesarean section. The plot displayed a generally symmetrical distribution of points, with many studies falling within the funnel plot's boundaries, suggesting the absence of significant publication bias among the included studies. The funnel plot examining publication bias across the included studies is depicted in Figure 7.

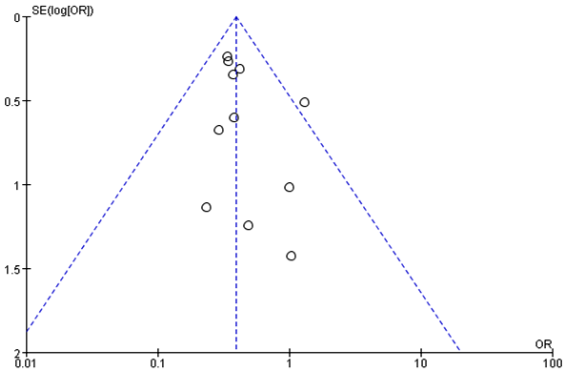

Figure 7.
Funnel plot of the incidence rate of surgical site infection after caesarean section

Caesarean section is a common surgical procedure in obstetrics, with surgical site infection being the most prevalent complication following caesarean delivery. Previous studies have identified age, obesity, medical history, concurrent genital tract infections, premature rupture of membranes and antibiotic usage as key factors influencing surgical site infections after caesarean section [21-23]. The antibiotics are commonly used medications for preventing surgical site infections; Nevertheless, inappropriate antibiotic use can lead to wastage of healthcare resources, the spread of bacterial resistance and increased rates of adverse reactions [24]. To assess the impact of prophylactic antibiotic use on surgical site infections after caesarean section, this study systematically evaluated twelve relevant studies. It was found that these studies mostly involved the administration of antibiotics through intravenous injection or oral ingestion. Intravenous injection allows drugs to be delivered directly into the bloodstream, exerting their effects through circulation [25]. Oral medications, on the other hand, need to pass through the gastrointestinal tract and be absorbed by the gastrointestinal mucosa before exerting their effects in the body. Oral drug absorption is slow and irregular, and drug efficacy can be influenced by gastrointestinal function and contents, with some drugs causing adverse gastrointestinal irritation [26]. Intravenous injection offers the advantage of rapid and comprehensive delivery to the treatment site, with drug components being more readily absorbed by patients. Nevertheless, it can lead to dependency and may cause significant irritation. Scarborough *et al*. implemented a comparative study on the efficiency of oral *versus* intravenous antibiotics for preventing bone and joint infections, finding neglectable difference in adverse events between different administration routes, while oral medication demonstrated higher cost-effectiveness [27]. Yetmar *et al*. also demonstrated neglectable difference in the 30-day treatment failure (including mortality, infection recurrence, or readmission) among bloodstream infection patients receiving oral or intravenous antibiotics, highlighting the importance of antibiotic type and dosage selection [28].

Among the twelve relevant studies included in this paper, patients receiving antibiotic prophylaxis were commonly administered drugs such as cefazolin, ceftriaxone, cefuroxime, azithromycin, metronidazole, or vancomycin. Cefazolin is a 1st-generation cephalosporin broad-spectrum antibiotic with anti-inflammatory and bactericidal properties [29]. Ceftriaxone is a third-generation cephalosporin antibiotic with a broad spectrum of antibacterial activity, stability against beta-lactamases, and low renal toxicity [30]. Cefuroxime is a second-generation cephalosporin antibiotic that retains the efficacy against the Gram-positive bacteria of first-generation drugs while offering greater stability in bactericidal effects and a broader spectrum of antibacterial activity [31]. Azithromycin belongs to the macrolide class of antibiotics, exhibiting excellent antibacterial activity against both Gram-positive and Gram-negative bacteria, and also inhibiting protein synthesis in pathogenic microorganisms [32].

Metronidazole is a synthetic nitroimidazole antibiotic effective against anaerobic bacteria and protozoa [33]. Gentamicin is an aminoglycoside antibiotic known for its heat stability and broad-spectrum antibacterial properties [34]. This indicates a diverse range of drugs used clinically for preventing post-caesarean section infections, with cephalosporin antibiotics being the most widely used. Our study found a significant reduction in postoperative surgical site infection rates in women receiving antibiotics compared to those in the non-antibiotic group. To prevent surgical site infections, it is recommended to administer antibiotics within 30 minutes to 2 hours before skin incision or immediately after clamping the umbilical cord.

