Post-Conceptional Exposure to Clomiphene Citrate and Congenital Malformations: A Cohort Study

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Word count:
- Abstract: 244/250
- Main text: 4532/6000
- Number of tables: 3
- Number of figures: 1
- Number of supplementary documents: 6
- Number of appendices: 1

ABSTRACT:

Introduction: Clomiphene citrate is an ovulation inductor for which inadvertent post-conceptional exposures may occur in early pregnancy. In preclinical studies, post-conceptional exposures showed a teratogenic effect in different species. In humans, to date, little is known about the outcomes of inadvertently post-conceptionally exposed pregnancies.

The objectives of our study were to assess the association between post-conceptional exposures to clomiphene citrate and major and minor congenital malformations in the offspring.

Methods: A retrospective cohort study of prospectively ascertained cases was undertaken, based on clinical data from the *Centre de Référence sur les Agents Tératogènes* (CRAT), Paris, France. Women with post-conceptional exposure to clomiphene citrate (n=309), and unexposed pregnant women (n=1236, 1:4 ratio) with prospectively collected data, known pregnancy outcome and delivery date prior to 01/02/2022, were matched by calendar year. An adjudication committee classified major and minor congenital malformations according to EUROCAT classification.

Results: Among post-conceptional exposed women, no increased risk of major malformation was found (crude Relative Risk = 0.64 95%CI [0.19; 2.15]) as compared to unexposed women. Three major and ten minor congenital malformations were reported in the exposed group. An increased risk of minor malformations was found (crude Relative Risk = 4.05 95%CI [1.70; 9.64]) although there was no specific clinical pattern.

Conclusion: Post-conceptional exposure to clomiphene citrate was not associated with an increased risk of major congenital malformations. Given potential confounding and information biases, the results about minor malformations should be interpreted with caution as no specific clinical pattern was identified.

Key Points:

- No association was found between post-conceptional exposure to Clomiphene Citrate and major congenital malformations.
- No cases of neural tube defects or hypospadias were found among the exposed group.

Declarations

The abstract of this research has previously been published in the journal Neurotoxicology and Teratology. (Volume 98, 2023, 107204, ISSN 0892-0362, https://doi.org/10.1016/j.ntt.2023.107204.(https://www.sciencedirect.com/science/article/pii/S089203622300504 5) and was presented during the 34th ENTIS meeting in August 2023.

Funding
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest
The authors declare that they have no potential conflicts of interest that might be relevant to the content of this article.

Availability of data and materials
Data can be provided by the authors upon request to the corresponding author (BM).

Ethics approval
The CRAT database has been authorized by the Commission nationale de l'informatique et des libertés (CNIL) on the 16th of May 1989 after the 89-41 deliberation process. It is recorded in the general treatment register of Assistance Publique Hôpitaux de Paris (APHP) (number 2021092110154). This study complied with general protection data regulation (GPDR) and the French regulation while conforming to the reference methodology MR-004 (number 20220516165545 in the general treatment register of APHP).

Consent for publication
Not applicable.

Consent to participate
Not relevant. Retrospective anonymized data were used.

Code availability
Code can be provided by the authors upon request to the corresponding author (BM).

Author contributions
EE, RN, BC and BM conceived and initiated the study; BC and BM supervised the study; BC and RN conducted all analyses; RN wrote the first version of the manuscript and BC and BM provided supervisory support and oversight. All authors reviewed, contributed to, and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgments
We would like to thank the Département Médico-Universitaire ESPRIT (APHP.Sorbonne) for the internship grant.
We would also like to thank the healthcare professionals over the years who have contacted the CRAT regarding clomiphene citrate exposures. The authors also wish to thank Sandrine Beurion, medical secretary for the CRAT, for her help in the retrieval of medical records.

Text

1 Introduction

Clomiphene citrate (CC) is an ovulation inductor intended to treat women diagnosed with anovulatory or oligo-ovulatory infertility who wish to conceive. It was initially marketed in 1967 by the pharmaceutical company Merrell (1). The treatment regimen is one tablet (50 mg) per day for a duration of 5 days, 2 to 5 days after the beginning of menstruation. The dose can be increased to 2 tablets per day (100 mg) when the first cycle of treatment does not lead to ovulation induction.

CC is a nonsteroidal triphenylethylene derivative consisting of a racemic mixture of two stereoisomers (enclomiphene and zuclomiphene). It acts as a selective oestrogen receptor modulator and has both oestrogen agonistic and anti-agonistic activities. As a result of the depletion of hypothalamic oestrogen receptors, it leads to an increase in gonadotrophin-releasing hormone (GnRH), which in turn release pituitary gonadotrophins, which stimulate the maturation and endocrine activity of the ovarian follicle (2). Due to its pharmacological properties, the probability of multiple pregnancies is increased when using CC. Several side effects can occur, notably, affecting the reproductive organs as well as vision impairment (3). More generally, CC related toxicity is still a matter of debate due to congenital malformations (CM) reported in animals, for example gastroschisis, cranioschisis, ablepharia, short limbs, cleft palates, hydrocephaly in rabbits (e-Table 1) and because some authors mention its potential genotoxicity (2,4) with *in vitro* increased DNA damage (5), increased micronucleus formation in rat bone marrow cells (6), increased chromosomal aberrations and micronucleus sister chromatid exchange in human lymphocytes (4).

As CC is an ovulation inductor, it is intended to be administered pre-conceptionally in order to increase chances of conception. In 2022, in France, around 150,000 boxes of CC were reimbursed to women of childbearing age (7). However, misuse of the medication may occur when menstruations are confused with possible early pregnancy bleeds. This leads to inadvertent exposures as an unknown pregnancy is already underway.

Due to preclinical data, these situations raise questions and concerns among healthcare professionals and pregnant women especially as data available for post-conceptional exposures in humans are scarce. About 250 cases of post-conceptional exposures can be identified in the literature, mostly based on small case series and case reports (8–10). These studies have no control groups and therefore do not allow for the assessment of a potential association between CC exposure during early pregnancy and pregnancy outcomes.

In this context, the main objective of our study was to assess the existence of an association between maternal post-conceptional exposure to CC and major congenital malformations (MCM) in the offspring. Our secondary objectives were to assess the existence of post-conceptional exposure to CC and minor CM and to provide a description of all congenital anomalies in both exposed and unexposed groups.

2 Methods

Reporting of the study followed the STROBE statements (11) (Appendix 1).

2.1 Study design and settings

We conducted a retrospective exposed/unexposed cohort study based on prospectively ascertained clinical data available from the French Teratology Information Service (TIS), *Centre de Référence sur les Agents Tératogènes* (CRAT), Paris. For more than forty years, the CRAT has collected data on pregnancy outcomes after exposures for which the centre was questioned for its expertise (12).

As medical data regarding pregnancies and their outcomes were collected prospectively, the outcomes (especially diagnosis of CM) were not known at the initial registration of the medical record.

2.2 Participants

Inclusion criteria were the following: prospective records of pregnancies with unknown outcomes at initial contact and completed follow-up, gestational age at initial contact prior to 22 weeks after last menstrual period (LMP) and delivery dates planned before the 1st of February 2022. Non-inclusion criteria were foetuses or children with chromosomal abnormalities and women who were exposed to known teratogens during pregnancy (medication and infections.), e-Table 2. We defined teratogenic medication following the CRAT's list of dangerous medication, regularly updated (13). These criteria applied to both the exposed and unexposed groups.

