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ORAL PRESENTATIONS

107194

Risk of major congenital malformation following maternal use of oral fluconazole during the first trimester of pregnancy: a systematic review and meta-analysis

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Introduction

The risk of major congenital malformations (MCM) related to fluconazole use during the first trimester of pregnancy (T1) remains controversial as some studies suggested an increased risk of MCM. Besides, the relationship between this risk and the cumulative dose of fluconazole is unclear. The aim of this systematic review and metaanalysis (SR/MA) was to assess the association between maternal use of oral fluconazole (low dose/high dose) during the first trimester of pregnancy and MCM, overall and by type of major malformation.

Methods

A systematic review was performed by searching Medline, Embase, Cochrane database of systematic reviews, CENTRAL, ICTRP and ClinicalTrials.gov up to January 2023. We included all reports of randomized controlled trials and observational studies evaluating the association between oral fluconazole intake during T1 and the risk of adverse fetal outcomes. ROBINS-I was used for risk of bias assessment. Meta-analyses were performed using fixed and random effects model.

Results

Among 1231 references, 9 studies carried out in North America and Europe were included. These were cohort studies ($n = 7$) and case-control studies ($n = 2$), mostly performed in the general population ($n = 8$), based on medico-administrative data ($n = 7$) or on registry data ($n = 1$). Eight studies assessed the risk of any MCM. There was a wide heterogeneity in terms of categorization of fluconazole cumulative dose, definition of the outcomes and types of MCM reported (in total 39 types of MCM were reported in included studies but only half types were reported by at least two studies). While there was a significant crude association between fluconazole use during T1 (whatever the dose) and any MCM (pooled estimate OR 1.18 95%CI (1.08–1.29), $I^2 = 23.5\%$, $n = 7$ studies), this association did not remain when combining adjusted estimates (OR 1.02 95%CI (0.98–1.07), $I^2 = 0\%$, $n = 6$). Consistent pooled results were obtained when we considered cumulative doses of fluconazole, i.e. low dose (≤150 mg) and high dose of fluconazole (>150 mg).

Conclusions

This study did not show a significantly increased risk of any MCM related to fluconazole use during T1 overall and considering a low/high level of exposure when combining adjusted estimates. Meta-analyses regarding the different types of MCM are underway. Given the wide heterogeneity between studies, this report highlights the importance of the use of standardised definitions for outcomes and when possible consensual and homogeneous exposition definition to facilitate the comparison across studies and the realization of SR/MA.

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Under publication, already out of date: need for living meta-analyses. Illustration from the metaPreg project, an innovative mode of dissemination

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Introduction

Knowledge about the risks of drugs during pregnancy is continuously evolving with a significant expansion in the number of epidemiological studies available in the scientific literature. To reflect these advances and keep up to date, systematic reviews and meta-analyses need to be regularly updated. Nevertheless due to the delay in the classical publishing process, some meta-analyses are

already out of date by the time of publication. Our aim is to illustrate the inadequacy between the acceleration of research and the current system of production and dissemination of synthetic data.

Methods

Two meta-analytic approaches were used to synthesize and disseminate data regarding the risk of Proton pump inhibitors use during pregnancy: i) a classical one with static meta-analysis and publication in a peer-reviewed journal and ii) an innovative one, i.e. the metaPreg project, with living meta-analysis available on a free online platform (http://metapreg.org/). Meta-analysis methods were similar in search methods, study selection, data extraction and synthesis, except that MEDLINE and Embase were searched until September 2022 and continuously, respectively.

Results

In the classical approach, the bibliographic search was performed in September 2022 and the manuscript submitted for publication in December 2022. Due to editorial limitations, the article only considered some malformative outcomes (with at least three studies), i.e. 11 studies related to 8 malformations. The editor notified us of the decision of acceptance with comments in February 2023. We sent our answers and the publication's final decision is still awaiting. Meanwhile, the living meta-analyses are continued, investigating 33 outcomes and including 4 additional studies published during the classical publication process, leading to change of results for 4 out of 8 outcomes of interest, with a difference in statistical significance for 2 of them: major congenital malformations (pooled OR 1.10 95% CI (0.95–1.26), $n = 6$ studies; I2 = 0%; 5618 exposed pregnancies versus pooled OR 1.07 95% CI (1.02–1.13), $n = 7$ studies; I2 = 0%; 46,158 exposed pregnancies); congenital heart defects (pooled OR 1.04 95% CI (0.77–1.40), $n = 3$ studies; I2 = 6%; 3161 exposed pregnancies versus pooled OR 1.09 95% CI (1.01–1.17), $n = 4$ studies; I2 = 0%; 43,701 exposed pregnancies).

Conclusions

With the classical mode, the results are still under publication and already out of date. The unprecedented acceleration of production of new results requires a change in the ecosystem of production and dissemination of syntheses. The metaPreg project was set up in 2018 as an attempt to provide a solution to this situation, with a free online platform to provide large-scale living evidence syntheses dedicated to the risk of drug use during pregnancy.

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Lamotrigine exposure during lactation – Concentrations and effects in the newborn

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Introduction

Previous studies on lamotrigine exposure during lactation have reported conflicting results regarding effects on the infants. The aim of this study was to investigate whether use of lamotrigine during lactation can be considered safe in a clinical setting.

Methods

Clinical effects in infants exposed to lamotrigine through lactation were analyzed. This retrospective cohort included mother-infant dyads participating in a clinical follow-up program in Stockholm 2011–2021. Main outcomes were infant lamotrigine serum concentration. Secondary outcomes were ratio between the infant and mothers' serum concentrations, infant growth, proportion of breastfeeding, advice on reducing breastfeeding and level of liver enzymes in the infant.

Results

In total 47 infants with a mean gestational age of 39 + 5 weeks and mean birth weight of 3517 g exposed to lamotrigine through human milk were included. Two thirds of the infants were exclusively breastfed from birth to >2 months of age. A total of 101 follow-up visits were included. Lamotrigine concentrations lower than the limit of detection at <5μmol/l were assessed as half of the lower limit, 2.5μmol/l. Mean infant lamotrigine serum concentration was 4.98μmol/l. Mean infant/mother ratio for lamotrigine was 0.27. The lamotrigine concentrations in infants were slightly higher in the first month of life, average 5.03 μmol/l, mean 2.50 μmol/l, with lower concentrations thereafter, average 4.93 μmol/l, mean 2.50 μmol/l at over one month of age. Around a fifth of the exposed infants reached a therapeutic serum level of lamotrigine. One infant presented with somnolence and absence attacks, symptoms likely linked to the drug exposure, and the infant recovered when breastfeeding was discontinued. Elevated levels of alanine aminotransferase (ALT) were seen in three infants, 14% of the exposed infants where liver enzymes were measured and the maximal ALT values were seen at age two to five months. All aspartate transaminase (AST) levels were within normal range, <1.4 μkat/l. The elevation of ALT was moderate and transient, with a maximum ALT value of 2.03 μkat/l in one infant (reference <0.85 mikrokat/l) which normalized at 10 months of age. At the visit at two weeks of age four infants (20%) had not reached their birth weight, and three infants had inadequate weight gain at the later follow-up visits. Four mothers were advised to reduce breastfeeding, one due to the absence attacks described above, two due to elevated infant lamotrigine serum concentrations and one was advised to reduce breastfeeding and try formula when the infant was showing signs of gastroesophageal reflux.

