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Efficacy of perioperative cefuroxime as a prophylactic antibiotic in women requiring caesarean section: a systematic review

Short running title: Cefuroxime pharmacokinetics and infection rates after CS

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Tweetable abstract (110 characters)

Inconclusive data reported on cefuroxime levels in women requiring C-Section, with no data in obese women.

Word count: 3498

Abstract

Intravenous (IV) Cefuroxime (CFX) is widely used in Caesarean Section (CS) as a prophylactic antibiotic. The objective of this systematic review to compare CFX concentration in maternal blood and adipose tissue with the incidence of surgical site infection (SSI) following IV CFX in non-obese and obese women undergoing CS. A search in Medline, EMBASE, Cochrane, Web of Science, CINHAL Plus, Scopus and Google Scholar was conducted without language or date restrictions. Published articles or abstracts reporting CFX concentration or rates of SSI following CFX IV administration in adult women requiring CS were included. Studies were screened by title and abstract. Quality of studies was assessed via the ClinPK Statement checklist (Pharmacokinetics studies), or Joanna Briggs Institute Critical Appraisal Tools (SSI studies). The Cochrane Effective Practice and Organisation of Care checklist evaluated the risk of bias (SSI studies). There were no studies evaluating CFX concentrations in obese women undergoing CS. For non-obese women, CFX plasma concentrations ranged from 9.85 to 95.25mg/L within 30-60min of administration (1500mg dose; 4 articles, n=108 women). Plasma CFX concentrations were above the minimum inhibitory concentration (8mg/L) for up to 3 hours post-dose. No studies reported on CFX concentration in adipose tissue. Reported rates of SSI were 4.7% and 6.8% after administration of a single 1500mg dose of CFX administrated after cord clamping (n=144 women). There is limited data on pharmacokinetics of CFX for CS. There were no studies that reported CFX concentrations or SSI in obese women.

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Keywords: Cefuroxime; Caesarean Section; Pharmacokinetics; Surgical Site Infection; Pregnant women; obese.

Introduction

The use of perioperative antibiotics has transformed the surgical landscape and it is standard practice for intravenous (IV) administration of a broad-spectrum antibiotic to minimise the incidence of surgical site infection (SSI). A single dose of IV prophylactic antibiotics is recommended at the time of caesarean section (CS) before skin incision(1). However, it is unclear if there is any advantage of one antibiotic over another, both in terms of choice of drug and dosage, in obese women undergoing CS. (1-4)

The prevalence of maternal obesity varies across the UK; in the East of England, the rate is 6.23%, whilst in London 3.46% are obese(5). The rate of CS in the obese population is 33.8% rising to 47.4% in class II or III obesity(6). The rate of post-CS infection is higher among obese pregnant women compared to those who are not obese (7). Women who were overweight, obese and morbidly obese had an adjusted odds ratio for infection of 1.64 (95% CI 1.22-2.1), 2.41 (95%CI 1.73-3.37) and 3.67 (95%CI 2.62-5.16) respectively (7).

The optimal doses of peri-CS antibiotics in the obese pregnant population is unclear. Several studies have investigated an increased dose of cefazolin (CFZ) (3 g) for obese pregnant women to achieve adequate antibiotic levels compared to the usual dose (2g) (8-10). Cefuroxime (CFX) is a second-generation cephalosporin, used in pregnancy due to a low incidence of side effects and a low level of protein binding (11). As with CFZ, CFX is excreted in an unaltered form by the kidneys. However, the lipophilicity of CFX is much lower than CFZ (logP values -0.167 vs. 0.3) (11-14). Therefore, higher doses of CFX may be required to achieve adequate adipose tissue levels and thus prevent SSI. The minimum inhibitory concentration (MIC) is the lowest concentration of an antibiotic that inhibits the growth of a certain strain of bacteria. The MIC of CFX for the most common causative bacteria of post-

CS infections is <1mg/L (15). Certain strains may require a higher concentration of 4mg/L or 8mg/L(16-18). In this review, MIC of 4 and 8 mg/L were chosen to evaluate appropriate CFX coverage for the intended population to ensure proper antibiotic coverage against these strains.

We sought to systematically review the literature to compare CFX concentrations in plasma and subcutaneous adipose tissue in non-obese and obese pregnant women requiring CS who were administered IV CFX peri-operatively; and to compare incidence of SSI in both groups.