Women were included in the exposed group if they had been exposed to CC at any time between 2 and 12 weeks after LMP, at any dosage and for any duration. Women were included in the unexposed group if they had not received CC in the 3 months preceding conception or at any time during pregnancy. The unexposed group was randomly identified in the database of the CRAT. Exposed and unexposed women were matched based on calendar year of initial contact with the CRAT (within 1 year).

2.3 Variables

Definitions

Gestational age was defined in weeks of amenorrhea, from the first day of the woman's LMP. Medical abortion is defined as a termination of a pregnancy for embryo/foetal and/or maternal health reasons. Elective termination of pregnancy is the termination of a pregnancy at the woman's request for reasons other than for embryo/foetal or maternal health. Miscarriage was defined as an abortion of a foetus before 22 weeks of amenorrhea or a weight of less than 500g. A miscarriage was considered as "early" if the expulsion of the foetus had taken place before 14 weeks of amenorrhea and "late" if the expulsion of the foetus was between 14 and 22 weeks of amenorrhea (14). Stillbirth was defined as the *in utero* death of a foetus from 22 weeks of amenorrhea onwards, or weighing at least 500g (15).

Outcomes / diagnostic criteria

Congenital malformations were searched for among live- and still-births, medical abortions and miscarriages for which information regarding the presence or absence of a congenital malformation was available. Congenital malformations were not searched for in elective terminations of pregnancy and ectopic pregnancies. We defined major (primary outcome) and minor CM (secondary outcome) according to the World Health Organization, as "structural or functional anomalies occurring *in utero*, identifiable at birth or later in life" (16). The following definitions were applied: major CM are structural changes that can have important medical, social or cosmetic consequences and that usually require a medical intervention; minor CM are anomalies that can lead to structural changes not necessarily leading to significant health problems during the neonatal period (17).

The study outcomes (major CM and minor CM) were classified according to the European classification of malformations EUROCAT (European Registration of Congenital Anomalies and Twins) Guide 1.4 (18). The major or minor characterisation of each defect was assessed collegially by the CRAT's medical team who were blinded to the exposure group. The characterisation of the severity of each defect was determined after consideration of the information provided by the healthcare professionals in the follow-up questionnaire sent out two months after the expected delivery date. All disagreements were resolved by discussion to reach consensus.

2.4 Data sources

Following CRAT's procedure, when a healthcare professional first contacts the centre, the patient's socio-demographic characteristics, medical history, information on the current pregnancy and current treatments are collected. Two months after the expected delivery date, a follow-up questionnaire is sent to the healthcare professional to collect information regarding progress of the pregnancy, the birth outcome, newborn health at birth particularly the presence or absence of any CM or neonatal diseases and any relevant related medical document.

Hence for this study, for each included patient, regardless of exposure to CC, the following items were extracted from the CRAT's medical database: maternal characteristics (year of initial contact with the CRAT and gestational age at contact, maternal age during pregnancy, parity, history of CM in other offspring and consanguinity); pregnancy outcome (miscarriage, elective and medical abortions, stillbirth, ectopic pregnancy and live birth); diagnosis of any CM (with details given by the healthcare professional); neonatal characteristics for live birth (sex, birthweight and gestational age at birth).

2.5 Statistical aspects

Sample size

Based on an exposed group of 309 women (exhaustive population of women complying with eligibility criteria from the CRAT's medical database), a baseline prevalence of major CM of 2.5% in the general population according to EUROCAT (19), a relative risk to be detected of 2.5 (considered as a substantial increase) of CM with an α risk of 5%, a power of more than 80% and a 1:4 exposed/unexposed ratio, we calculated the need to include at least 1236 unexposed women in the study, randomly identified within the CRAT database.

Statistical analysis

Statistical analyses were conducted using SAS® V9.4 (SAS Institute Cary, NC). The significance level was fixed at 5%. For each variable, the number of missing values was described but not replaced. The characteristics were described in exposed and unexposed groups, especially qualitative variables were described using frequencies or percentages. The 95% confidence intervals of the prevalences of major and minor CM were

calculated using the exact method. Characteristics of women and newborn in exposed and unexposed groups were compared using chi-squared or Fisher tests.

The prevalence of malformation for each group was calculated with the denominator based on live- and still-births, medical abortions and miscarriages for which the information whether a congenital malformation was searched for was available in our database. Relative risks (RR) were calculated to assess the association between exposure and outcomes. The dependant variable was the presence or absence of a major CM (primary outcome) or minor CM (secondary outcome), and the independent variable was post-conceptional exposure to CC. Crude relative risks were calculated as the high prevalence of missing data did not allow us to perform multi-variable analyses on confounding factors of interest, however we did perform complementary sensitivity analyses for our primary and secondary outcomes adjusting for maternal age using logistic regression.

2.6 Ethics and regulatory aspects

The CRAT database has been authorized by the Commission nationale de l'informatique et des libertés (CNIL) on the 16th of May 1989 after the 89-41 deliberation process. It is recorded in the general treatment register of Assistance Publique Hôpitaux de Paris (APHP) (number 2021092110154). This study complied with general protection data regulation (GPDR) and the French regulation while conforming to the reference methodology MR-004 (number 20220516165545 in the general treatment register of APHP).

3 Results

3.1 Participants

A total of 474 prospectively collected medical records with a CC exposure were identified from the CRAT's medical database. After excluding records that did not match our inclusion criteria, our exposed group was comprised of 309 women exposed to CC at any time, between 2 and 12 weeks after LMP, at any dosage and for any duration (Figure 1). The unexposed group was comprised of 1236 women for which healthcare professionals had contacted the CRAT with a query and who matched our inclusion criteria.

3.2 Characteristics of exposed and unexposed groups

Maternal characteristics are presented in Table 1.a. Most initial contacts with the CRAT were made between 1990 and 2000 (43.4% of all medical records). Exposed women were significantly younger than unexposed women ($p = 0.0005$): women exposed to CC post-conceptionally were mostly between the ages of 25 and 29 years (39.8%) and 15.1% were 35 or older at the time of pregnancy while in the unexposed group, women were mostly between the ages of 30 and 34 years (32.4%) and 25.1% of women were 35 or older. More than half of the exposed women were nulliparous (53.3%) and had only been exposed to CC (68.6%). CC dosages were not reported due to important missing data. For unexposed women, these characteristics were 39.1% and 45.6% respectively, $p < 0.0001$ for both comparisons. The main other expositions among women exposed to CC were in descending order: sex hormones, especially progestin (32.0%); vitamins and supplements (10.5%); pituitary hormones (6.6%); antibiotics (6.1%, mainly amoxicillin); inactivated/inert vaccines (5.5%); analgesics (3.9%, mainly paracetamol); imaging tests (3.3%); anxiolytic benzodiazepines (2.8%), medication for gastrointestinal disorders (2.8%). There was no significant difference in terms of history of CM in previous pregnancies between groups ($p = 0.18$).

3.3 Pregnancy outcomes

Pregnancy outcomes and characteristics of newborns are presented in Table 1.b and 1.c respectively. The distribution of the pregnancy outcomes (live births, miscarriages, stillbirths, elective termination of pregnancies,

medical abortions, ectopic pregnancies) was not statistically different between the two groups of exposed and unexposed women (p = 0.0622).

Among live-births, no significant differences were observed for neonatal characteristics (sex, gestational age at birth and birth weight), between both groups. Specifically, regarding gestational age at birth, 12% of newborns in the exposed group were born prematurely (before 37 weeks since LMP) and 8.6% in the unexposed group (Table 1.c).