Conclusion

Lamotrigine exposure during lactation can be considered safe in a clinical setting with a strict follow-up of the infants. The follow-up program ensures that parents are well-informed regarding the follow-up and the potential risks of lactation during treatment with lamotrigine. Serious adverse events are uncommon but the effect of lamotrigine exposure on liver enzymes needs further investigation.

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107197
Placental passage of lithium and neonatal complications after lithium exposure

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Introduction

The neonatal effects after fetal exposure to lithium are scarcely studied. The aim of this study was to assess placental transfusion of lithium and the relation between infant serum lithium concentrations and clinical effects in the exposed infants.

Methods

This retrospective study focused on women treated with lithium during pregnancy and their newborn infants, born between 2006 and 2021 in Stockholm, Sweden. Information on serum lithium concentrations in mothers and infants at delivery and infant clinical status was obtained from medical records. Placental passage was assessed by relating lithium concentration measured in cord blood to maternal serum concentration. Neonatal complications were compared between a high exposure group (HEG, infant serum lithium concentrations ≥0.6 meq/l) and a low exposure group (LEG, <0.6 meq/l).

Results

A total of 25 infant-mother dyads consented to be included in the study. The mean infant/mother ratio of lithium serum concentrations was 1.1 in both groups, with a strong correlation between the maternal and infant lithium concentrations, Pearson's R 0.87, $p < 0.01$. There was no statistically significant difference between the HEG and LEG in APGAR scores, birth weight, gestational age or the length of the hospital stay. The admission rate to neonatal ward was 29% in HEG vs 11% in LEG ($p = 0.55$), need of neonatal resuscitation 29% in HEG vs 17% in LEG ($p = 0.60$), and the rate of any neonatal complications 86% in HEG vs 56% in LEG ($p = 0.36$). The length of stay at the neonatal ward for the admitted infants was 1–2 days in both groups.

Conclusions

Our study confirms that lithium passes freely across the placenta with lithium concentrations equilibrated between maternal and fetal circulations. Thus, maternal lithium therapy does result in a considerable lithium exposure to the fetus. In our study, neonatal morbidity was common amongst the exposed infants. A tendency towards more complications was seen in the HEG, but without a statistically significant difference between the groups, potentially due to the small sample size. All symptoms were considered mild and transient. This study suggests that lithium use, when strictly monitored and with serum lithium levels within the therapeutic interval, can be safely continued during pregnancy when needed. The fact that the neonatal morbidity seemed lower in the LEG supports the recommendation of keeping the maternal lithium concentration as low as possible towards the end of the pregnancy. A limitation of the study is the frequent polypharmacy with other psychotropic drugs amongst the women, potentially overestimating the neonatal morbidity connected to fetal exposure to lithium. Even though this cohort was the largest single cohort studied to date, it was still too small to find a statistically significant correlation between the serum lithium concentrations and the clinical symptoms. Larger studies are needed to confirm the correlation.

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IMI ConcePTION core data elements for pregnancy pharmacovigilance studies using primary source data collection methods

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Introduction

The Innovative Medicines Initiative's ConcePTION project aims to develop a series of operational recommendations to optimise and standardise data collection techniques, analysis, and reporting in pregnancy pharmacovigilance (PregPV) research to improve data harmonisation and evidence synthesis capabilities. Here we describe the development of a reference framework of core data elements (CDEs) recommended for collection in primary source PregPV studies.

Methods

The recommendations were developed by an expert working group highly experienced in operating PregPV monitoring systems in industry, academic or clinical settings. Candidate CDEs were identified through a scoping review of data collection tools and data catalogues from established PregPV systems. Multiple rounds of open discussion and debate were undertaken to assess the suitability of including the candidate data elements within the CDE recommendations framework. For inclusion, candidate data elements needed to provide direct or indirect information that could be used to generate statistics for the prevalence of adverse pregnancy, fetal or neonatal outcomes, or longer-term childhood health and neurodevelopment. Data elements relating to co-variable risk factors for adverse outcomes were also included. Each of the CDEs included in the framework were defined and suggested data formats were developed. Selected data elements were classified as essential if it was judged that outcome statistics could not be generated without their collection. The recommendations provided in the framework represent a consensus opinion of the expert working group.

Results

The CDE recommendations framework was produced after 20 rounds of revisions and is comprised of 98 individual data elements, arranged into 14 tables. 63 data elements were identified as essential

for studying the risk of adverse pregnancy, fetal or infant outcomes, and 71 data elements were considered essential for studying longer-term childhood outcomes. The CDE items relate to administrative or data collection functions, maternal and paternal health, obstetric details and complications, medication exposure, pregnancy outcome, fetal outcome, and longer-term child health and neurodevelopment. Interactive tables which can be searched and filtered are publicly available via the ENTIS website (www.entis-org.eu/cde).

Conclusions

Through the publication and promotion of these recommendations, we aim to provide a reference framework for researchers developing primary source data collection tools for PregPV. Successful uptake of the recommendations may help to improve the availability and quality of evidence-based information regarding the safety of medication use in pregnancy.

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107199
Monitoring of lamotrigine concentrations in five breastfed newborns

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Introduction

Lamotrigine is a first-line treatment for epilepsy/bipolar disorder during pregnancy based on extensive published data, which could suggest that breast feeding under lamotrigine does not cause problems for the breastfed child. However, current data on breastfeeding shows marked inter-individual variability and substantial exposure of the breastfed child which could lead to the occurrence of adverse effects. Clinical monitoring of breastfed children is thus required, as well as careful monitoring of lamotrigine serum levels, liver enzymes and/or complete blood counts.

Methods

We present a prospective case series of five mother/child pairs. Children were exposed to lamotrigine during pregnancy and breastfeeding and followed-up for up to 15 months in the oldest case. Breastfeeding duration was from 3 weeks to 4 months, maternal doses were 50–400 mg/day for epilepsy ($n = 3$) or psychiatric indication ($n = 2$).

