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Use of Dicloxacillin and Risk of Pregnancy among Users of Oral Contraceptives

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Abstract: The antibiotic dicloxacillin has been shown to induce drug-metabolizing CYP enzymes to a clinically relevant extent. In this study, we investigated whether the use of dicloxacillin confers an increased risk of unwanted pregnancy among oral contraceptive users. The study population comprised Danish women falling pregnant (1997–2015) during oral contraceptive use, defined as having filled a prescription for an oral contraceptive within 120 days both before and after the estimated date of conception. Data were analysed using a case-crossover approach. For each woman, we assessed the use of dicloxacillin preceding the date of conception and during 10 previous control periods and estimated the odds ratio for such unintended pregnancies associated with the use of dicloxacillin. Among 364 women using dicloxacillin prior to conception, 40 (11%) were exposed to dicloxacillin at the time of conception, yielding an odds ratio (OR) associating use of dicloxacillin to unintended pregnancy of 1.18 (95% CI 0.84–1.65). Supplementary and sensitivity analyses generally returned similar estimates, except for a slightly increased risk among users of progestogen-only oral contraceptives (OR 1.83, 95% CI 0.63–5.34). Analysis of other antibiotics as negative controls yielded results close to unity (ORs ranging from 0.83 to 1.13). In conclusion, our study found no evidence for an increased risk of oral contraceptive failure when using dicloxacillin. However, acknowledging study limitations, we suggest the use of supplementary barrier methods during treatment with dicloxacillin, until our findings are confirmed in further studies.

In a clinical drug–drug interaction study, we recently documented that the beta-lactamase-resistant antibiotic dicloxacillin induces the activity of the major drug-metabolizing cytochrome P450 enzymes (CYP) CYP2C19, CYP2C9 and CYP3A4 to a clinically relevant extent [1]. These enzymes, especially CYP3A4, are central to the metabolism of many commonly used drugs [2], which raises the question to what extent initiation of dicloxacillin treatment may result in clinically relevant drug–drug interactions [3].

The metabolism of oestrogens and progestogens is primarily catalysed by CYP3A4 [4]. We therefore hypothesized that use of dicloxacillin could be associated with an increased risk of contraceptive failure and unwanted pregnancy among oral contraceptive users. To test this hypothesis, we conducted a case-crossover study of oral contraceptive users who became involuntarily pregnant, according to linked data from several Danish health registries from 1997 through 2015.

Material and Methods

Data sources. The nationwide Danish registries offer full coverage of the entire Danish population for most aspects of health, and unambiguous linkage between different registries can be achieved using the CPR number, a unique identifier assigned to all Danish residents [5]. In this study, we obtained data from the Register of Legally Induced Abortions, the Medical Birth Registry (Bliddal *et al.*, 2018), the Danish National Prescription Registry [6] and the Danish Patient Registry [7]. A description of these data sources is provided in Appendix A, while all definitions and codes are provided in Appendix B.

Study design. The case-crossover design is a technique that is particularly suitable for effects of transient exposures. In brief, cases' exposure at the time of their outcome is compared with the same persons' exposure at prior points in time. As the comparison is strictly within-person, all characteristics that are stable over time are eliminated as potential confounders. The exposure of interest in our study, use of dicloxacillin, is almost exclusively transient, and there is little or no carry-over of the induced CYP3A4 metabolism from dicloxacillin between exposed and unexposed follow-ups. Consequently, a case-cross-over study would be appropriate to address this research question. A full account of the properties of the case-crossover technique can be found elsewhere [8,9].

Study population. As required by the case-crossover design, the study population must consist of individuals experiencing the outcome of interest that also at some point in time was exposed to the exposure of interest [8]. To ascertain the study population, we sampled women with seemingly unintended pregnancy from two separate data sources. Using the Abortion Registry, we identified women undergoing elective abortion and from the Medical Birth Registry, we identified women giving birth (1997–2015), while for both groups requiring that they had used oral contraceptives at the time of conception. This was defined as having filled a prescription for an oral contraceptive both within 120 days before and after the estimated date of conception. We excluded women sampled from the Abortion Registry that had recorded medical reason for the abortion, for example a malformation.