There was a total of 42 CM identified among pregnancy outcomes for which the information whether a congenital malformation was searched for among exposed and unexposed groups, respectively n=262 and n=1062 (e-Table 3). No significant crude association was found between exposure to CC at any time between 2 and 12 weeks after LMP and the occurrence of major CM (cRR = 0.64, 95% CI [0.19; 2.15]) (Table 2). However, a significant crude association was found between post-conceptional exposure to CC and an increased risk of minor CM (cRR = 4.05, 95% CI [1.70; 9.64]). These results remained stable after adjustment for maternal age for both minor CM and major CM (Table 2).

3.4 Description of congenital malformations

The 42 CM were identified among live- and still-births, and medical abortions (no congenital malformation reported among miscarriages with documented foetopathology). Among those, 22 were classified as major: three in the exposed group (prevalence of major CM 1.2% (95%CI [0.2; 3.3]) and 19 in the unexposed group (1.8% (95%CI [1.1; 2.8])), (p = 0.5967). Each foetus or child presented only one CM.

Among the foetuses exposed to CC, the three major CM were heterogeneous, and isolated (Table 3), affecting the urinary, respiratory and digestive systems namely: renal agenesis (CC exposure from 3.5 to 4.2 weeks after LMP), pulmonary adenomatosis (CC exposure from 6.2 to 6.6 weeks after LMP) and oesophageal atresia (CC exposure from 5.2 to 5.6 weeks after LMP). In the unexposed group, among the observed MCM, there was one spina bifida, one microcephaly and two hypospadias.

Twenty malformations were classified as minor: ten in the exposed group (prevalence of minor CM: 3.8% (95%CI [1.9; 6.9]) and ten in the unexposed group (0.9% (95%CI [0.5; 1.7]) (p = 0.0022).

The 20 minor CM are presented in Table 3. Similarly to major CM, among the foetuses exposed to CC these minor CM affected different organ systems and were isolated, namely: calcaneovalgus foot (CC exposure from

6 to 6.4 weeks after LMP), hip subluxation (CC exposure from 6 to 6.5 weeks after LMP), trigger thumb (CC exposure from 5.1 to 5.5 weeks after LMP), pyelic dilatation (CC exposure from 3.4 to 4.3 weeks after LMP), bilateral pyelic dilatation (CC exposure from 4 to 4.5 weeks after LMP), systolic murmur possibly due to a patent ductus arteriosus (CC exposure from 7.4 to 8.3 weeks after LMP), cryptorchidism (CC exposure from 5.1 to 5.3 weeks after LMP), vaginal mucosa protrusion *(*CC exposure from 1.5 to 2.2 weeks after LMP), testicular ectopia (CC exposure from 5 to 5.4 weeks after LMP) and pyloric stenosis (CC exposure from 3 to 3.4 weeks after LMP). A detailed description of minor and major congenital malformation cases is available in e-Table 4 (major malformations) and e-Table 5 (minor malformations).

4 Discussion

4.1 Key results

To date, our study reports the largest cohort of women (n = 309) exposed to CC post-conceptionally and followed prospectively. We did not show an association between post-conceptional exposures to CC and major CM, with prevalences of 1.2% and 1.8% in exposed and unexposed groups respectively (crude relative risk 0.64 (95%CI [0.19; 2.15])). However, a significant association was found between post-conceptional CC exposure and minor CM, although these CM did not appear to present a homogenous clinical pattern.

4.2 Strengths

A notable strength of our study besides its large size, is the fact that our data were collected in a single centre, the CRAT, rather than heterogenous case series from different centres. This allowed us to maintain a standardised approach in data collection and analysis, reducing variability that may arise from multi-centre data. Also, our study included a comparative group of pregnant women unexposed to CC from the same centre, making our study not only descriptive but also comparative unlike previous reports.

Furthermore, we chose to include only pregnancies prospectively registered before 22 weeks after LMP. This term of pregnancy is concomitant with an obstetrical ultrasound of the second trimester which is routinely performed in France for all women to screen for possible CM. This allowed us to avoid potential selection bias (i.e inclusion of foetuses with CM already diagnosed by ultrasound).

Another strength is that the clinical data used in this study were collected from healthcare professionals (physicians, pharmacists and midwives). Obtaining information directly from healthcare professionals enables easier, standardised interpretation of outcomes as well as less declarative errors that may result from the transmission of this type of information by the patients themselves (with potential memory bias).

Descriptions of CM were based on data provided by the healthcare professionals with, when necessary, additional information (imaging report, anatomopathological examinations...). The categorisation between major and minor CM were ascertained by the CRAT's medical team, blinded to the exposure, allowing an accurate and homogeneous assessment following the standardised European classification of malformations EUROCAT (19). This procedure limited the risk of classification bias.

4.3 Limitations

Nevertheless, limitations of our study should be addressed.

We recognize that cumulative incidences to represent the occurring pregnancy outcomes would have been the most adequate way to proceed in order to take into account the delayed study entry and to present the progressive occurrence of these competing events. Nevertheless, in our routine data collection, it was sometimes difficult to obtain the exact date of some pregnancy outcomes from the healthcare professional (especially for elective termination of pregnancy and miscarriage). Hence, the calculation of cumulative incidence would have led us to exclude subjects, especially for the previously mentioned outcomes, leading to inaccurate estimates. In this context we relied on the presentation of the number and proportion of pregnancy outcomes which was the least erroneous way to report these elements.

Due to the large amount of missing data, adjustment for relevant confounding factors such as alcohol and tobacco consumption during pregnancy could not be performed. Also, important amounts of missing values were observed for other types of exposures among women, particularly for example for all supplements systematically recommended to pregnant women in France (i.e. vitamin D at the beginning of the third trimester or iron supplements to treat anaemia). Moreover, other confounding factors of interest were not taken into account: periconceptional folic acid intake, diabetes, Body Mass Index (BMI) and the presence of a family history of CM as were suggested by Greenland and Ackerman, 1995 (20).

Furthermore, due to the sample size of the group of women exposed to CC, we were unable to study the association between this exposure and the occurrence of specific CM, but the observed CM did not reveal any specific malformative patterns.

Although minor malformations are in general underreported, we defined the assessment of minor congenital malformations following postconceptional CC exposure a priori as a secondary objective in our research protocol. This was decided independently of the risk of underreporting of the outcome. Furthermore, we believe that the study of minor malformations is clinically relevant. Although minor isolated malformations are "(…) structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual" (17), the occurrence of multiple minor malformations in one individual may be impactful.

Also, it was not possible to compare the group of women exposed to CC, with a group of women unexposed to CC, who were comparable in terms of infertility but exposed to other drugs indicated for infertility. This would

have allowed us to control for potential confounding factors related to the maternal condition. Nevertheless, the number of women available in the CRAT database, exposed to other infertility treatments that could have been included in the study as unexposed, was insufficient to reach the number of subjects needed to achieve a statistical power of at least 80%.

Lastly, the applicability of the study results may be limited to populations similar to the one studied due to the nationwide nature of the study. The women included in our study came from across the whole of France where the ethnical majority is Caucasian. It may therefore be difficult to compare our study populations with other kinds of ethnicities.

4.4 Previous data and interpretation

Up to now, the literature focuses on pregnancies induced by CC while data on post-conceptional inadvertent exposures is rather scarce. Our study provides relevant and substantial material on this issue.

In the past, an increased risk of major CM for pregnancies having been induced by CC was discussed and not confirmed. Indeed, some publications about pre-conceptional CC exposures reported increased risks of neural tube defects and hypospadias in children born to mothers having used CC to induce ovulation. Wu *et al*., 2006 found a positive association between pre-conceptional CC exposure and neural tube defects (ORa = 12.4, 95%CI [3.3; 46.6]). However, some elements of this study question its validity (21). Only three pregnancies exposed to CC periconceptionally resulted in neural tube defects at birth. The odds-ratio was adjusted for ethnicity only and no other confounding factors such as maternal age, folic acid supplementation, infertility or history of congenital anomalies in the family were studied.