Results

Children had an average of 5.2 samplings (range 3–7) during their first six months of life, one at birth, reflecting in utero exposure, another one month later and thereafter depending on the value of the last result. Except for one child (maternal dose 50 mg/d), all infants had one or more plasma level dosages corresponding to a therapeutic concentration in adults (range: 1.2–2.9 mg/l; mean = 2.2 mg/l) more than one month after delivery. Two children had at least one plasma level expected in an adult treated for epilepsy (2.8 and 2.9 mg/l). Plasma levels decreased in each case with a switch to mixed feeding or maternal dose reduction. Interindividual differences were also observed in this series. For example, a five-week-old child presented with a plasma level of 2.2 mg/l and a maternal dose of 150 mg/d, that decreased to 1.6 mg/l after 6 weeks of maternal lamotrigine dose of 100 mg/d. Serum levels of lamotrigine in another child, 2 months old, were 2.8 mg/l for a maternal dose of 400 mg/d, that decreased to 1.2 mg/l after one month of gradual weaning and under detection one month later. No adverse effects were observed, but a tendency to show hyperextend backwards and chewing was observed in a one 10 week old child and another child developed transient neutropenia and increased transaminases (although etiology has not yet been ruled out).

Conclusions

Although adverse events are rarely reported, lamotrigine has a variable but always high Relative Infant Dose (9.2 to 18.3%), reflecting high exposure of the child, as confirmed by our case series. It is necessary to specify the sampling time according to the mother's intake and the child's sucking to obtain precise results. Close follow-up appears to be necessary, but raises questions about taking numerous samples in very young children. Moreover, the longterm consequences of infant exposure to an antiepileptic at therapeutic levels are unknown.

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107200
Use of medication for gastroesophageal reflux during pregnancy and adverse birth outcomes

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Introduction

Symptoms of gastroesophageal reflux disease occur in approximately half of all pregnancies. Consequently, many pregnant people use over-the-counter medication, including antacids and proton pump inhibitors (PPIs), to treat these symptoms, but data on the safety of use during pregnancy are scarce. Therefore, we aimed to determine whether calcium-based antacid and PPI use during pregnancy is associated with selected adverse birth outcomes.

Methods

In this prospective cohort study, we included 9153 pregnancies enrolled in the PRIDE Study (2012–2019) and The Dutch Pregnancy Drug Register (2014–2019). Validated web-based questionnaires and obstetric records were used to collect data on exposures (use of calcium-based antacids and PPIs, including details on timing of use and dosage), outcomes (preterm birth, low birth weight, small-for-gestational-age [SGA], and low Ponderal Index), and confounders.

We fitted crude and weighted modified Poisson regression models and Cox proportional hazard models for use of calcium-based antacids and PPIs before gestational day 161 and time-varying exposures after gestational day 160, respectively, using inverse probability of treatment weighting.

Results

Calcium-based antacid use before gestational day 161 was not associated with any of the outcome measures, but use after gestational day 160 was associated with a decreased risk of low birth weight (hazard ratio [HR] 0.5, 95% confidence interval [CI] 0.3–0.9) and SGA (HR 0.6, 95% CI 0.4–0.8). We observed increased risks for use of high-dose PPIs before gestational day 161 and preterm birth (risk ratio [RR] 2.3, 95% CI 1.2–4.4) and low birth weight (RR 2.9, 95% CI 1.4–6.0), whereas any PPI use after gestational day 160 was associated with low birth weight (HR 2.0, 95% CI 1.2–3.6), SGA (HR 1.5, 95% CI 1.0–2.3), and low Ponderal Index (HR 2.3, 95% CI 1.3–4.2).

Conclusions

Use of calcium-based antacids seemed safe during pregnancy with regard to birth outcomes, with associations that may be explained by reverse causation. PPI use in early and late pregnancy, however, was associated with multiple adverse birth outcomes including preterm birth, low birth weight, SGA and low Ponderal Index, warranting restraint use of this over-the-counter medication during pregnancy.

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107201

Neurodevelopmental outcomes in children and adults with Fetal Valproate Spectrum Disorder: A contribution from the ConcePTION project

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Introduction

Fetal Valproate Spectrum Disorder (FVSD, ICD-11 LD2F.03) is a condition that can occur following exposure to Sodium Valproate in utero and consists of a recognisable pattern of physical and neurodevelopmental impairments. Existing research has primarily focused on younger children and has not specifically investigated neurodevelopmental outcomes in individuals with a formal diagnosis of FVSD. This study describes the neurodevelopmental phenotype of older children and adults with FVSD in order to promote optimal diagnostic practice and clinical management.

Methods

In this cross-sectional study, 90 caregivers were recruited and completed a series of questionnaires regarding the neurodevelopmental outcomes of 146 individuals aged 7–37 years ($M = 18.1$), including individuals with a formal diagnosis of FVSD ($n = 99$), individuals exposed to Valproate but without an FVSD diagnosis ($n = 24$), and individuals not exposed to Valproate ($N = 23$). The mean dose of valproate exposure for individuals with an FVSD diagnosis was 1470 mg/day.

Results

Individuals with a diagnosis FVSD showed significantly higher levels of moderate (43.4%) and severe (14.4%) cognitive impairment than other groups ($p = 0.003$). This group also required significantly higher levels formal educational support (77.6%, $p < 0.001$), and displayed poorer academic competence than individuals not exposed to Valproate ($p = 0.001$). A large proportion of individuals with an FVSD diagnosis were reported to be at risk for overall psychosocial problems (62.6%), as well as specific internalising (64.3%) and attention (55.5%) problems. However, rates of externalising problems were lower than in the non-exposed group. High rates of neurodevelopmental disorders, particularly autistic spectrum conditions (62.9%) and intellectual disability (51.0%) appear to be particularly central to the FVSD phenotype. Specific and significant sensory difficulties were also reported in 80.6% of FVSD diagnosed individuals. There was no evidence of a statistical dose-dependent effect, likely due to the high mean dose of exposure having a uniformly negative impact across the sample. Individuals with FVSD had required a significant number of health and child development services.

Conclusions

Children and young adults with a diagnosis of FVSD are at an increased risk of a range of altered neurodevelopmental outcomes, highlighting the need for a multidisciplinary approach to clinical management across the lifespan.

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107202

Artificial intelligence for determination of medication compatible with breastfeeding

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Introduction

Artificial intelligence is becoming a useful tool in clinical treatment. We have previously published an explainable machine-learning algorithm for drug use in pregnancy based on multimodal data and suggest an orthogonal ensemble for modeling multimodal data. The model was trained with a set of labeled drugs and processed over 100,000 textual responses collected by a large teratology information service. Structured textual information is

incorporated into the model by applying clustering analysis to textual features. Many medications that are not allowed during pregnancy are also not compatible with breastfeeding. Nevertheless, there are differences and there are medications that are not compatible with breastfeeding but are allowed during pregnancy, and vice versa. The current study aims to train the algorithm on lactation-related questions. In addition, it will be used to suggest whether drugs without any data are compatible with breastfeeding.