Due to variations in reported data for pharmacokinetics (PK) and the infection rates, we conducted separate systematic reviews for each output parameter: (a) the CFX PK systematic review (CFX-PK) of studies on CFX concentrations in plasma and adipose tissue in pregnant women and (b) the systematic review of CFX and postsurgical infection (CFX-INF).

Scope of the Research

In March 2018, a search was conducted using the Cochrane Library's Cochrane Database of Systematic Reviews (CDSR) to identify any systematic reviews or meta-analyses addressing the search questions. There were no systematic reviews or meta-analyses evaluating the PK or rate of infection of CFX in pregnant women undergoing CS.

Reporting Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used as guidance thorough this systematic review (Appendixes: Table S7) (19).

Methods

Search Strategy and data bases

Relevant electronic databases were searched using a research strategy that was constructed using Medical Subject Headings (MeSH) terms and keywords from MEDLINE, using the term harvesting template suggested by the National Institute of Health (Appendixes: S1). The strategy was then adapted to the other databases to establish homogenous search terms in all the databases selected (Appendixes: Table S6).

The following databases were searched including all available years, with no restrictions on the language or study setting: MEDLINE/Ovid (1948 to March 2018), Embase (1974 to March 2018), the Cochrane Library's CDSR, CINAHL Plus, Scopus and Web of Science (search until March 2018 for CFX-PK, until April for CFX-INF). The search was updated in May 2019.

An additional specific search was conducted using Google Scholar, with the following phrases for each systematic review with no time restrictions. The first two-hundred titles were reviewed.

1- **CFX-PK** "pharmacokinetics of cefuroxime in pregnancy". Last searched on 31 May 2019

2- **CFX-INF** "Cefuroxime and infection in caesarean section". Last searched on 31 May 2019

The references of the included articles, were screened to identify additional articles of interest; the articles identified were then added and screened for eligibility.

Protocol and registration

The systematic reviews' protocols were registered on the International prospective register of systematic reviews (CRD42018106945 and CRD42018107192).

Relevant Articles

References yielded from the databases were exported into EndNote X8, and the duplicates were removed. The articles were then screened by titles and abstracts (Appendices Table S1). Full text of each article was examined to further assess eligibility.

Quality Assessment and Risk of Bias

The quality and risk of bias assessment were done by two reviewers (HA, HB), in case of conflicts, a discussion was made with a third reviewer for a final decision (HC).

Pharmacokinetics studies:

For the CFX-PK, the ClinPK Statement checklist was used to evaluate the quality of the methodology in each of the PK studies and risk of bias(20). This checklist was comprehensively formulated specifically for PK studies; it was used previously in a similar study (21). The checklist contained 24 items; however, 4 items (11, 12, 20 and 21) were excluded from this study because they were irrelevant to the inclusion criteria (Appendices: Table S2). If the item was applicable and existed in the study, it was scored as 2. If the item was applicable and did not exist in the study, it was scored as a 0 for that item. If the item was not applicable or there was insufficient data, the item was scored as 1. Therefore, the total score for the modified ClinPK Statement checklist used in this study was 40.

Infection studies:

Study quality for CFX-INF was assessed by the Joanna Briggs Institute (JBI) Critical Appraisal Tools (22). This tool was selected as it comprehensively assesses different types of study design. For the risk of bias, the Cochrane Effective Practice and Organisation of Care (EPOC) checklist was used (23).

Data Analysis

Whenever applicable, the mean and standard deviation (SD) was calculated for the concentration or rate of infection. Meta-analysis and statistical analysis was performed where applicable.

Results

Cefuroxime pharmacokinetics systematic review

Literature Retrieval and Study Selection

Sixty-six titles were identified from the search strategy. After removing duplicates, 48 records were screened for inclusion based on the titles and abstracts, resulting in 37 studies being excluded (Figure 1). The full text of 11 studies were reviewed to assess eligibility. Four studies fulfilled the inclusion criteria, and were evaluated for the risk of bias and quality. The PK data was then extracted for further analysis. None of those studies reported PK in obese pregnant women. No additional studies were identified that were eligible for inclusion in the updated search conducted in May 2019.

Data Extraction

The PK data was extracted from the studies directly as reported or calculated based on figures presented (e.g. extraction from the time-concentration curve using an online website (24)) (Table 1). A time-concentration curve was generated for each of the included studies (Figure 2). In the study by Bousfield et al.(25), the data provided for the maternal blood was presented as scattered data in a graph with no differentiation of each time-point for each patient, nor mean plasma concentration for each time point, based on 10 patients.