Other studies presented further limitations in particularly incomplete adjustment for confounding factors known to increase the risk of neural tube defects and imprecise exposure times (especially differentiating pre-conceptional use of CC only from post-conceptional exposures). Significant associations between CC exposure and hypospadias were found by Meijer *et al*., 2006 (OR = 6.1, 95%CI [1.4 ; 26.3]) and Lind *et al*., 2013 (ORa = 1.9, 95%CI [1.1; 3.2]) (22,23). Nevertheless, Sørensen *et al*., 2005 did not find any positive associations between CC exposures and hypospadias (24). Besides, the meta-analysis of Auffret *et al.* 2019, data regarding peri-conceptional CC exposure did not show a statistically significant increase in neural tube defects (25) after *in utero* exposure.

A recurrent difficulty with the studies regarding periconceptional CC exposures is to obtain the precise periods at which these women were exposed. For example, the large cohort of Weller et al., is comprised of a total of 1872 women exposed to CC "from 2 months before conception through the first month of pregnancy". However, there is no mention in this report of how many exposures were solely post-conceptional. One can imagine that given the indication of the drug, most of these exposures happened in the 2 months prior to conception rather than in the month following conception (22). In our study, we chose to restrict the exposure period from 2 to 12 weeks since LMP in order to focus specifically on post-conceptional exposures during early pregnancy.

Regarding post-conceptional exposure to CC, preclinical data raised concerns related to potential teratogenic effects before human data were available (2). In animal studies, CC has been shown to exert a role on the female and foetal reproductive tract. Indeed, histological anomalies of the reproductive tract were observed in female rodents who had received post-natal administrations of CC as well as their female offspring exposed to CC *in utero* (e-Table 1c) (26–28). Embryo lethal and fetotoxic effects were observed in mice, rats and rabbits (29–32). Conversely, in non-human primates receiving doses comparable to clinical use, no anomalies were reported (33). In high doses, CC was found to be a teratogen and fetotoxic causing hydramnios and congenital cataracts in rats; gastroschisis, cranioschisis, hydrocephaly and cleft palates in rabbits; numerous anomalies in mice (e-Table 1a and 1b).

A brief description of the clinical studies in the context of post-conceptional exposure to CC is available in e-Table 6. In 1976, the pharmaceutical company Merrell published a series of 158 women who had been exposed post-conceptionally to CC among which 7 infants presented CM. Their description did not suggest a link to a specific type of malformation as the infants presented inguinal hernia; hydrocephaly, myelomeningocele, and tracheoesophageal fistula; pectus excavatum, asymmetrical head and hammer toe; unequal conjoined twins; umbilical hernia; bilaterally undescended testes; syndactyly. Furthermore, in 1996, Carlier *et al.* presented a further series of 25 women exposed to CC post-conceptionally (8). Among these the outcomes were five pregnancy terminations, three miscarriages, 16 live births including one CM (fibular agenesis). Finally, in 2014, de Vries *et al*., published a case series of post-conceptional exposures to CC between 2 and 14 weeks of gestation (9). Among 35 pregnant women for which the birth outcomes were recorded, two were miscarriages (at 9 and 21 weeks of gestation) and two congenital anomalies (one case of hydrocele for an exposure at 3 weeks of pregnancy, and one diaphragmatic hernia for an exposure at 5 weeks of

pregnancy) were reported and the other 31 outcomes were live births with no malformations. These post-conceptional studies, despite being scarce, do not indicate any patterns of CM.

Here, we did not show a significant association between post-conceptional exposure to CC and the occurrence of major CM in the offspring. Interestingly, no cases of neural tube defects or hypospadias were observed in the group exposed post-conceptionally to CC.

However, we found a significant association between the use of CC in the post-conceptional period and the occurrence of minor CM but their full description did not show any specific malformative pattern. It should also be noted that these malformations were isolated (only one minor malformation per child and no malformative syndrome). This result should be the subject of a cautious discussion. Indeed, the fact that the clinical picture of the minor CM identified in the exposed group is not homogeneous does not support the clinical relevance of this result. This result could be due to chance or explained by bias. Indeed, the results could also be related to incomplete consideration of confounding factors, especially risk factors for CM mentioned previously. We could, also for example, hypothesize a differential information bias between the groups. For example, a better identification of minor CM in the newborns of women with a history of infertility who had been exposed to CC during pregnancy, a context which could have raised concerns and led to closer examination of the newborns.

Further analyses with different unexposed groups could be useful to determine whether this association persists (for example, choosing an unexposed group of women who received ovulation induction by gonadotrophins, so that the comparison group is comparable in terms of infertility and related clinical context and outcomes).

5 Conclusion

Our study did not show an increased risk of major CM following post-conceptional exposures to CC (cRR = 0.64, 95%CI [0.19; 2.15]). Besides, we found no cases of neural tube defects or hypospadias among the exposed group. Given potential confounding and information biases, the interpretation of the increased risk of minor CM (cRR = 4.05, 95%CI [1.70; 9.64]) should be made with caution, especially since no specific pattern of CM was identified in the offspring of post-conceptionally exposed women, rendering the causality behind such an association debatable.

As they stand, our results should not be worrisome neither for women inadvertently exposed post-conceptionally to CC nor for health professionals regarding malformative risks. A collaborative study with other Teratology Information Service (TIS) centres could replicate this study and strengthen our observations by considering data from other clinical databases, with various comparison groups, and controlling for more confounding factors.

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Tables – **Post-conceptional exposure to clomiphene citrate and birth outcomes: a cohort study**

Table 1: Characteristics of women (1a), pregnancy outcomes (1.b) and characteristics of liveborn infants (1.c) in post-conceptional clomiphene citrate (CC) exposed and unexposed groups

	Exposed to CC (N = 309)			Unexposed to CC (N = 1236)			
	n	**%**	**MV: n (%)**	**n**	**%**	**MV: n (%)**	**P values**
1.a Characteristics of the women							
Time of contact with the CRAT			0 (0)			0 (0)	
before 1990	85	27.5		328	26.5		
1990-1999	134	43.4		536	43.4		0.97
2000-2009	47	15.2		200	16.2		
since 2010	43	13.9		172	13.9		
Gestational age at time of contact (weeks after LMP)			2* (0.6)			0 (0)	
< 6	56	18.2		182	14.7		
6-13	207	67.5		847	68.5		0.24
14-21	44	14.3		207	16.8		
Maternal age (years)			30 (9.7)			151 (12.2)	
< 25	31	11.1		141	13.0		
25-29	111	39.8		320	29.5		
30-34	95	34.0		352	32.4		**0.0005**
35-39	36	12.9		198	18.3		
≥ 40	6	2.2		74	6.8		
Parity †			67 (21.7)			258 (20.9)	
0	129	53.3		382	39.1		
1	93	38.4		288	29.4		**<0.0001**
≥ 2	20	8.3		308	31.5		
More than one exposure during pregnancy #			0 (0)			0 (0)	
Yes	97	31.4		673	54.4		**<0.0001**
No	212	68.6		563	45.6		
History of congenital malformations in previous pregnancies ‡			47 (15.2)			264 (21.4)	
Yes	0	0.0		15	4.5		0.18
Consanguinity			0 (0)			3 (0.2)	
Yes	1	0.3		4	0.3		1.0
1.b Pregnancy outcomes							
			0 (0)			0 (0)	
Live-birth	257	83.2		1063	86.0		
Miscarriage	30	9.7		69	5.6		
Elective termination of pregnancy	16	5.2		85	6.9		0.06
Medical abortion	3	1.0		10	0.8		
Stillbirth	1	0.3		7	0.6		
Ectopic pregnancy	2	0.6		2	0.2		
1.c Live-born infants							
Sex			19 (7.4)			65 (6.1)	
Females	124	52.1		499	50.0		0.56
Males	114	47.9		499	50.0		
Gestational age at birth (weeks after LMP)			16 (6.2)			64 (6.0)	0.43
< 32	3	1.2		9	1.9		