Methods

In this study, we have developed multimodal machine-learning models for the prediction of medication safety during lactation. We focused our efforts on tabular and molecule-related features to train ensemble-based machine-learning models. We evaluated our models using a variety of evaluation schemes.

Results

The area under the receiver characteristic curve (AUC) of 0.921 for cross-validation was applied to a dataset of 270 manually labeled drugs. We also report an AUC of 0.963 for evaluating our results on a second, independent dataset, labeled by a second group of experts. On these two datasets, the highest performing model uses pregnancy safety and tabular, handcrafted drug features to predict lactation safety. Later, we collected another dataset, consisting of 14 drugs, whose lactation safety is not aligned with pregnancy safety; we obtained an AUC of 0.906 on this dataset for a model trained with tabular, handcrafted, and molecule-based features only. For the latter model, the most contributing features identified through SHAP analysis are antineoplastic agents (increased risk), anti-infective agents (decreased risk), and narrow therapeutic drugs (increased risk). For example, Liraglutide (AUC = 0.048) and rosuvastatin (AUC = 0.401) demonstrate the strengths and limitations of the model.

Conclusions

Our models can be used to enable intelligent decisions when the available data is scarce.

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107203
Expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies

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Introduction

Exposure *in utero* to certain medications can disrupt processes of fetal brain development, leading to a continuum of neurodevelopmental difficulties. Recognizing the deficiency of neurodevelopmental investigations within pregnancy pharmacovigilance, an international Neurodevelopmental Expert Working Group (NEWG) was convened to achieve consensus regarding the core neurodevelopmental outcomes and optimization of methodological approaches.

Methods

A modified Delphi study was undertaken based on stakeholder and expert input. Stakeholders (patient, pharmaceutical, academic and regulatory) were invited to define topics, pertaining to neurodevelopmental investigations in medication-exposed pregnancies. Experts were identified for their experience regarding neurodevelopmental outcomes following medicinal, substances of misuse or environmental exposures *in utero*. Two questionnaire rounds and a virtual discussion meeting were used to explore expert opinion on the topics identified by the Stakeholders.

Results

Twenty-five experts, from 13 countries and professionally diverse backgrounds took part in the development of 11 recommendations. Recommendations focus on the importance of neurodevelopment as a core feature of pregnancy pharmacovigilance, when studies should be undertaken and a core set of distinct but interrelated neurodevelopmental skills or diagnoses which require investigation. Investigations should start in infancy with an extended period of investigation into adolescence, with more frequent sampling during rapid periods of development. Measurement of neurodevelopmental skills and symptoms are optimized through a standardized approach to assessment by blinded skilled assessors. Additionally, recommendations are made regarding comparator groups, exposure factors, a core set of confounding and mediating variables, attrition, reporting of results and the required improvements in funding for potential later emerging effects.

Conclusions

An improved focus on neurodevelopmental outcomes is required in pregnancy pharmacovigilance and should be guided by these 11 recommendations. It is unlikely that all recommendations can be met by a single study, and therefore a triangulation of evidence from different study designs is required.

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107204

Post-conceptional exposure to clomiphene citrate and congenital malformations: A cohort study

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Introduction

Clomiphene citrate (CC) is an ovulation inductor widely used among women of childbearing age. However, inadvertent post-conceptional (PC) exposures may occur in early pregnancies when gestational status is not already known. These situations raise concerns among health professionals because preclinical studies report a teratogenic effect of CC. However, in humans, publications on PC exposures are scarce (around 250 cases) and come from small case series and case reports. Furthermore, neural tube defects and hypospadias have been suggested as birth defects induced by CC. The objectives of our study were to assess the association between maternal PC exposure to CC and the occurrence of major (MCM, main objective) and minor congenital malformations (mMC, secondary objective).

Methods

We conducted a retrospective cohort study, based on the clinical data from *Centre de Référence sur les Agents Tératogènes* (CRAT), Paris, France. Women with a PC exposure to CC and unexposed women (1:4 ratio) were matched on the year of referral. Eligibility criteria for both groups were: prospective collection of data, known birth outcome and delivery date before 01/02/22. The major or minor characterisation of each congenital malformation according to EUROCAT was established by an adjudication committee run by CRAT's medical team (teratology experts blinded to the exposure group). Associations were assessed using crude Relative Risks (cRR).

Results

We included 309 women exposed to CC post-conceptionally and 1236 unexposed pregnant women. Exposed women were significantly younger than unexposed women ($p = 0.0005$) and more than half of them were nulliparous (53.3% vs 39.1%). No increased risk of MCM was found (cRR = 0.80 95%CI[0.28; 2.32]) among post-conceptionally exposed women. Four MCM (trigger thumb, renal agenesis, pulmonary adenomatosis and oesophageal atresia) and nine mCM (calcaneovalgus foot, hip subluxation, pyelocalyceal dilatation, hypotonia of the renal pelvis, patent ductus arteriosus in a preterm newborn, cryptorchidism, vaginal mucosa prolapse, testicular ectopia and pyloric stenosis) were reported in the exposed group. An increased risk of mCM was found (cRR = 3.60 95% CI [1.48; 8.78]) although these did not appear to present a specific clinical pattern.

Conclusions

Our study did not show an increased risk of MCM for post-conceptional exposures to CC with no cases of neural tube defects or hypospadias identified among the exposed group. Given potential confusion and information biases, the results of an increased risk of mCM should be interpreted with caution. Furthermore, no specific pattern of mCM was identified. As they stand, our results should not be worrisome neither for women exposed post-conceptionally to CC nor for health professionals.

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107205

A comparison of self-reported offspring's congenital birth abnormalities with data provided by general practitioners; data from the Dutch Pregnancy Drug Register

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Introduction

The presence of a congenital abnormality in a newborn is often one of the primary outcomes in drugs-safety studies. But how valid and accurate is the information on congenital abnormalities when provided by the mother herself (i.e. participants of the study)? The aim of this study is to validate the information on congenital abnormalities reported by participants in our cohort study with information available among their general practitioners (GPs).

Methods

Of all participants included in the Dutch Pregnancy Drug Register with a singleton livebirth and who provided consent, the GPs were approached. GPs were requested to provide information on possible congenital abnormalities of the offspring. Data was collected between 2015 and 2021. Reported congenital abnormalities by both participants and GPs were first blindly ICD10-coded and EUROCAT-classified as either Minor or Major by two independent researchers. Discrepancies were discussed with a clinical geneticist. Differences in reported abnormalities between the participant and their GP were assessed.

