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1 Efficacy of perioperative cefuroxime as a prophylactic 2 antibiotic in women requiring caesarean section: a 3 systematic review

4 **Short running title: Cefuroxime pharmacokinetics and infection rates after CS**

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25 **Tweetable abstract (110 characters)**

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

28 Word count: 3498

29 Abstract

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

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

52 Introduction

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

59 The prevalence of maternal obesity varies across the UK; in the East of England, the rate is
60 6.23%, whilst in London 3.46% are obese(5). The rate of CS in the obese population is 33.8%
61 rising to 47.4% in class II or III obesity(6). The rate of post-CS infection is higher among
62 obese pregnant women compared to those who are not obese (7). Women who were
63 overweight, obese and morbidly obese had an adjusted odds ratio for infection of 1.64 (95%
64 CI 1.22-2.1), 2.41 (95%CI 1.73-3.37) and 3.67 (95%CI 2.62-5.16) respectively (7).

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

75 CS infections is <1mg/L (15). Certain strains may require a higher concentration of 4mg/L or
76 8mg/L(16-18). In this review, MIC of 4 and 8 mg/L were chosen to evaluate appropriate CFX
77 coverage for the intended population to ensure proper antibiotic coverage against these
78 strains.

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

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

87 [Scope of the Research](#)

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

92 [Reporting Strategy](#)

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

95 [Methods](#)

96 [Search Strategy and data bases](#)

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

102 The following databases were searched including all available years, with no restrictions on
103 the language or study setting: MEDLINE/Ovid (1948 to March 2018), Embase (1974 to March
104 2018), the Cochrane Library's CDSR, CINAHL Plus, Scopus and Web of Science (search until
105 March 2018 for CFX-PK, until April for CFX-INF). The search was updated in May 2019.

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

109 **1- CFX-PK** "pharmacokinetics of cefuroxime in pregnancy". Last searched on 31 May 2019

110 **2- CFX-INF** "Cefuroxime and infection in caesarean section". Last searched on 31 May 2019

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

113 [Protocol and registration](#)

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

116 [Relevant Articles](#)

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

120 [Quality Assessment and Risk of Bias](#)

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

123 [Pharmacokinetics studies:](#)

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

133 [Infection studies:](#)

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

138 [Data Analysis](#)

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

142 [Results](#)

143 [Cefuroxime pharmacokinetics systematic review](#)

144 **Literature Retrieval and Study Selection**

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

152 **Data Extraction**

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

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

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

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

177 Bousfield et al.(25) investigated an IV bolus administration of 1500 mg of CFX pre-delivery in
178 10 pregnant women in labour who delivered vaginally and 10 pregnant women scheduled
179 for elective CS. In the CS deliveries, the CFX injection time varied from 48 min to 337 min
180 prior to delivery. The maternal blood was analysed for CFX quantification before delivery
181 and at 30 min intervals until delivery.

182 Roumen et al.(26) evaluated the PK of CFX in 6 pregnant patients with preterm premature
183 membrane ruptures, 4 of whom underwent CS. The authors measured CFX concentrations
184 in the maternal plasma, amniotic fluid, umbilical cord blood and placental blood after three
185 IV doses of 1500 mg of CFX (8 hours apart)(26). The mean± SD CFX plasma levels and were
186 32.55±5.20 mg/L 1 hour after the injection (for 4 patients) and 1.50±0.43 mg/L after 8 hours
187 (for 3 patients). This study did not report the body weights of the pregnant women.

188 Holt et al.(15) compared two doses of CFX (750 vs. 1500 mg) in patients that had similar
189 median body weights (71.5 vs. 74 kg, respectively). The authors reported that the CFX
190 placental transfer during delivery was unaffected by the mother's body weight, with no
191 information reported regarding the effect of mothers' body weight on maternal CFX
192 concentration. Additionally, in the low dose group (750 mg of CFX), the mean sampling time
193 was shorter than in the higher dose group (1500 mg of CFX), although this was not
194 statistically significant: 65 minutes [95% confidence interval (CI)=48.8–96.5] vs. 37 minutes
195 (95% CI=22.8–58.3), respectively. In a subset analysis with comparable sampling time of the
196 low dose group (47 minutes, 95% CI=32.1–67.5), maternal blood CFX concentrations were
197 dose dependent. The group administered the higher CFX dose (1500 mg) had significantly
198 higher CFX concentrations in the maternal blood when compared to the subset of those
199 administered the lower dose (750 mg) (CFX concentration 51.9 vs. 19.4, $P<0.001$) (15). Holt
200 et al.(15) concluded that 31% of women administered the lower dose (750 mg) would have
201 insufficient CFX concentrations against some strains of *Escherichia coli* (*E. coli*) and *Klebsiella*
202 at 75 min post administration.