	32-36	26	10.8	69	6.9		
	37-39	52	21.6	216	21.6		
	≥ 39	160	66.4	705	70.6		
Birth weight (in grams)				21 (8.2)		79 (7.4)	
	< 2500g	22	9.3	68	6.9		0.21
	2500-3499g	147	62.3	621	63.1		
	≥ 3500g	67	28.4	295	30.0		

Legend: CC: Clomiphene citrate, MV: Missing values, LMP: last menstrual period
Bold values denote statistical significance at the $p < 0.05$ level.
* Two medical records for which the time of contact with the CRAT were not available and which were closely examined confirming that the date was prior to 22 weeks of gestation (prospective record definition)
† Ongoing pregnancies not included
‡ Among women having given birth previously (exposed group: 113 and unexposed group: 332)
# For the exposed group, “Yes” refers to the exposure to CC as well as another exposure, “No” refers to the exposure to CC only

Table 2: Association between congenital malformations and CC exposure among live and stillbirths, medical abortions and miscarriages

	Exposed to CC (N=262#)		Unexposed to CC (N=1062#)						
	n	%	n	%	P values	cRR	95% CI	aOR	95% CI
Major congenital anomalies									
Yes	43	1.2	19	1.8	0.60	0.64	0.19 - 2.15	0.79	0.23 - 2.74
Minor congenital anomalies									
Yes	10	3.8	10	0.9	0.002	4.05	1.70 - 9.64	4.44	1.81 - 10.93

Legend: CC: Clomiphene citrate, LMP: 95% CI: Confidence Interval at 95%, cRR: crude Relative Risk, aOR: adjusted Odds Ratio

Among pregnancies for which information on the presence or absence of congenital anomaly was available; Information on congenital malformation was missing for 13/1320 live-births, 2/8 stillbirths, 6/13 medical abortions, 95/99 miscarriages

Table 3: Major and minor congenital malformations in exposed and unexposed groups to clomiphene citrate (CC)

Organ system	N° of congenital malformation	Congenital malformation #	Exposed to CC	Unexposed to CC
Major congenital malformations				
Skeletal	#1	Polydactyly		1
	#2	Hexadactyly		1
	#3	Upper limb anomaly		1
	#4	Equinovarus foot		1
	#5	Symbrachydactyly (missing 4 fingers) + clubfoot		1
	#6	Bilateral equinovarus clubfoot		1
	#7	Craniosynostosis		1
Nervous	#8	Spina bifida and ventricular dilation		1
	#9	Microcephaly + incomplete brain development		1
Urinary	#10	Unilateral renal agenesis	1	
	#11	Duplicated kidney (regression at 6 postnatal months)		1
	#12	Suspected bilateral polycystic kidney disease		1
Cardiovascular	#13	Atrial septal defect		1
	#14	Patent ductus arteriosus		1
	#15	Large non-restrictive peri-membranous Ventricular Septal Defect and mild pulmonary stenosis		1
Respiratory	#16	Pulmonary adenomatosis	1	
Reproductive	#17 and #18	Hypospadias		2
Digestive	#19	Type III esophageal atresia	1	
	#20	Gastroschisis - Digestive atresia with perforation		1
	#21	Omphalocele		1
Other	#22	VACTERL syndrome, cord atresia with thrombosis		1
Total			**3**	**19**
Minor congenital malformations				
Skeletal	#1	Left calcaneovalgus foot	1	
	#2	Varus of the forefoot		1
	#3	Bilateral varus of the midfoot		1
Muscular	#4	Hip subluxation	1	
	#5	Nevus lipomatosus cutaneous superficialis (Hoffman – Zurhelle)		1
	#6	Trigger thumb	1	
Urinary	#7 and #8	Pyelic dilatation	1	1
	#9	Bilateral pyelic dilatation	1	
Cardiovascular	#10	Systolic murmur possibly due to a patent ductus arteriosus "(not confirmed)"	1	
	#11	Heart murmur		1
Reproductive	#12	Testicular ectopia	1	
	#13	Cryptorchidism	1	
	#14	Vaginal mucosa protrusion	1	
Digestive	#15 - #18	Pyloric stenosis	1	3
Other	#19	Short lingual frenulum		1
	#20	Tongue-tie (ankyloglossia)		1
Total			**10**	**10**

Only one minor malformation per child

Supplementary information – **Post-conceptional exposure to clomiphene citrate and birth outcomes: a cohort study**

e-Table 1 - Preclinical studies of the effects of clomiphene citrate on embryo-fetal and post-natal development

Species	**Doses**	**Exposure dates**	**Observations**	**References**
Table 1a: *In utero* exposures to CC (rodents)				
Mice	1, 2, 4 and 6 mg/kg (PO)	GD 8	Morphological, morphometric and histological anomalies	Ara and Asmatullah, 2011 (1)
Rats	2 mg/kg	GD 5-12	Cellular anomalies of the reproductive organs	McCormack and Clark, 1979 (2)0/0/0000 0:00:00 AM
	Single administrations of 2, 10, 50 or 200 mg/kg (SC)	GD 6, 8, 10, 12 and 14	Hydramnios and congenital cataracts	Eneroth *et al.*, 1970 (3)
Table 1b: *In utero* exposures to CC (non-rodents)				
Lagomorph - rabbit	7.5 mg/kg	GD 1	Gastroschisis, cranioschisis, ablepharia, short limbs, cleft palates	Morris, 1970 (4)
	20 mg/kg	GD 2	Hydrocephaly	
Non Human Primate – *Macaca mulatta*	1.5 – 4.5 mg/kg/day (PO) *(similar to clinical doses)*	1.5 mg/kg at GD 20-22 2.0 mg/kg at GD 23-25 3.0 mg/kg at GD 16-36 4.5 mg/kg at GD 23-25 or at GD 24 0.75 mg/kg at GD 17-29	No fetal anomalies	Courtney and Valerio, 1968 (5)
	0.75 – 1.5 mg/kg/day (IM)	1.5 mg/kg at GD 23-25		
Table 1c: Post-natal exposures to CC (rodents)				
Mice	20 mg SC pellets	nr	Hyperplastic epithelial of the vagina *(similar to diethylstilbestrol)*	Cunha *et al.*, 1987 (6)
	5 µg/day	PND 1-5	Histological urogenital anomalies	Gorwill *et al.*, 1982 (7)
Rats	10 to 500 µg (SC)	PND 1	Anomalies of the female reproductive organs *(similar to diethylstilbestrol)*	Clark *et al.*, 1977 (8)

Legend: GD: gestational day; PO: per os; SC: subcutaneous; IM: intramuscular; nr: not reported; PND: post-natal day

e-Table 2 - List of known teratogens during pregnancy (medications, infections) considered as non inclusion criteria