Results

A total of 552 participants' GPs responded to the request to provide information (response rate of 75.3%). For 82 newborns a congenital abnormality was reported by the participant, the GP or both. Participants reported 69 congenital abnormalities and GPs reported 76 congenital abnormalities, leading to a total of 145. Of these abnormalities 107, (73.8%) were classified as Minor abnormalities and 38 (26.2%) were classified as Major abnormalities. The most frequently reported congenital abnormality was hip dysplasia ($n = 25$) followed by ankyloglossia ($n = 12$). In case both the GP and the participant reported a congenital abnormality ($n = 40$; 27.6%), these abnormalities were coded identically with the same ICD10-code in 33 cases (82.5%), and coded differently in 7 cases (17.5%). In 36 (24.8%) cases, only the GP reported a congenital abnormality, while similarly in 29 (20.0%) cases, only the participant reported a congenital abnormality. Finally, when looking at newborns with at least one Major abnormality reported by their GP ($n = 20$), the majority of participants (70%) also reported a Major abnormality, while 10% reported a Minor abnormality and 20% of participants did not report any abnormality. On the contrary, there was one case where only the participant reported a Major abnormality while the GP reported none.

Conclusion

Mothers can adequately report the congenital abnormality from their newborn in detail since 4 out 5 of their reported congenital abnormalities are ICD10-coded identically with their GPs. However, still many abnormalities remain unreported by both the participants and GPs. Overall, 30% of newborns with Major abnormalities according to the GP are missed when only considering information provided by participants. This could possibly be explained by a difference in the follow-up period. Hence, using self-reported questionnaire data solely from the mother to assess congenital abnormalities among offspring, proves to be a method which should be used with caution in drugs-safety studies.

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107206

A new Teratology Information Service in Milan: The experience from the first nine months (Presented at the ENTIS business meeting)

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Introduction

The need for drugs' use during pregnancy and lactation is common, but the knowledge about their risks and benefits among both women and healthcare workers is often lacking, with a consequent risk of underprescription or misuse. Teratogen Information Services (TIS) counsel thousands of patients in several countries every year: some studies demonstrated the efficacy of TIS in advocating the correct use of drugs. In June 2022, Milan Poison Control Centre (MPCC) opened a specific free-of-charge call service for medication safety during pregnancy and breastfeeding in Italy for both patients and healthcare professionals, available from Monday to Friday, 5 h per day.

Methods

This is a retrospective descriptive epidemiological study based on the calls received by MPCC for medication use during pregnancy and lactation from June 2022 to February 2023. Demographic and medical data were collected at the time of referral. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Results

We received 1270 calls during the analyzed period: 304 (23.9%) concerned pregnancy, 966 (76.1%) lactation. Main callers were patients (1139, 89.7%), 129 (10.2%) healthcare professionals. The counselings for pregnancy concerned I trimester (0–13 weeks) in 106 cases (34.9%), II (14–27 weeks) in 86 (28.3%), III (from 28 weeks) in 74 (24.3%); 17 (5.6%) were women planning pregnancy. Among the calls about breastfeeding, 172 (17.8%) concerned newborns (0–1 months), 271 (28.1%) infants aged 2–6 months, 174 (18%) infants aged 7–12 months, and 218 (22.6%) children older than 12 months. ATC groups involved were the following: nervous system (19.6%), systemic anti-infectives (13.7%), musculo-skeletal system (13.4%), respiratory system (12.8%), alimentary tract and metabolism (10.7%), hormonal preparations (5.6%), cardiovascular system (4.2%), dermatologicals (3.8%), genito-urinary system and sex hormones (3.5%), sensory organs (2.4%), blood system (2%), antiparasitic (1.8%), antineoplastic and immunomodulating agents (0.7%). 4.2% of the calls concerned Over The Counter, herbal and homeopathic medications.

Conclusion

Since its opening, the new Milan TIS service has counseled several patients and professionals in Italy for the safety of a great variety of medications in each trimester of pregnancy and during early and mid-late lactation. Further promotion of the service among the population of pregnant and breastfeeding women and healthcare professionals is crucial. The study limitation was incomplete data recording: a more accurate collection is necessary to avoid missing information in the future.

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107207

The BELpREG registration system on perinatal medication use and mother-infant outcomes: preliminary insights into the cohort's characteristics (Presented at the ENTIS business meeting)

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Introduction

BELpREG is the Belgian registration system collecting real-world data on perinatal medication use and mother-infant outcomes through online questionnaires. Women receive questionnaires each four weeks during pregnancy and until eight weeks postpartum.

Methods

Data collection started in November 2022. All Dutch-speaking pregnant women, ≥18 years, can enroll. On February 16th, 2023, the preliminary data were extracted and analyzed in terms of the total

number and characteristics of participants and were compared with population statistics. The prevalence and type of medication use were also explored, as well as the follow-up rates over successive questionnaires.

Results

Overall, 121 women initiated the enrolment procedure, of which 98 eventually signed the consent (81%). Most women were between 25 and 34 years (91%) and were recruited via social media (39%) or healthcare professionals (28%). Median gestational age at enrolment was 20 weeks (range: 4–39). Compared to the non-pregnant population, our cohort consisted of more highly educated women (91% vs. 53%) - with an education in healthcare (44% vs. 25%), women with the Belgian nationality (94% vs. 70%), and women with a higher income (55% vs. 33%). Women who were unemployed in the past year were underrepresented (2% vs. 29%). More pregnancies following a fertility treatment were included (15% vs. 8%). Further, 92% indicated in the first questionnaire that they used a medicine since the start of their pregnancy. Analgesics (54%), systemic antihistamines (41%), vaccines (18%), drugs for acid-related disorders (16%) and nasal preparations (13%) were the most frequently reported categories, with paracetamol (54%) and doxylamine/pyridoxine (32%) as most often reported ingredients. Despite the relative long duration needed to complete the first questionnaire (median: 27 min), 79% fully completed it. Of all follow-up invitations sent, completion rates for the 1st, 2nd and 3rd follow-up and postpartum questionnaire were 71%, 72%, 61% and 67%, respectively.

Conclusions

Data collection on perinatal medication exposure and mother-infant outcomes is currently ongoing in BELpREG. Preliminary results show that participants may not be entirely representative for the perinatal population in Belgium, requiring additional efforts to involve other (sub)groups.