Comparison of PK findings from Cefuroxime dose in women prior to CS

The studies identified in non-obese pregnant women will be discussed in chronological order in order to evaluate the growing body of knowledge of CFX PK in CS. It should be noted that the quality of three of the studies was low. The ClinPK Statement checklist scores were 24, 25 and 31 out of 40 for the Bousfield et al.(25), Roumen et al.(26) and Holt et al.(15) studies, respectively. However, Lalic-Popovic et al.(11) scored higher, with a ClinPK Statement checklist score of 38/40 (Appendixes: Table S3). All studies were included, despite low ClinPK score, due to the paucity of data identified. This difference in quality was primarily due to the date of publication and the greater emphasis on methodology and reporting in recent times. All of the studies measured CFX concentrations using high-performance liquid chromatography, with the exception of the study by Bousfield et al.(25), in which the agar plate diffusion method was used. None of the included studies investigated CFX adipose tissue concentrations.

At time points closest to one hour, there was great variation in reported mean CFX concentrations: 9.47 mg/L, 32.55 mg/L and 74.76 mg/L in Lalic-Popovic et al.(11), Roumen et al.(26) and Bousfield et al.(25) studies, respectively (average CFX concentration was calculated from four points closer to one hour in Bousfield et al.(25)). These differences may relate to the interpatient variability or the assay methods used.

Bousfield et al.(25) investigated an IV bolus administration of 1500 mg of CFX pre-delivery in 10 pregnant women in labour who delivered vaginally and 10 pregnant women scheduled for elective CS. In the CS deliveries, the CFX injection time varied from 48 min to 337 min prior to delivery. The maternal blood was analysed for CFX quantification before delivery and at 30 min intervals until delivery.

Roumen et al.(26) evaluated the PK of CFX in 6 pregnant patients with preterm premature membrane ruptures, 4 of whom underwent CS. The authors measured CFX concentrations in the maternal plasma, amniotic fluid, umbilical cord blood and placental blood after three IV doses of 1500 mg of CFX (8 hours apart)(26). The mean± SD CFX plasma levels and were 32.55±5.20 mg/L 1 hour after the injection (for 4 patients) and 1.50±0.43 mg/L after 8 hours (for 3 patients). This study did not report the body weights of the pregnant women.

Holt et al.(15) compared two doses of CFX (750 vs. 1500 mg) in patients that had similar median body weights (71.5 vs. 74 kg, respectively). The authors reported that the CFX placental transfer during delivery was unaffected by the mother's body weight, with no information reported regarding the effect of mothers' body weight on maternal CFX concentration. Additionally, in the low dose group (750 mg of CFX), the mean sampling time was shorter than in the higher dose group (1500 mg of CFX), although this was not statistically significant: 65 minutes [95% confidence interval (CI)=48.8–96.5] vs. 37 minutes (95% CI=22.8–58.3), respectively. In a subset analysis with comparable sampling time of the low dose group (47 minutes, 95% CI=32.1–67.5), maternal blood CFX concentrations were dose dependent. The group administered the higher CFX dose (1500 mg) had significantly higher CFX concentrations in the maternal blood when compared to the subset of those administered the lower dose (750 mg) (CFX concentration 51.9 vs. 19.4, $P<0.001$) (15). Holt et al.(15) concluded that 31% of women administered the lower dose (750 mg) would have insufficient CFX concentrations against some strains of *Escherichia coli* (*E. coli*) and *Klebsiella* at 75 min post administration.

In a recent study, a dose of 1500 mg CFX pre-CS was investigated in healthy, hypertensive and diabetic pregnant women(11). Initial means of CFX plasma concentration were comparable among the three groups. The mean CFX concentration in plasma at delivery in

206 the diabetic group was significantly higher than those in the other groups (18.54±7.30 mg/L
207 in diabetic group, 9.47±6.28 mg/L in control group and 11.53±8.54 mg/L in hypertensive
208 group; $P \leq 0.05$). The diabetic group had shorter sampling time (t=56.14±31.12 min)
209 compared to the control group (t=99.28±47.76 min) and hypertensive group (t=79.57±54.04
210 min). It should be noted that the minimum CFX plasma concentration reported at time of
211 delivery were 0.9 mg/L, 2.04 mg/L and 9.85 mg/L in the control, hypertensive and diabetic
212 group, respectively. Lean body weight-normalised volume of distribution, a hypothetical
213 volume expressing the extent of drug distribution in plasma and body, of CFX was
214 significantly lower in the diabetic group than in the control and hypertensive groups
215 (537.78±91.73ml/kg in diabetic group; 1364.58±621.98 m/Kg in control group and
216 1120.92±515.24 ml/Kg in hypertensive group; $P \leq 0.05$). This difference in volume of
217 distribution may relate to the low logP value of CFX and its poor penetration into lipophilic
218 tissues.