Medication
Valproic acid
Acitretin
Diethystilbestrol
Isotretinoin (oral administration) and other retinoids (alitretinoin)
Misoprostol
Mycophenolic acid
Thalidomide
Testosterone and danazol (effect only seen on female foetuses)
Mitotic inhibitors (methotrexate, cyclophosphamide…),
Chemotherapy
Lithium
Carbimazole
Vitamin K agonists (warfarine, acenocoumarol, fluindione)
Specific anti-seizure drugs (carbamazepine, phenobarbital, topiramate)
Allopurinol
Cotrimoxazole
High dose fluconazole
Trimethoprim
Infections
Rubella
Toxoplasmosis
Cytomegalovirus
Parvovirus B19
Zika

e-Table 3. Availability and missing data on congenital malformation according to pregnancy outcomes and clomiphene citrate (CC) exposure

	Exposed to CC			**Unexposed to CC**		
	Total	Number considered for analyses	Number of missing data	Total	Number considered for analyses	Number of missing data
Pregnancy outcomes considered for congenital malformations, total	291	262	29	1149	1062	87
Live-birth	257	256	1	1063	1051	12
Stillbirth	1	1	0	7	5	2
Medical abortion	3	2	1	10	5	5
Miscarriage	30	3	27	69	1	68

e-Table 4 - Major congenital malformation cases - details of pregnancy outcomes and maternal characteristics

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
Skeletal	**#1**	**Polydactyly**	**E-**	Amoxicillin: about 17 weeks since LMP Erythromycin: about 16 weeks since LMP Intravenous Pyelogram: at 2.3 weeks since LMP	Male (weight = 2,940g, height = 53 cm) born at 42 weeks since LMP by caesarean section with a good adaptation to extrauterine life (Apgar score at 5 minutes = 10). 35-year-old mother, no consumption of alcohol or tobacco. History of one elective abortion. Asthma treated by beta agonist, cholecystectomy, suspicion of pyelonephritis in the first trimester of pregnancy and breast abscess.
	#2	**Hexadactyly**	**E-**	Penicillamine: from 2 to 4 weeks since LMP	Female (weight = 3,680g, height = 51 cm, HC = 34 cm) born at 40 weeks since LMP by vaginal delivery with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 10). 32-year-old mother, no consumption of alcohol or tobacco. History of a renal-urinary lithiasis. 2 children and history of one elective abortion.
	#3	**Upper limb anomaly**	**E-**	Alprazolam: from 0.4 to 6.1 weeks since LMP	Fœtus with upper limb anomaly seen on ultrasound (no further information available). Medical abortion.
	#4	**Equinovarus foot**	**E-**	Fondaparinux: from 0 to 3 weeks since LMP	Female (weight = 3,870g, height = 52 cm) born at 41 weeks since LMP by caesarean section with a good adaptation to extrauterine life (Apgar scores at 1, 5 and 10 minutes = 10) 41-year-old mother, no consumption of alcohol or

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
					tobacco with obesity. 1 child and history of 2 elective abortions.
	#5	**Symbrachydactyly (missing 4 fingers) + clubfoot**	**E-**	Adalimumab: from 0 to 40.5 weeks since LMP Fluoxetine: from 0 to 5 weeks since LMP Salazopyrin: from 0 to 5 weeks since LMP Alprazolam: from 0 to 5 weeks since LMP	Female (weight = 3,750g, height = 50 cm, HC = 36 cm) born at 40 weeks since LMP by vaginal delivery with a good adaptation to extrauterine life (Apgar score at 1 minute = 10). 40-year-old mother, treated for depression and severe ankylosing spondylitis. 2 children and history of 1 miscarriage.
	#6	**Bilateral equinovarus clubfoot**	**E-**	Isoprinosine: from 8 to 9 weeks since LMP	Male (weight = 3,040g, height = 47 cm, HC = 34 cm) born at 42 weeks since LMP by vaginal delivery with a good adaptation to extrauterine life (Apgar scores at 1, 5 and 10 minutes = 10). 44-year-old mother, no consumption of alcohol or tobacco. Recurrent genital herpes and anemia. History of 1 medical abortion (no further information available).
	#7	**Craniosynostosis**	**E-**	Prednisone: at 39.3 weeks since LMP Paroxetine: from 0 to 15 weeks since LMP	Female (weight = 3,140g, height = 49 cm, HC = 35 cm) born at 40 weeks since LMP by vaginal delivery with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 10) 36-year-old mother, treated for depression and hypophysitis during pregnancy. 1 child.

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
Nervous	**#8**	**Spina bifida and ventricular dilation**	**E-**	Pipemidic acid: from 12 to 13.3 weeks since LMP	Fœtus with spina bifida and ventricular dilatation visible on the ultrasound. Normal karyotype. Medical abortion at 21 weeks since LMP. Mother consuming neither alcohol nor tobacco. 2 children.
	#9	**Microcephaly + incomplete brain development**	**E-**	Ketoconazole: from 2 to 3 weeks since LMP	Male (weight = 2,500g, height = 47 cm) born at 40 weeks since LMP by caesarean section with signs of hypoxia at birth. 28-year-old mother, no consumption of alcohol or tobacco. History of appendicectomy and fibroadenomas of the breast. History of 1 elective abortion.
Urinary	**#10**	**Unilateral Renal agenesis**	E+	**Clomiphene: from 3.5 to 4.2 weeks since LMP** Folic acid	Male (weight = 4,200 g, height = 52 cm, HC = 36 cm) born at 41 weeks since LMP. Good adaptation to extrauterine life (Apgar scores 1, 5 and 10 minutes = 10; 10; 10). At 13 weeks, the ultrasound showed nuchal translucency at 2 mm and a suspicion of right renal agenesis. 30-year-old mother, no consumption of alcohol or tobacco with obesity. Anxio-depressive disorder, chronic lower back pain, migraines, infertility with signs of premature ovarian failure. History of 1 miscarriage and 1 child.

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
	#11	**Duplicated kidney (regression at 6 postnatal months)**	**E-**	Atovaquone/proguanil: from 6.6 to 8.1 weeks since LMP Yellow fever vaccine	Male (weight = 3,320g, height = 49 cm, HC = 35 cm) born at 40 weeks since LMP by caesarean section. Apgar scores 1, 5 and 10 = 7; 8; 8. Ultrasound showing a unilateral renal duplicity. 30-year-old mother, consuming alcohol and tobacco.
	#12	**Suspected bilateral polycystic kidney disease** (with no further detail)	**E-**	Chemotherapy 5 years prior to this pregnancy: Adriamycin Bleomycin Dacarbazine Vinblastine sulfate	Female (weight = 3,660g, height = 51 cm, HC = 35.5 cm) born at 39 weeks since LMP by vaginal delivery, with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 10). 24-year-old mother, Hodgkin's lymphoma 5 years prior to pregnancy. 2 children and history of 1 elective abortion.
Cardiovascular	**#13**	**Atrial septal defect**	**E-**	Ionophoresis twice a week	Female (weight = 1,090g) born by vaginal delivery at 29 weeks since LMP. Apgar scores at 1 and 5 minutes = 7 and 8. Newborn transferred at birth to NICU due to prematurity. 42-year-old mother, no consumption of alcohol or tobacco, history of one elective abortion.
	#14	**Patent ductus arteriosus**	**E-**	Ketoconazole: until 2.4 weeks since LMP	Male (weight = 2,670g, taille = 47 cm, HC = 33 cm) born at 37 weeks since LMP by caesarean section, with a good adaptation to extrauterine life (Apgar scores at 1 minute = 9). 27-year-old mother, no consumption of alcohol or