Nevertheless, considering the safety of newborns, narrow-spectrum antibiotics are recommended after cord clamping during caesarean section. Research by Lamont *et al*. demonstrated that preoperative use of broad-spectrum antibiotics before caesarean section significantly reduces postoperative surgical site infections without adverse effects on newborns [35]. Prophylactic antibiotic use thus serves as a protective factor against infections following caesarean section.

Nevertheless, the effectiveness of different antibiotics in preventing surgical site infections following caesarean section varies. Li *et al*. conducted a systematic review of 15 relevant studies evaluating the impact of cefazolin on post-caesarean section surgical site infections. They found significant differences in the preventive effects of surgical site infections based on factors such as dosage (low or high), timing of administration (after cord clamping or before skin incision) and form of administration (single drug or combination with other antibiotics). Overall, they confirmed that cefazolin effectively controls surgical site infections in caesarean section procedures [36]. Zachariassen *et al*. found that the concentration of cefuroxime in newborn blood significantly increased within 15 to 60 minutes after a single dose administered before skin incision, with a median half-life of 3.5 hours [37]. Alrammaal *et al*., through meta-analysis, demonstrated that the incidence of surgical site infections after intravenous cefuroxime administration in obese and non-obese women was 6.8% and 4.7%, respectively, with no significant difference [38]. Skeith *et al*. [39] and Harper *et al*. [40] confirmed that adding azithromycin to standard cephalosporin antimicrobial regimens significantly reduces post-caesarean section endometritis and other complications, while also effectively lowering costs and improving maternal outcomes. Markwei *et al*. demonstrated that adjunctive azithromycin, metronidazole, or clarithromycin formulations with cefazolin significantly reduce surgical site infections following caesarean section compared to cefazolin alone, along with a shorter hospital stay [41]. This suggests that combination antibiotic therapy is more effective in reducing the occurrence of the surgical site infections and other complications following caesarean section compared to monotherapy. Therefore, future considerations should further explore the effects of different types, dosages and combination therapy regimens on surgical site infections following caesarean section.

Prophylactic antibiotic use during caesarean section effectively reduces the risk of postoperative complications such as fever, endometritis, urinary tract infections and surgical site infections. Moulton *et al*. demonstrated that among 2,419 caesarean section patients, catheter-associated urinary tract infections demonstrated an incidence of 1.5%, with *Escherichia coli*, *Enterococcus faecalis* and *Streptococcus agalactiae* being common pathogens [42]. Post-caesarean section urinary tract infections may be associated with immunosuppression and the poor personal hygiene. Among the included literature, only four studies were related to the incidence of urinary tract infections, and the research findings indicated that antibiotic group had a lower incidence of postoperative urinary tract infections but with no significant difference *versus* non-antibiotic group. This suggests that further investigation is needed to determine the effectiveness of prophylactic antibiotic use in preventing post-caesarean section urinary tract infections. Endometritis is a pelvic inflammatory disease characterised by bacterial invasion of the endometrium following cervical prevention and is considered a complication of caesarean section [43]. Improper surgical techniques during caesarean section or inadequate postoperative care can lead to the development of endometritis. Wei *et al*. demonstrated that the incidence of chronic endometritis after caesarean section is approximately 20.5% to 28.8%, and caesarean scar defects may increase the risk of the chronic endometritis [44]. In this study, it was observed that compared to the non-antibiotic group, the incidence of post-caesarean section endometritis was significantly reduced in the antibiotic group. Jansson *et al*. found that the incidence of postoperative endometritis in selective caesarean section patients decreased by about 60% with prophylactic antibiotic use [45]. This suggests that prophylactic antibiotic use can effectively reduce the incidence of the post-caesarean section endometritis, promoting postpartum recovery and improving pregnancy outcomes for patients.

Conclusions

In conclusion, this meta-analysis found that prophylactic antibiotic use effectively reduces the incidence of post-caesarean section surgical site infections and endometritis. Nevertheless, this work has certain limitations, and future research should include more studies to analyse the effects of various types of antibiotics, dosages and timing of administration on the rate of post-caesarean section surgical site infections. Overall, this work provides valuable insights for the prevention of surgical site infections following caesarean section.

Conflict of interest

The authors declare no conflict of interest.

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