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The date of ovulation leading to pregnancy, which will correspond to the time of oral contraceptive failure, was estimated based on the recorded gestational week (recorded at the time of abortion or birth). This date was used as the index date. From the 24,859 eligible pregnancies recorded in the two data sources, we identified 364 women (1.5%) who had filled at least one prescription for dicloxacillin within 168 days before their index date (see below) and, thus, entered the final study population. Of these women, 88% underwent elective abortion while 12% gave birth. A full account of the two sampling procedures is provided in Appendix C.

Exposure. Use of dicloxacillin was ascertained based on prescription fills recorded in the Prescription Registry [6]. Considering the CYP-inducing effects of dicloxacillin as the mediator of a potential association and the fact that patients typically receive 7–10 days of dicloxacillin treatment, we considered the time 'at risk' to be an interval from the time of filling a dicloxacillin prescription and 14 days onwards [10]. This assumption was subject to a sensitivity analysis (see below). We assessed the use of dicloxacillin at the index date by checking whether a prescription was filled within the last 14 days prior to the index date (i.e. date of ovulation leading to pregnancy). For each woman, we further assessed the use of dicloxacillin at 10 control dates, spread evenly from 168 days prior to the index date to 28 days prior to the index date (i.e. with 14 days of interval). In this way, the time interval from 27 to 14 days prior to index date was used as a washout and thereby disregarded. By inspecting time trends of abortions and dicloxacillin use, we ascertained that there was no clear seasonality or trend over time in any of these events and thus trend adjustment was not necessary [11].

Analyses. Using conditional logistic regression, we estimated the odds ratio (OR) associating use of dicloxacillin (at the time of conception) with unwanted pregnancy. As the case-crossover design inherently controls for time-invariant confounders [9], no further confounder adjustment was performed.

We performed several pre-planned subgroup and sensitivity analyses. Firstly, we performed subgroup analyses by type of oral contraceptive (combined *versus* progestogen-only oral contraceptives, as these might differ in their susceptibility to the putative drug–drug interaction with dicloxacillin), as well as in subgroups restricted to women sampled from the abortion and birth registry, respectively. Secondly, we repeated the analysis instead of focusing on flucloxacillin, the second-most used beta-lactamase-resistant drug in Denmark [12], which might also possess CYP-inducing properties [1]. Thirdly, we repeated the analyses for antibiotic drugs with no suspected CYP-inducing potential as negative controls (phenoxymethylpenicillin, amoxicillin and macrolides). Fourthly, two approaches were deployed to address the uncertainty in establishing the exact date of ovulation, the uncertainty regarding the duration of a clinically meaningful CYP induction [13] and the uncertainty in identifying the appropriate risk period, that is at what time during the menstrual cycle use of dicloxacillin confers an increased risk of later pregnancy. To this end, we both conducted a sensitivity analysis increasing the time at risk to 28 days (up from 14) after having filled a dicloxacillin prescription and shifted the main risk window back to −28 to −14 days before ovulation and forward to the

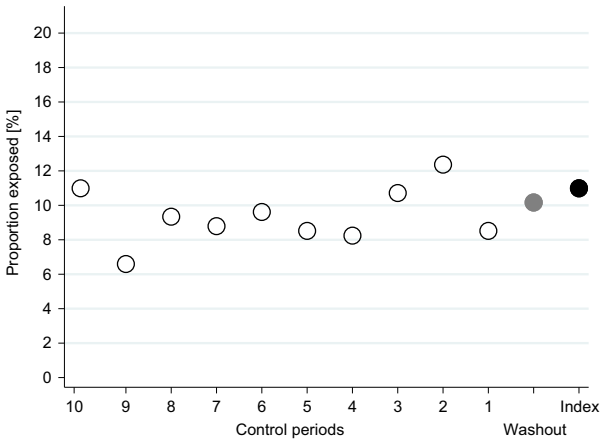

Fig. 1. The proportion of women in the study population who had used dicloxacillin in 14-day windows from the 14 days leading up to conception (index, black), the 14 days preceding the index window (washout, grey) and in 10 control periods (white), each representing a 14-day period from 168 days to 28 days prior to conception.