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
					tobacco. History of infertility.
	#15	**Large non-restrictive peri-membranous Ventricular Septal Defect and mild pulmonary stenosis**	**E-**	Nadroparin calcium: from 0 to 39.5 weeks since LMP Rosuvastatin: from 0 to 6 weeks since LMP Escitalopram: from 0 to 6 weeks since LMP Clopidogrel: from 0 to 6 weeks since LMP Levothyroxine	Male (weight= 2,926g, height = 50 cm, HC = 34 cm) born by caesarean section at 38 weeks since LMP with a good adaptation to extrauterine life (Apgar scores at 1, 5 and 10 minutes = 9, 10 and 10). 34-year-old mother, no consumption of alcohol or tobacco, with obesity and a history of ischemic stroke, depression and hypothyroidism.
Respiratory	**#16**	**Pulmonary adenomatosis**	**E+**	**Clomiphene: from 6.2 to 6.6 weeks since LMP**	Female (weight = 1,500 g, height = 40 cm, HC = 29 cm) born by vaginal delivery at 32 weeks since LMP. Good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 9 and 10). Newborn transferred to NICU for a duration of 26 days due to prematurity and *E.coli* infection. Infant death at 1 month. Abnormal placenta. 24-year-old mother, no consumption of alcohol or tobacco. Premature delivery threat during pregnancy.
Reproductive	**#17**	**Hypospadias**	**E-**	Tetanos vaccine	Male (weight = 3,300g, height = 53 cm, HC = 35 cm) born at 41 weeks since LMP by vaginal delivery with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 9 and 10). 36-year-old mother, no consumption of alcohol or tobacco.

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
					2 children, history of 1 miscarriage.
	#18	**Hypospadias**	**E-**	Methenamine: from 2.3 to 3.2 weeks since LMP	Male (weight = 2,880g and height = 50 cm) born at 40 weeks since LMP by vaginal delivery with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 9 and 10). 30-year-old mother, no consumption of alcohol or tobacco. Use of anti-histamines and history of infertility (with no further detail). Urinary tract infection during pregnancy and cervical cerclage.
Digestive	**#19**	**Type III esophageal atresia**	**E+**	**Clomiphene: from 5.2 to 5.6 SA** Dydrogesterone	Child (weight = 3,160g, height = 52 cm, HC = 33 cm) born at 38 weeks since LMP by vaginal delivery. Apgar scores at 1 and 5 minutes = 8 and 6. Abnormal placenta and moderate respiratory distress with favorable evolution. 30-year-old mother, no consumption of alcohol or tobacco.
	#20	**Laparoschisis – (Digestive atresia with perforation)**	**E-**	Bromazepam: from 0 to 1 weeks since LMP Fluoxetine: from 0 to 1 weeks since LMP Oxazepam: at 0 weeks since LMP Tianeptine: at 0 weeks since LMP Ethinylestradiol and	Child born by vaginal delivery at 36 weeks since LMP. 29-year-old mother, no consumption of alcohol or tobacco, treated for depression. 2 children and history of 1 elective abortion.

Organ system	Number of MCM	Type of MCM	Group	Exposures	Pregnancy outcome and maternal characteristics
				norgestrel: from 0 to 15 weeks since LMP	
	#21	**Omphalocele**	**E-**	Diflucortolone: from 0 to 6 weeks since LMP	Female (weight = 3,000g) born at 42 weeks since LMP by induced labour with a good adaptation to extrauterine life (Apgar score at 1 minute = 10). Operation of omphalocele during the first hours of life. Mother consuming neither alcohol nor tobacco. 4 children.
Other	**#22**	**VACTERL syndrome, cord atresia with thrombosis**	**E-**	Fluoxetin	Twin pregnancy with *in utero* death of one of the 2 foetuses. Fœtus with fetal growth restriction. 27-year-old mother, no consumption of alcohol or tobacco.

Shaded lines refer to cases of women having been exposed to clomiphene citrate **(**CC) (E+).
Women from unexposed group are presented as (E-).
HC: Head Circumference
LMP: Last Menstrual Period
MCM: Major Congenital Malformation
NICU: Neonatal Intensive Care Unit
Not all exposure times were available explaining the absent information in some cases.

e-Table 5 - Minor congenital malformation cases - details of pregnancy outcomes and maternal characteristics

Organ System	Number of mCM	mCM	Group	Exposures	Pregnancy outcome and maternal characteristics
Skeletal	**#1**	**Left calcaneovalgus foot**	**E+**	**Clomiphene: from 6 to 6.4 weeks since LMP** Ethinylestradiol: from 4.0 to 5.2 weeks since LMP	Female (weight = 2,290g, height = 45 cm, HC = 32 cm) born at 39 weeks since LMP by vaginal birth with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 9 and 10). Fetal growth restriction detected during ultrasounds. 23-year-old mother, no consumption of alcohol and smoking 15 cigarettes per day. Infertility after first child (weight = 2,570 g).
	#2	**Varus of the forefoot**	**E-**	Rubella vaccine	Female (weight = 3,400g, HC = 34 cm), born at 40 weeks since LMP with a good adaptation to extrauterine life (Apgar scores at 1, 5 and 10 minutes = 9, 10 and 10). 30-year-old mother, no consumption of alcohol or tobacco. Cerclage during pregnancy. History of 2 miscarriages.
	#3	**Bilateral varus of the midfoot**	**E-**	Mefloquine: at about 4 weeks since LMP Progesterone: at about 36 weeks since LMP	Male (weight = 3,860g, height = 50 cm, PC: 34.5 cm) born by vaginal birth at 38 weeks since LMP with apgar scores at 1, 5 and 10 minutes = 9, 10 and 10. 35-year-old mother, no consumption of alcohol or tobacco. Premature delivery threat. History of 1 ectopic pregnancy and 2 children.
Muscular	**#4**	**Hip subluxation**	**E+**	**Clomiphene: from 6 to 6.5 weeks since LMP** Hydroxyestrone diacetate: from 6 to 6.5 weeks since LMP Nystatin: from 6 to 6.5	Female (weight = 3,300g), born at 40 weeks since LMP. 34-year-old mother, no consumption of alcohol or tobacco. History of appendicectomy, adenoidectomy and tonsillectomy and history of hepatitis A. Hospitalization for premature delivery threat.

				weeks since LMP Salbutamol Progesterone	
	#5	**Nevus lipomatosus cutaneous superficialis (Hoffman – Zurhelle)**	**E-**	Febarbamate: at 6 weeks since LMP Paroxetine: at 6 weeks since LMP Ethinylestradiol and levonorgestrel: at 4 weeks since LMP	Female (weight = 3,210g, height = 49 cm, HC = 33 cm), born at 41 weeks since LMP by cesarean section with good adaptation to extrauterine life (Apgar score at 1 minute = 10). Normal karyotype 46 XX, abnormal placenta. 32-year-old mother, no consumption of alcohol of tobacco. Depression and history of alcoholism. 2 children.
	#6	**Trigger thumb** (with no further detail)	E+	**Clomiphene: from 5.1 to 5.5 weeks since LMP** Prednisone: at 5.0 weeks since LMP Pipemidic acid Progesterone	Male (weight = 2,920g, height = 48 cm, HC = 35 cm) born at 38 weeks since LMP by caesarean section with a good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 10). 29-year-old mother, no consumption of alcohol or tobacco. Endometriosis, luteal phase defect, multinodular goiter with ankylosing spondylitis with predominantly peripheral involvement (advanced right coxitis). Lymphatic homograft received in the past. History of 1 miscarriage.
Urinary	**#7**	**Pyelic dilation**	**E+**	**Clomiphene: from 3.4 to 4.3 weeks since LMP**	Female (weight = 3,000g) born by vaginal birth at 39 weeks since LMP. 31-year-old mother. Premature birth threat.
	#8	**Pyelic dilation**	**E-**	Venlafaxine: from 0 to 25 weeks since LMP Mirtazapine: from 0 to 25 weeks since LMP Zolpidem: from 0 to 5	Male (weight = 3,080g, height = 50 cm, HC = 33.5 cm) born by vaginal birth at 35 weeks since LMP. Apgar scores at 1; 5 and 10 minutes = 2; 7; 9. Death-like appearance at birth and newborn transferred to NICU for 18 day.