219 ## Cefuroxime and Caesarean Section surgical site infection

220 **Literature Retrieval, Study Selection and Data Extraction**

221 Fifty-seven records were screened for inclusion based on the titles and abstracts (Figure 1).
222 The full text of 13 studies were reviewed to assess their eligibility. Three studies were
223 eligible, and they were evaluated for the risk of bias and quality. Data were extracted (Table
224 2). Included studies evaluated single dose CFX administered after umbilical cord clamping;
225 of those, 2 studies evaluated 1500 mg dosages and 1 study evaluated a 750 mg dose.
226 Further data interpretation was not manageable as the 2 studies had different comparators;
227 one study compared CFX to no antibiotic and the other to ampicillin/sulbactam
228 antibiotic(27-29). No additional studies were identified that were eligible for inclusion in the
229 updated search conducted in May 2019

Comparison of rate of infection reported in selected studies

All three studies were randomised controlled trials (27-29) Two studies had acceptable quality assessment and risk of bias evaluation, except for Kristensen et al (Appendixes: Table S4 and S5).(27). Kirstensen et al.[23] compared CFX (750mg) vs. no antibiotic, Rizk et al.(28) compared CFX (1500mg) vs. no antibiotic and Ziogos et al.(29) compared CFX (1500mg) vs. ampicillin/Sulbactam (3g). Patients were monitored for infection by medical team while patients were hospitalised for delivery until discharged in all studies (27-29); in addition to a weekly clinical and laboratory monitoring for 30-days in Ziogos et al.(29) and at a 6 weeks post-op visit in Rizk et al.(28). Reported rates of infection are listed in table 2. Kristensen et al.(27) demonstrated a clear advantage of IV CFX, where 1.96% of patients had a defined infection in the treatment group compared to 19.2% in the group that did not receive antibiotics. Although this was not replicated in the Rizk et al.(28) study, as higher dose of CFX (1500mg) was given to 59 women and no antibiotic to 61 women. The rate of SSI were 6.8% in CFX group compared to 4.9% in the "no antibiotic" groups. Finally, in the Ziogos et al.(29) study the incidence of SSI was 4.7% in 85 women who received 1500mg CFX compared to 6.6% in 91 women who received ampicillin/Sulbactam.

The mean± SD of body weights of the women in Rizk et al.(28) study were 87±23 in CFX group vs. 81±17 in control group; while in Kristensen et al.(27) it were, at operation, 74.9± 11.7 in CFX group vs. 75.6 ± 11.5 in control group. In Ziogos et al.(29), 44.7% of CFX group and 41.8% of the ampicillin/sulbactam group had a BMI of ≥ 30 kg/m^2; the authors did not report infection rate when groups are classified by antibiotic administered and BMI. In this study, the univariate analysis showed no association between the overall post-op infection or post-op SSI with BMI (regardless to the antibiotic assigned). Our robust search strategy

did not identify studies evaluating the SSI after CS in obese pregnant women who were given CFX perioperatively.

Discussion

Cefuroxime plasma and adipose tissue concentration in obese pregnant women

There was no information regarding CFX concentrations in obese pregnant women to allow comparison to non-obese women. Therefore, we evaluated plasma CFX concentrations in the non-obese population from literature identified through our search (9.85 to 95.25 mg/L within 30-60 min of administration 1500 mg CFX) with reported median CFX plasma concertation in the same population (57.2 mg/L, 82 min after administration of 2g CFZ) (8). The lipophilicity of CFX is lower than of CFZ, logP values are -0.167 and 0.3, respectively (11-14). This fact, suggests that CFX is less able to penetrate adipose tissue compared to CFZ; therefore, the concentrations of CFX theoretically suspected to be lower than the reported median CFZ adipose tissue concentrations. The median adipose concentration values for CFZ in an obese population at skin incision ranged from 4.70 to 10.7 µg/g following a 2g dose of CFZ and from 6.35 to 22.4 µg/g following a 3g dose of CFZ (4, 8-10).