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POSTER PRESENTATIONS

107208

Thiopurines use during pregnancy: A systematic review and updated meta-analysis of observational studies

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Introduction

Meta-analyses about thiopurines use in pregnancy conducted until today were limited to women with inflammatory bowel disease (IBD) exclusively. The last one was conducted in 2020 and several significant studies have been published since. The aim of this study was to examine the risk of thiopurines (azathioprine and/or its active metabolite 6-mercaptopurine) use during pregnancy considering new data and regardless of indication thereby increasing statistical power.

Methods

A systematic literature search in PubMed, EMBASE and Web of Science was performed for dates up to 28 October 2022, using a proprietary collaborative WEB-based meta-analysis platform (metaPreg.org). All studies investigating the effects of thiopurines use during pregnancy with a comparator group were included. Comparator groups were unexposed to thiopurines and i) unsick; ii) sick pregnant women, or iii) sick pregnant women exposed to other medications indicated in these diseases. Outcomes with more than 7 studies were considered in this meta-analysis. Data were extracted. Adjusted odds ratio (ORs) were pooled using random effects models. Sensitivity analyses were performed according to study designs; types of control group and adjustment (yes/no). Publication bias was investigated using funnel plots. The Egger's test or Trim and fill method were performed. ROBINS-I tool was used to assess the risk of bias.

Results

The database search extracted 862 studies of which 22 were included which represents up to 4813 exposed women. Compared to women not exposed, our meta-analysis reported a statistically increased risk of major malformations (OR 1.49 (1.09–2.05); *p*-value = 0.01; I^2 = 0%; *n* = 8 studies) after thiopurines 1st trimester exposure; of preterm births (OR 1.83 (1.58–2.11); *p*-value<0.01; I2 = 10%; *n* = 16 studies) and Low Birth Weight (LBW) (OR 1.62 (1.12–2.34); p-value = 0.01; I^2 = 31%; *n* = 12 studies) but not of Small for gestational age (OR 0.91 (0.64–1.30); p-value = 0.61; I^2 = 51%; *n* = 8 studies) after thiopurines exposure during pregnancy. Assessment of the risk of bias reveals that all studies included are at critical risk of bias for at least one domain, mostly due to confounding. Sensibility analyses show substantially similar results between subgroups.

Conclusions

Thiopurines exposure during pregnancy might be associated with an increased risk of major malformations, preterm birth and LBW. The large number of studies included increased the statistical power. The main limitation of our meta-analyses is the high risk of bias of included studies, especially in terms of confusion. Therefore, results should be considered with caution and further well-conducted studies are needed to draw conclusions for clinical practice in such clinical complex situations.

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107209

Chronic medication and breastfeeding, avoiding behavior in Dutch women

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Introduction

Breastfeeding offers many advantages, both to mother and child. For women with chronic medication, a careful consideration should be made if it will be safe for the infant to start breastfeeding. We studied the situation in the Netherlands: do mothers decide to refrain from breastfeeding for the right reasons?

Methods

Data from the Dutch Pregnancy Drug Register were used for this study. This register was set up to obtain insight into the safety of drug use by women during pregnancy and breastfeeding. Pregnant women in the Netherlands are invited to sign up. Participating women receive 6 online questionnaires, three during pregnancy and three after birth.

For the first analysis of this study we selected participants who decided not to breastfeed because of the medication they used. How large is this group and which drugs were involved? The most frequently mentioned drugs from the first analysis were used as the starting point for the second analysis. How many participants who use that particular drug will start breastfeeding, and how many will not?

Results

.Of the 4276 women included, most women (88%) started breastfeeding. About 12% decided not to start. Within this last group, 11% ($n = 57$) described medication as the reason for not starting. Single drugs (groups) most often mentioned in the first analysis were lithium, lamotrigine and SSRIs, all used for chronic diseases. The second analysis showed that all 5 women in the register who used lithium did not start breastfeeding. A valid choice, since breastfeeding is usually not recommended while using lithium. Of the 13 women in the register taking lamotrigine, 5 (almost 40%) did not start breastfeeding due to concern about the drug. This concern is unnecessary because women with epilepsy who use chronic lamotrigine are generally recommended to start breastfeeding. With respect to the 32 participating women using an SSRI, 10 (almost 40%) did not start breastfeeding out of concern about the drug. It became clear that fluoxetine was the SSRI least trusted: all 5 fluoxetine users did not start breastfeeding. Of all SSRIs, fluoxetine is indeed the least favorite choice during breastfeeding, due to relatively large amounts entering the milk. However, women who used fluoxetine during their pregnancy can continue to use it while breastfeeding. When selecting the group of SSRIs except fluoxetine, the percentage of women who started breastfeeding appeared to be higher. However, still 15% (5 of 32) decided not to start due to undue concern about the medicine.

Conclusions

Among the 12% of women who do not start breastfeeding, 1 in 10 (11%) mentioned that drug use played a role in their decision not to breastfeed. However, the use of some of the mentioned drugs like lamotrigine or an SSRI is no reason to be concerned about negative effects on the infant. With better information for both healthcare provider and pregnant women we hope to improve this situation.

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107210

Improving data collection in pregnancy safety studies: Towards standardization of data elements in pregnancy reports from public and private partners (ConcePTION)

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Introduction

The Innovative Medicines Initiative's ConcePTION project aims to develop a series of operational recommendations to optimise and standardise data collection techniques, analysis, and reporting in pregnancy pharmacovigilance research to improve data harmonisation and evidence synthesis capabilities. As part of this work a reference framework of core data elements (CDEs) recommended for collection in primary source PregPV studies was developed.The aim of this study was to assess the ability of a variety of data access providers (DAPs) using different types of data sources to align their data collection variables, including clinical definitions, with the CDE recommendations. Studies of multiple sclerosis drugs were considered in this pilot.

Methods

Four pregnancy registries (Gilenya Pregnancy Registry, Novartis; Aubagio, Sanofi; Aubagio, OTIS/Sanofi; the Dutch Pregnancy Drug Register, Lareb), two enhanced pharmacovigilance programs (Gilenya PRIM, Novartis; MAPLE-MS, Merck KGaA) and four Teratology Information Services (United-Kingdom, Israel and Switzerland) participated in the study. This study assessed 51 items from the CDE covering administrative functions, maternal/pregnancy details, medical history, medication exposure details, as well as maternal, pregnancy and infant outcomes. Each DAP classified the variables from their databases for each CDE item as follows: 1) variable taken from an existing field 2) variable derived by combining data; 3) variable with divergent definition; 4) missing variable.

Results

The majority of the CDE variables (85%, $n = 305/357$) were matched either directly by the DAPs' original variables or could be derived by combining different variables (12%, $n = 42/357$). For very few CDE items, alignment of the DAPs variables was not possible either because of divergent definitions (1%, $n = 3/357$) or because relevant information was not collected or missing (2%, $n = 7/357$).