				weeks since LMP Quetiapine: from 0 to 5 weeks since LMP Bupropion: from 0 to 5 weeks since LMP	Respiratory distress, hypertonia (morphine administration). 41-year-old mother, with personality disorder and gestational diabetes. History of breast cancer. Septic choc at birth, materno-fœtal infection after chorioamnionitis.
	#9	**Bilateral** pyelic **dilatation**	**E+**	**Clomiphene: from 4 to 4.5 weeks since LMP** Folic acid: from 0 to 12 weeks since LMP Ebastin	Male (weight = 3230 g, height = 47 cm, HC = 34 cm) born at 39 weeks since LMP by vaginal birth. Good adaptation to extrauterine life (Apgar scores at 1, 5 and 10 minutes = 10). Hypotonia of the renal pelvis detected at 3rd trimester ultrasound. Confirmation at 1 and 6 months old of the hypotonia of the renal pelvis (dilatation < 10 mm). 36-year-old mother, no consumption of alcohol or tobacco. History of appendicectomy and adenoidectomy. 1 child.
Cardiovascular	**#10**	**Systolic murmur possibly due to a patent ductus arteriosus "(not confirmed)"**	**E+**	**Clomiphene: from 7.4 to 8.3 weeks since LMP**	Child born at 39 weeks since LMP with Apgar scores at 1 and 5 minutes = 9 and 10. 31-year-old mother, no consumption of alcohol or tobacco. 1 child and history of 1 *in utero* fœtal death at 5 months of pregnancy.
	#11	**Heart murmur**	**E-**	Apixaban: from 0 to 5 weeks since LMP Enoxaparin sodium: from 5 to 39 weeks since LMP	Female (weight = 2,815g, height = 49.5 cm, HC = 34 cm) born by vaginal birth at 39 weeks since LMP with a good adaptation to extrauterine life (Apgar scores at 1, 5 and 10 minutes = 10). Regression of ventricular septal defect at 10 months. 24-year-old mother, no consumption of alcohol or tobacco with obesity.

					History of deep vein thrombosis with pulmonary embolisms. History of 1 elective abortion.
Reproductive	**#12**	**Testicular ectopia**	**E+**	**Clomiphene: from 5 to 5.4 weeks since LMP** Bromocriptine: from 6.3 to 8 weeks since LMP	Male (weight = 3,710g, height = 50 cm, HC = 36.5 cm) born at 40 weeks since LMP by vaginal birth, with good adaptation to extrauterine life (Apgar score at 1 minute = 10). 28-year-old mother, no consumption of alcohol or tobacco.
	#13	**Cryptorchidism**	**E+**	**Clomiphene: from 5.1 to 5.3 weeks since LMP**	Male born by vaginal birth at 40 weeks since LMP. CLOMID® administration by error (no history of infertility in this woman). 32-year-old mother, no consumption of alcohol or tobacco.
	#14	**Vaginal mucosa protrusion**	**E+**	**Clomiphene: from 1.5 to 2.2 weeks since LMP** Chlormadinone acetate: from 1.5 to 3 weeks since LMP	Female (weight = 3,180g) born by vaginal birth at 40 weeks since LMP. Good adaptation to extrauterine life (Apgar score = 10). 31-year-old mother, no consumption of alcohol or tobacco. 1 child and history of 1 miscarriage.
Digestive	**#15**	**Pyloric stenosis**	**E+**	**Clomiphene: from 3 to 3.4 weeks since LMP**	Male (weight = 1,600g) (twin pregnancy by artificial insemination by donor). Vaginal birth. Newborn transferred to NICU for 15 days. 36-year-old mother, no consumption of alcohol or tobacco. 1 child, history of 1 miscarriage and 1 elective abortion.
	#16	**Pyloric stenosis**	**E-**	Prednisone Vibramycin: from 2.3 to 3 weeks since LMP	Male (weight = 2,830g) born by vaginal birth at 39 weeks since LMP with an Apgar score at 1 minute of 10. 30-year-old mother, no consumption of alcohol and tobacco with a history of viral hepatitis at 13 weeks since LMP, anemia, von Willebrand disease and necrosis of a fibroma. 1 child.
	#17	**Pyloric stenosis**	**E-**	Ursodesoxycholic acid: from 0 to 4 weeks since	Male (weight = 4,230g, height = 52 cm, HC = 34 cm) born by cesarian section at 41 weeks since LMP. Good adaptation to

				LMP Mesalamine: from 0 to 4 weeks since LMP	extrauterine life (Apgar scores at 1 and 5 minutes = 9; 10). 37-year-old mother, no consumption of alcohol or tobacco, with disabling obsessive neurosis. 1 child.
	#18	**Pyloric stenosis**	**E-**	Insulin: from 15 to 38 weeks since LMP Clomipramine: from 18 to 38 weeks since LMP Gliclazide: from 6 to 15 weeks since LMP Acarbose: from 0 to 6 weeks since LMP Citalopram: at 18 weeks since LMP Alprazolam: occasionally around 18 weeks since LMP	Male (weight = 4,110 g, height = 51 cm, HC = 37 cm) born by cesarian section at 38 weeks since LMP. Apgar scores at 1, 5 and 10 minutes = 10). Macrosomia detected at 3rd ultrasound. Newborn transferred to NICU. 33-year-old mother, with hypertension and diabetes. 1 child.
Other	**#19**	**Short lingual frenulum**	**E-**	Griseofulvin: at 4.2 weeks since LMP	Female (weight = 3,320 g) born by vaginal birth at 40 weeks since LMP. Good adaptation to extrauterine life (Apgar scores at 1 and 5 minutes = 10). 24-year-old mother, consumption of alcohol, not of tobacco. History of chlamydia, pelvic inflammatory disease, leukorrhea and fever. During pregnancy infection to dermatophytes. 1 child.

	#20	**Tongue-tie (ankyloglossia)**	**E-**	Small bowel follow-through at 5 weeks since LMP	Male (weight = 2,300 g), born by vaginal delivery at 36 weeks since LMP. Newborn transferred to NICU for 8 days due to prematurity. 31-year-old mother, no consumption of alcohol or tobacco. 1 child and history of 1 elective abortion.

Shaded lines refer to cases of women having been exposed to clomiphene citrate (CC) (E+).
Women from unexposed group are presented as (E-).
HC: Head Circumference
LMP: Last Menstrual Period
mCM: minor Congeenital Malformation
NICU: Neonatal Intensive Care Unit

e-Table 6. Epidemiological case-series of post-conception exposures to clomiphene citrate

Population size	Pregnancy outcome	References
n = 158	7 congenital malformations	Merrell National Laboratories, 1976 (9)
n = 25	5 pregnancy terminations 3 miscarriages 16 live births including 1 congenital malformation (fibular agenesis)	Carlier *et al.,* 1996 (10)
n = 35*	2 miscarriages (at 9 and 21 weeks of gestation) 2 births with congenital malformations (hydrocele: exposure at 3 weeks, diaphragmatic hernia: exposure at 5 weeks) 31 live births with no malformation	De Vries *et al.*, 2014 (11)

*Exposures at any time between 2 and 14 gestational weeks

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