Table 1.

Risk of unintended pregnancy during oral contraceptive use associated with the use of dicloxacillin and other antibiotics in a case material consisting of women undergoing elective abortions.

	No. women	Exposed at time of conception	Odds ratio (95% CI)
Main analysis	364	40	1.18 (0.84–1.65)
Type of oral contraceptives			
Combination oral contraceptives	336	36	1.13 (0.80–1.61)
Progestogen oral contraceptives	28	n < 5	1.83 (0.63–5.34)
Restricted analyses			
Excluding women with recent hospitalization	364	75	1.18 (0.91–1.54)
Excluding users of CYP-inducers	356	37	1.10 (0.78–1.55)
Only including first-time abortions	353	24	0.70 (0.46–1.07)
Only women identified via abortions	320	37	1.26 (0.89–1.79)
Only women identified via births	44	n < 5	0.64 (0.20–2.10)
Other exposure windows			
Using 28-day exposure windows	364	75	1.18 (0.91–1.54)
Shifting time at risk 14 days backwards	356	37	1.10 (0.78–1.55)
Shifting time at risk 14 days forward	353	24	0.70 (0.46–1.07)
Exposure to other antibiotics			
Flucloxacillin	13	n < 5	1.00 (0.13–7.81)
Phenoxymethylpenicillin	3,260	266	0.83 (0.73–0.94)
Amoxicillin	387	39	1.13 (0.81–1.57)
Macrolides	1,991	171	0.90 (0.77–1.05)

day of ovulation and 14 days onwards (compared to the main analysis of the 14 days leading up to the date of ovulation). Fifthly, we assessed the potential influence from a decrease in sexual activity relating to infection (i.e. time-varying confounding). To this end, we restricted to women with less severe infection, by excluding women with any recorded hospital contact according to the Patient Registry within 180 days prior to the index date. Sixthly, to test whether our results were influenced by the use of other drugs with CYP-inducing activity, we removed all women with the use of such drugs within 180 days prior to and 30 days after the index date (including rifampicin, carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, barbiturates and protease inhibitors). Finally, we restricted the analysis to first-ever abortions or births.

Other. All analyses were performed with STATA v14 (StataCorp, College Station, TX, USA). The Danish Health Data Authority approved the study (approval 2015-54-0993). According to Danish law, ethical approval is not required for registry-based studies [14].

Results

The study population comprised 364 women with a median age of 23 [interquartile range (IQR) 19–29]. Of these, 40 (11%) were exposed to dicloxacillin at the time of ovulation, which was comparable to the prevalence of dicloxacillin use in the control windows (fig. 1). This yielded an overall OR associating use of dicloxacillin to unintended pregnancy of 1.18 (95% CI 0.84–1.65); the inferential statistical analyses are presented in table 1. Stratification by type of oral contraceptive (illustrated in fig. 2) returned a slightly higher OR specifically for progestogen-based oral contraceptives, although with limited statistical precision (OR 1.83, 95% CI 0.63–5.34). Using a wider exposure window of 28 days did not change the observed association (OR 1.18, 95% CI 0.91–1.54), and neither did shifting the primary exposure window back in time to 27 to 14 days before conception (OR 1.10, 95% CI 0.78–1.55). Using a primary exposure window from the date of conception and 14 days onwards yielded a slightly lower OR of 0.70 (95% CI, 0.46–1.07). Analyses for other antibiotics included as negative controls consistently returned estimates at or slightly below unity (ORs ranging from 0.83 to 1.13). The estimates for flucloxacillin had poor statistical precision, yielding an OR of 1.00 (95% CI 0.13–7.81).