Conclusions

DAPs were able to match a very high proportion of the CDE items, indicating that alignment of dataset content and clinical definitions by diverse stakeholders is feasible, an important prerequisite for harmonization and exchange of data analysis.

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107211

Prenatal cannabis exposure and the risk for neuropsychiatric anomalies in the offspring: A systematic review and meta-analysis

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[1]lead presenter.

Introduction

As cannabis use becomes more common worldwide, an increase in its use is also observed among women of reproductive age, including during pregnancy. Several studies examined the possible impact of prenatal cannabis exposure on children's psychiatric and neurobehavioral development. However, the variability and inconsistency in the associations observed make it difficult to fully evaluate the risks and potential harm of in-utero cannabis exposure. Therefore, our objective is to evaluate the existing data and assess the association between cannabis exposure during pregnancy and the risk for neuropsychiatric outcomes in the offspring.

Methods

We followed the PRISMA 2020 guidelines for systematic review and meta-analysis. MEDLINE, EMBASE, and Cochrane databases were searched up to August 2022. Data were independently screened for eligibility and extracted by two reviewers. Studies were eligible for inclusion if they reported quantitative data on long-term neuropsychiatric outcomes in the offspring prenatally exposed to cannabis versus control. Data were pooled using random-effects models.

Results

Fourteen eligible observational studies were included in the review, and twelve were included in the final quantitative analysis. The pooled odds ratio (OR) for ADHD was 1.12 (95% confidence interval (CI): 1.00–1.27); for ASD, the pooled risk ratio (RR) was 1.18 (95% CI 0.7–1.97); for psychotic symptoms, the pooled RR was 1.18 (95% CI 0.95–1.45); for anxiety, the pooled OR was 1.63 (95% CI 0.78–3.40); and for offspring's marijuana use the pooled OR was 1.2 (1.01–1.42).

Conclusions

There was no association between exposure to cannabis during pregnancy and ADHD, ASD, psychotic symptoms anxiety in the offspring. The association between prenatal cannabis exposure and the mildly increased risk for ADHD might be due to residual confounding and not because of the exposure. These results should be interpreted with caution, given the observational nature of the studies and the potential for residual confounding.

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107212

The prevalence and type of safety questions on paternal medication use: A cross-sectional analysis in Belgium

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Introduction

Little is known about the risks of paternal medication use regarding reproductive health, although safety questions among users may exist. The extent and type of safety questions men have on this topic have not been thoroughly investigated. This study aimed to gain insight into the information needs of men about the risks of paternal medication use on their fertility, the course of pregnancy and the health of offspring.

Methods

A cross-sectional, anonymous web survey was distributed in Belgium through social media and healthcare professionals between September 2022 and March 2023. All Dutch-speaking men between 18 and 50 years and (occasionally) using medication could participate. The survey consisted of questions on 1) personal characteristics, including chronic conditions and medication use, 2) information needs on the risks of paternal medication use, and 3) perception towards the availability of safety information about paternal medication use. Ethical approval (MP021730) and online consent of participants were obtained.

Results

In total, 249 men participated of which 73% completed the survey. Most participants were between 18 and 30 years (62%), while 31% already had children, 13% was pregnant or trying to get pregnant as a couple, 7% had followed fertility treatment and 23% was (being) educated in healthcare. Chronic conditions were reported by 40% of participants (mostly hay fever, asthma, or atopic dermatitis), and 22% indicated using medication(s) daily. Overall, 20% had already questioned the risks of medication use for their fertility. Second, 12% stated having already wondered whether paternal medication use could have adverse effects on the course of pregnancy. Third, 13% cited having already reflected upon potential adverse effects of paternal medication use on offspring. Although safety questions often did not relate to a specific medicine, the most questioned medicines were analgesics, psychotropics (mainly antidepressants) and immunosuppressants. One-third answered that their safety questions related to the occurrence of 'specific' risks for pregnancy or offspring. Finally, 15% reported having ever questioned whether medication could be present in semen, and 5% whether to use a condom to avoid the transfer of medication through semen. However, all respondents (97%) agreed that reliable information on the safe use of paternal medication should be available. Therefore, they prefer to receive information via general practitioners (71%), pharmacists (61%) and the leaflet (56%).

Conclusions

Up to 20% of men do have questions on the potential risks of paternal medication use on their fertility, the course of pregnancy and the health of offspring. Since most questions were on a general level, the safety of analgesics, antidepressants and immunosuppressants were also regularly questioned. Clinicians and TIS centres could use these insights to tailor evidence-based information to male patients' information needs.

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107213
Pregnancy outcomes following maternal favipiravir exposure: A case series

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Introduction
Favipiravir is an antiviral drug that is commonly used to treat influenza by inhibiting RNA polymerase activity. It is also included in the antiviral treatment of COVID-19 cases in the "COVID-19 Adult Patient Treatment" guide published by the Turkish Ministry of Health. However, it is contraindicated for use in pregnant women with COVID-19 due to reports of embryonic deaths and teratogenicity in animal studies. The risk assessment of favipiravir in humans is limited due to insufficient data.

Methods
Data of pregnant women exposed to favipiravir during their pregnancies were collected from Terafar database at Izmir Kâtip Celebi University Teratology Information, Training, and Research Center between 2020 and 2021. Routine pregnancy check-ups and fetal ultrasound scans at 20 weeks were performed and recorded by the obstetrics clinic, and newborn developmental assessments using the Denver Developmental Screening Test were performed and recorded by the pediatric neurology clinic.

Results
The standard daily dosage of favipiravir, taken orally, was typically 1200 mg per day (ranging from 600 to 3200 mg/day) for 1–5 days. The median gestational age at birth was 38 weeks (ranging from 33 to 40 weeks). The study identified 57 pregnancies exposed to favipiravir, with 46 known outcomes. Of these, 38 resulted in live births (including 1 set of twins), 7 elective terminations, and 1 intrauterine death. Among 38 live births, 33 had no congenital malformations. The remaining five infants had malformations, including major malformations such as congenital ichthyosis, hydronephrosis, and cleft-lip palate, as well as minor malformations such as pleural effusion and patent foramen ovale. The Denver developmental tests were normal for all five infants. Of 18 infants undergoing developmental screening tests, 15 had normal Denver tests. Language development was observed in a 16-month-old baby at 12–13 months, while an 8-month-old infant exhibited development at the 6-month level. Language development in a 17-month-old infant was observed at 13–14 months, and all three infants did not exhibit any congenital malformations.