203 In a recent study, a dose of 1500 mg CFX pre-CS was investigated in healthy, hypertensive
204 and diabetic pregnant women(11). Initial means of CFX plasma concentration were
205 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 ($t=56.14 \pm 31.12$ min)
209 compared to the control group ($t=99.28 \pm 47.76$ min) and hypertensive group ($t=79.57 \pm 54.04$
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

230 **Comparison of rate of infection reported in selected studies**

231 All three studies were randomised controlled trials (27-29) Two studies had acceptable
232 quality assessment and risk of bias evaluation, except for Kristensen et al (Appendixes: Table
233 S4 and S5).(27). Kirstensen et al.²³ compared CFX (750mg) vs. no antibiotic, Rizk et al.(28)
234 compared CFX (1500mg) vs. no antibiotic and Ziogos et al.(29) compared CFX (1500mg) vs.
235 ampicillin/Sulbactam (3g). Patients were monitored for infection by medical team while
236 patients were hospitalised for delivery until discharged in all studies (27-29); in addition to a
237 weekly clinical and laboratory monitoring for 30-days in Ziogos et al.(29) and at a 6 weeks
238 post-op visit in Rizk et al.(28). Reported rates of infection are listed in table 2. Kristensen et
239 al.(27) demonstrated a clear advantage of IV CFX, where 1.96% of patients had a defined
240 infection in the treatment group compared to 19.2% in the group that did not receive
241 antibiotics. Although this was not replicated in the Rizk et al.(28) study, as higher dose of
242 CFX (1500mg) was given to 59 women and no antibiotic to 61 women. The rate of SSI were
243 6.8% in CFX group compared to 4.9% in the “no antibiotic” groups. Finally, in the Ziogos et
244 al.(29) study the incidence of SSI was 4.7% in 85 women who received 1500mg CFX
245 compared to 6.6% in 91 women who received ampicillin/Sulbactam.

246 The mean± SD of body weights of the women in Rizk et al.(28) study were 87±23 in CFX
247 group vs. 81±17 in control group; while in Kristensen et al.(27) it were, at operation, 74.9±
248 11.7 in CFX group vs. 75.6 ± 11.5 in control group. In Ziogos et al.(29), 44.7% of CFX group
249 and 41.8% of the ampicillin/sulbactam group had a BMI of ≥ 30 kg/m²; the authors did not
250 report infection rate when groups are classified by antibiotic administered and BMI. In this
251 study, the univariate analysis showed no association between the overall post-op infection
252 or post-op SSI with BMI (regardless to the antibiotic assigned). Our robust search strategy

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

255 Discussion

256 Cefuroxime plasma and adipose tissue concentration in obese pregnant women

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

268 One study reported plasma and adipose tissue concentration of CFX in six morbidly obese
269 non-pregnant patients(30). The mean± SD maximum concentration (C_{max}) of CFX in plasma
270 was 66.8±18.9mg/L at 0.60±0.22 hour post dose, while CFX C_{max} in adipose tissue was
271 39.2±26.4 µg/g at 1.00±0.28 hour post dose (30). Although these results show reasonable
272 penetration of CFX into adipose tissue, the authors reported insufficient MIC against *E. Coli*
273 at times of prolonged surgeries (30). However, due to the unique physiological changes
274 associated with pregnancy, specifically, with plasma volume expansion, it is inaccurate
275 practice to extrapolate these results to the pregnant cohort of women undergoing CS (31).

276 [Rate of post caesarean section infection](#)

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

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

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

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

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

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

305 Strengths of the Study

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

309 Study limitations

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

315 Conclusions

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

320 CFX in non-obese pregnant women requiring CS is very sparse. There were no studies
321 evaluating the rate of infection of single dose CFX administered as the current guidelines
322 (30-60 min before skin incision). Owing to the importance of antibiotic resistance, future
323 research should prioritise evaluating CFX concentration in adipose tissue for both non-obese
324 and obese pregnant women to ensure therapeutic effectiveness from a pharmacological
325 and clinical perspective.

326 [Disclosure of interest](#)

327 The Authors have no conflicts to declare.

328 [Contribution to Authorship](#)

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

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