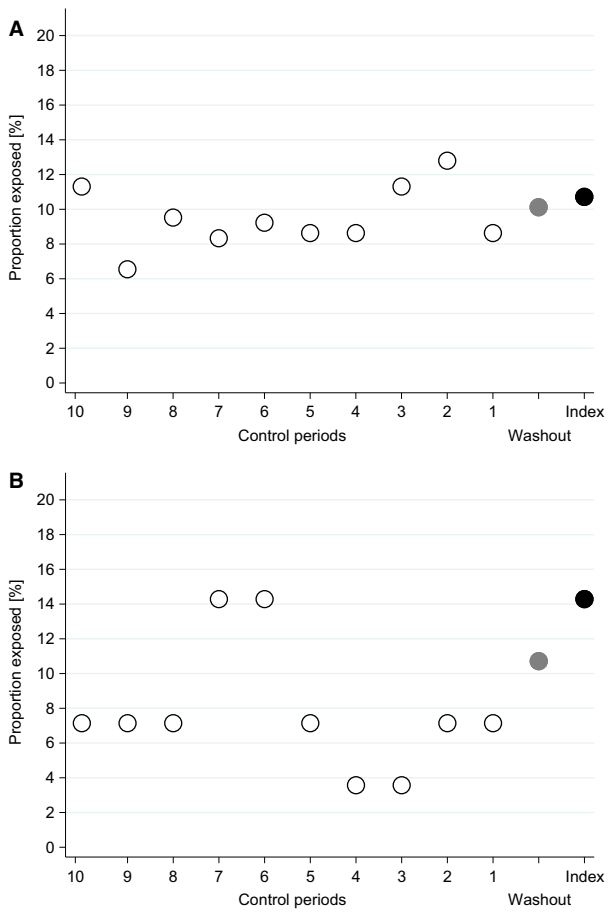

Fig. 2. The proportion of women using combination oral contraceptives (panel A) and progestogen oral contraceptives (panel B) who had used dicloxacillin in 14-day windows from the 14 days leading up to conception (index, black), the 14 days preceding the index window (washout, grey) and in 10 control periods (white), each representing a 14-day period from 168 days to 28 days prior to conception.

Discussion

In this nationwide case-crossover study, we found no evidence of a clinically meaningful increased risk of oral contraception failure associated with the use of dicloxacillin.

The primary strength of our study is the large and nationwide background material, allowing meaningful assessment of a somewhat rare drug exposure such as dicloxacillin. Further, the data sources used are extensively used for research purposes and are generally considered of high validity [6,7]. Lastly, the use of a self-controlled design handles any confounding factors that would likely distort the direct comparison between young women using antibiotics *versus* those not using these drugs, as also highlighted by others [15,16]. Some potential limitations also need to be considered. The self-controlled design only handles time-invariant patient characteristics and not time-varying confounders. Time-varying confounders in our study might include changes in sexual activity in relation to infection or temporary use of alternative means of birth control due to fear of an interaction with dicloxacillin (further discussed below). The finding of inverse associations for phenoxymethylpenicillin and macrolides suggests such effects might be present in the study. Another potential limitation is our use of proxies for unintended pregnancy. As we have applied conservative proxies, this will primarily lead to a loss of statistical power, as not all eligible women were included. However, as these proxies are unlikely to be associated with the women's use of dicloxacillin or susceptibility to the potential drug–drug interaction, we consider it unlikely that any systematic error should arise from this.