One study reported plasma and adipose tissue concentration of CFX in six morbidly obese non-pregnant patients(30). The mean± SD maximum concentration (C_{max}) of CFX in plasma was 66.8±18.9mg/L at 0.60±0.22 hour post dose, while CFX C_{max} in adipose tissue was 39.2±26.4 µg/g at 1.00±0.28 hour post dose (30). Although these results show reasonable penetration of CFX into adipose tissue, the authors reported insufficient MIC against *E. Coli* at times of prolonged surgeries (30). However, due to the unique physiological changes associated with pregnancy, specifically, with plasma volume expansion, it is inaccurate practice to extrapolate these results to the pregnant cohort of women undergoing CS (31).

Rate of post caesarean section infection

The lowest rate of infection in the CFX group was reported by Kristensen et al.(27) which is interesting because patients received lower doses of CFX (750 mg) at non-elective CS. The relatively short period of follow-up (till discharge) could explain the low rate of infection(7). That this study was undertaken in 1990 could be a reflection both of the bacterial sensitivity to antibiotics and the population at the time. As previously indicated, maternal BMI has increased with time, as has antimicrobial resistance in recent times (32).

The highest rate of infection in the CFX groups was found in the study by Rizk et al.(28). Mean± SD weight reported in this study was 87±23 kg for CFX group; this study had the fewest number of patients (n=59) for CFX group compared to same group in other studies. However, in this study only patients requiring elective CS were included, in contrast to the other studies (non-elective in Kristensen et al.(27) and both elective and non-elective in Ziogos et al.(29)).

A recent systematic review highlighted the need for evaluating infection control bundle, infection control practice and intrinsic risk factors to assess their impact on post CS SSI (33). These would not have been in existence at the time the studies on perioperative CFX and infection were undertaken, and thus, none of the studies reported on the delivery of infection prevention bundles of care. We are therefore unable to comment if bundles of care impacted on the SSI rate.

To the best of our knowledge there were no studies specifically investigating the rate of infection when CFX was administrated 30-60 min before skin incision; in this review, all included studies administrated CFX after cord clamping. This is not the current practice,

since it will not allow enough time for the drug to reach the adipose tissue and provide sufficient coverage at the time of surgery (4).

A published protocol of a Danish randomised control study evaluating the rate of infection post CS was found (34); the study aimed to compare a single dose of 1500 mg CFX administered 15-60 minutes before skin incision to the same dose after cord clamping. However, the study status was withdrawn in 2013, with no patients enrolled. The exact reasons for withdrawal of the study are unknown (34).

Strengths of the Study

This research is the first systematic view that addressed CFX concentrations and rate of SSI in pregnant women requiring CS. The novelty of this search will enable further research in this field to determine appropriate dosing strategies for CFX.

Study limitations

Our search strategy could not identify one related study in CFX-INF; nevertheless, the study was not eligible(35). In CFX-PK, a total of 108 pregnant women were included in the CFX group, of whom 5 delivered spontaneously. It was considered that the type of anaesthesia and fluid administered in CS could affect the PK of drugs, specifically volume of distribution. Nevertheless, the effect of these convergences could be minor.

Conclusions

To the best of our knowledge, there is no study evaluating the effectiveness of CFX (in terms of CFX concentration or rate of infection post-CS) as a single IV dose peri-CS in obese pregnant women. Additionally, there were no studies assessing CFX concentrations in adipose tissue of non-obese pregnant women requiring CS. Evidence regarding the use of

CFX in non-obese pregnant women requiring CS is very sparse. There were no studies evaluating the rate of infection of single dose CFX administered as the current guidelines (30-60 min before skin incision). Owing to the importance of antibiotic resistance, future research should prioritise evaluating CFX concentration in adipose tissue for both non-obese and obese pregnant women to ensure therapeutic effectiveness from a pharmacological and clinical perspective.

Disclosure of interest

The Authors have no conflicts to declare.

Contribution to Authorship

HAR was involved in search planning, screening, data extraction, quality assessment, interpretation of outcome data and writing of manuscript. HB and HC were involved in search conceptualization, data extraction, quality assessment, interpretation of outcome data and editing of manuscript. KM was involved in search conceptualization, interpretation of outcome data and final editing of manuscript.

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