Considering the substantiated and biologically plausible pharmacological rationale underlying our hypothesis of an association between use of dicloxacillin and oral contraceptive failure [1], possible reasons for the lack of an observed association need to be considered. Several factors might bias our estimates downwards. Firstly, package inserts for oral

contraceptives warn against the potential of drug–drug interactions with antibiotics in general, while the package insert for dicloxacillin specifically warns against the potential of an interaction between dicloxacillin and oral contraceptives. This may result in some women either abstaining from intercourse or using supplementary birth control while using dicloxacillin, both of which would bias our estimates downwards. Secondly, some women might not be 'at risk' of pregnancy if no intercourse took place, regardless of any drug–drug interaction and unintended ovulation. This will bias our estimates towards unity, although this bias might be mitigated by our case-only design, restricting to women ultimately falling pregnant. Thirdly, some women might not ingest the dicloxacillin that they have filled. While the use of fill data, as compared to prescription data [17], mitigates this to some extent, such misclassification of exposure would also confer a bias towards unity. Lastly, despite that concomitant administration of dicloxacillin results in an approximate twofold increase in CYP3A4 activity [1], such may not suffice to reduce the effect of oral contraception to a clinically important extent. This will also bias our estimates towards unity. This explanation is supported by a study of the very strong CYP inducer rifampicin that only resulted in ovulation in 11 of 21 oral contraceptive users [18]. The higher OR observed among users of progestogen-only oral contraceptives might, despite limited statistical precision, also support this. The pharmacokinetics of progestogen-only oral contraceptives may be more sensitive to induction of metabolism [19], and clinical efficacy might therefore also be more susceptible to the mitigation through dicloxacillin. In summation, multiple factors might either mask or mitigate the effect of dicloxacillin. Lastly, the generally limited statistical precision of the estimates is in play, as our results are also compatible with a 50% increased risk of unintended pregnancy.

It has previously been suggested that use of antibiotics in general might influence the use of oral contraceptives [20,21]. With the exception of rifampicin, which has been shown to confer a risk of oral contraceptive failure [22], this alleged risk has largely been 'debunked' [23]. Importantly, the putative mechanism for such interactions is that of altered enterohepatic recirculation of hormones [24] and not of induction of CYP enzymes. Our null findings for other antibiotics (phenoxymethylpenicillin, amoxicillin and macrolides) are in line with both theoretical considerations [23] and a previous observational study [15]. One previous study by Koopmans *et al.* [16], however, found a weak association with oral contraceptive failure. While their study seems comparable to ours, one potential explanation might pertain to their definition of the date of conception (set as 270 days prior to date of birth) which for full-term pregnancies (up to 294 days) might result in antibiotic treatment during early pregnancy (e.g. due to urinary tract infections or unspecific symptoms) to be classified as 'causing' the pregnancy.

In conclusion, our findings did not imply an association between use of dicloxacillin and the risk of oral contraceptive failure. However, oral contraceptive failure may have severe social consequences [25,26]. Acknowledging the limited statistical power and the potential downward biases present in our study, as well as the increased risks seen specifically for progestogen-only oral contraceptives, we therefore suggest supplementary physical barrier methods be used until 2 weeks after discontinuation of dicloxacillin, at least until further studies confirm the lack of an association.

Conflict of Interests

The authors have stated explicitly that there are no conflict of interests in connection with this article.

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Appendix A

Data sources

The Register of legally induced abortions (Abortion Registry) was established in October 1973 to record and analyse medical aspects of terminations and Danish women's use hereof. Simultaneously, reporting was made compulsory for all abortions performed in Denmark. The registry was based on hospital paper records until 1994, after which it was based on coupling of records from the Danish National Patient Registry (see below) and other sources. In 1995, the electronic data in the ABR were purified and compressed so any records in the data sources of examinations, treatments and procedures within 60 days were interpreted as one termination. The registry contains information on the woman's age and residence, gestational age at termination, method of termination, date and place of termination, and legal foundation for termination. Further, data are recorded regarding indications and complications defined by ICD-10 classified diagnoses and detailed information of the performed procedures. In 2004, private hospitals and clinics were approved to perform legally induced abortions and the registry contains data from these as well.

The Danish Medical Birth Registry (MBR) contains data on all deliveries in Denmark, including both hospital-based and home deliveries. The registry in its current form was established in 1973 to monitor annual deliveries and provide data for research and national statistics. The registry was based on paper forms until the introduction of electronic reporting in 1997. The electronic registry has primarily been based on the Danish National Patient Registry supplemented with electronic birth reports from home deliveries and stillbirths. The registry contains vast amounts of information, including detailed birth data for the newborn, civil status for both parents, procedures before and during labour, and complications during pregnancy and delivery.

The Danish National Prescription Registry contains data on all prescription drugs dispensed to Danish citizens since 1995. The data include type of drug, date of dispensing and quantity. The dosing information and the indication for prescribing are not available. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by WHO.

The Danish National Patient Register contains nationwide data on all non-psychiatric hospital admissions since 1977, and both psychiatric and non-psychiatric outpatient contacts since 1995. Discharge/contact diagnoses have been coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994.

Appendix B

Codes and definitions

Diagnostic codes related to abortion	ICD-10 codes
Pregnancies with abortive outcome	O00-O08
Ectopic pregnancy	O00
Hydatidiform mole	O01
Abnormal products of conception incl missed abortion	O02
Spontaneous abortion	O03
Medical abortion (before 12 full weeks of gestation)	O04
Medical abortion (after 12 full weeks of gestation)	O05
Medical abortion (consultation permission for under-aged)	O06
Failed attempted abortion	O07
Complications after abortion	O08

Procedure codes related to abortion	Procedure codes
Medical – termination of pregnancy	BKHD
Operation – termination of pregnancy	KLCH
Operational termination of pregnancy after spontaneous or induced abortion	KMBA

Drugs	ATC codes
Oral contraceptives	
Combined oral contraceptives	G03AA-AB
Progestogen-only contraceptives	G03AC
Antibiotics	
Dicloxacillin	J01CF01
Flucloxacillin	J01CF05
Phenoxymethylpenicillin	J01CE02
Amoxicillin	J01CA04

(continued)

Appendix B.. (continued)

Drugs	ATC codes
Macrolides	J01FA
Other drugs	
Rifampicin	J04AB02
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Eslicarbazepine	N03AF04
Phenytoin	N03AB02
Barbiturates	N01AF, N01AG, N03AA, N05CA, N05CB
Protease inhibitors	J05AE

Appendix C
Sampling

Abortion Registry

The case material defined by elective abortions was sampled as follows. First, we identified a total of 301,207 abortions among 217,429 unique women in the Abortion Registry, coded as an elective abortion between 1997 and 2015. Records with no data on gestational week were excluded (0.6%; n = 1939). We required that the date of conception was during the use of oral contraceptives, by requiring that the woman had filled a prescription for an oral contraceptive both within 120 days before and after the conception (excluding 92.2%, n = 275,904). We included two further restrictions to elective abortions that were indicators of unintended pregnancy (that is, our outcome of interest). To this end, we first excluded abortions preceded (within 180 days of the abortion) by a recent spontaneous abortion, which among women undergoing elective abortion would indicate a missed abortion (0.9%; n = 216). Second, we excluded women who underwent abortion due to an identified congenital malformation (0.4%; n = 83). Lastly, we restricted the material to the first eligible abortion for each woman (excluding 5.9%, n = 1352). This yielded a final cohort of 21,713 pregnancies.

Medical Birth Registry

The case material defined by births was sampled as follows. Firstly, we identified all 685,037 unique women with 1,212,744 recorded births in the Medical Birth Registry between 1997 and 2015. We excluded births with missing gestational age (2.1%; n = 24,330). The date of the ovulation leading to pregnancy was based on the date of birth and recorded gestational age. We required that the date of conception was during use of oral contraceptives, by requiring that the woman had filled a prescription for an oral contraceptive both within 120 days before and after the conception (excluding 99.7%, n = 1,156,180). Lastly, we restricted to the first remaining birth for each woman (excluding 0.9%, n = 30). This yielded a final cohort of 3390 pregnancies.

Combining into final study population

From the 21,713 and 3390 women identified above, we removed 244 duplicates (women registered with both an eligible abortion and birth). From the resulting pool of 24,859 pregnancies, we identified 364 women (1.5%) who had filled at least one prescription for dicloxacillin within 168 days before their index date.