Conclusions
Favipiravir caused birth defects and reduced fetal viability in animals, but human studies reported normal pregnancy outcomes. In pregnant monkeys, favipiravir 200 mg/kg/day produced cleft palate in 2 of 5 fetuses. We also observed one infant had a cleft palate-lip after exposure to favipiravir during pregnancy, but the timing of exposure didn't align with the sensitive period for this malformation. Similarly, the other cases of malformations don't seem to be consistent in terms of the sensitive period and type of malformation. Further research is needed to draw definitive conclusions about the possible risks of favipiravir exposure in pregnancy.

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107214
The development of a mobile app to inform pregnant women and their healthcare providers about the safety of over-the-counter medicines during pregnancy and breastfeeding

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Introduction
Information on the safety of medication use during pregnancy tends to be too complicated, incoherent and difficult to find for pregnant women. Nevertheless, over 80% of pregnant women use any form of medicine at some point in their pregnancy. Hence, there is a need to make information on safe medicine use during pregnancy more easily accessible. Particularly with regard to over-the-counter (OTC) medicines, it is very important to empower pregnant women to actively look up safety information since consultation with a healthcare provider is not required. The aim of this project is to develop a user-friendly E-Health tool (a mobile app) with evidence-based information about the safety of primarly OTC medicines. In addition, the mobile app will also automatically link with our digital Knowledge Bank, where information about the safety of prescribed medicines is displayed. The desire is that it is both possible to search for safety information on specific medicines and also to search for common pregnancy symptoms were the app then provides the preferred medicines.

Methods
This two-year project will consist of five phases. During the preparation phase (1) focus groups will be organised with both pregnant women and healthcare providers to perform a needs assessment (e.g. what facilities should the mobile app have?). During the development phase (2) the mobile app will be built by an experienced IT company. In the pre-implementation phase (3) a prototype of the mobile app will be tested intensively and final adjustments will be made. During the implementation phase (4) the mobile app will be launched in accordance with an appropriate implementation strategy, e.g. by a large national promotional campaign. Finally, the project will be evaluated in the evaluation phase (5), where the usability and reach of the mobile app will be assessed.

Results
Two sorts of data will be collected throughout the project; development data and evaluation data. As for the development results, data will be collected through the results of the focus groups, needs assessment for functionalities of the app, testing the mobile app (user-friendliness), and the feedback which the mobile app collects (satisfaction). Evaluation results include; the number of app downloads, most used search terms in the mobile app, increase in the number of visitors to our Knowledge Bank and increase in the number of participants in our pregnancy cohort study.

Conclusions

The grant proposal for this project has recently been approved and we aim to launch the mobile app in the spring of 2024. Our project has the potential to improve the safe usage of medicines during the pregnancy and breastfeeding period by improving the accessibility of health information everywhere, to empower women to make safe choices to improve their own health and the health of their offspring.

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107215

Dopamine agonists pramipexole, ropinirole and rotigotine for the treatment of restless legs syndrome in pregnancy

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Introduction

Restless legs syndrome (RLS) is common during pregnancy, affecting approximately one in five pregnant women in Western countries. The dopamine agonists pramipexole, ropinirole and rotigotine, which have longer half-lives than levodopa, were approved for the treatment of RLS between 2004 and 2008. However, only few published data on its use in human pregnancy are available to date.

Methods

In a prospective follow-up study we collected data of pregnancy outcomes after treatment with ropinirole, pramipexole, and rotigotine between 2007 and 2021. Our Teratology Information Service (TIS Ulm / Germany) was contacted by physicians or patients after conception during female treatment with these dopamine agonists. Three months after the estimated date of birth, the inquirers received a structured questionnaire to document the course and outcome of the pregnancy.

Results

28 mostly unplanned pregnancies were included in the analysis (pramipexole $n = 16$, ropinirole $n = 8$, rotigotine $n = 4$). Four patients decided to terminate their pregnancy between week 9 and 12 because of lack of experience with these drugs. Two pregnancies ended with spontaneous abortions. 22 pregnancies were continued to term, with medication being maintained until term in nine cases. The other patients stopped the medication after their pregnancy was diagnosed in the first trimester. In addition to 21 healthy newborns, one newborn with hydronephrosis was registered (pramipexole up to wk. 8). No major malformation was observed. 7 girls and 15 boys were born between wk. 31/6 and wk. 41/1 (median wk. 38/3) with a median birth weight of 3270 g (range 1480–3950 g).

Conclusions

These preliminary data on the use of the dopamine agonists pramipexole, ropinirole and rotigotine in pregnancy do not indicate a severe teratogenic effect of the drugs, but given the limited data, use during pregnancy should be avoided if possible. If a pregnancy occurs on these drugs a detailed sonographic diagnosis is recommended, as long as there is no sufficient experience.

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107216

Development of a toolkit to stimulate reporting and participation in studies/registries for pregnant and breastfeeding women

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Introduction

Task 5.3 of the IMI ConcepTION project (www.imi-conception.eu) aims to engage healthcare professionals (HCPs) and pregnant and/or breastfeeding women, to stimulate reporting through pharmacovigilance systems, by increasing awareness that women and HCPs can play an active role in generating evidence for medicine safety in pregnancy and breastfeeding. Here we describe a communications Toolkit developed by Task 5.3, for teratology information services (TISs), health authorities, pharmacovigilance centers and other stakeholders who collect exposure data on medicines use in pregnancy and breastfeeding, in Europe and beyond. The Toolkit is designed to facilitate the planning and initiation of a communication campaign for the general population, pregnant women/women of reproductive age or health care professionals, at little cost. This work has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking ConcePTION grant no. 821520.

Methods

The IMI ConcePTION Task 5.3 team benefits from the expertise of communication strategists and representatives from several ENTIS-affiliated TIS and pharma companies. Two pilot communications campaigns were conducted to promote engagement and participation in pregnancy registries, one in the Netherlands (https://www.moedersvanmorgen.nl) and one in the United Kingdom (https://www.medicinesinpregnancy.org/). The results and learnings of these campaigns on key indicators (such as registry inclusions, website traffic and Twitter engagement) were used to develop the Toolkit.

Results

The Toolkit is an easy-to-use guide to support the planning and running of communications campaigns. It includes general recommendations to develop push-pull strategies and value propositions to support targeted communications, a step-by-step guide to tailor example messages to the target audiences, and adaptable and affordable materials for digital and print communications and social media campaigns. All of the messages and materials can be tailored to the local context and language.

Conclusions

The Toolkit was launched on 15th March 2023 in the webinar 'How-to guide for campaigns to stimulate reporting of exposed pregnancies,' and is freely available on Zenodo: https://zenodo.org/record/7734196#.ZBM-YJHP2Uk. The team encourages TISs and other stakeholders to consider using the Toolkit to enhance their current communication campaigns to increase awareness about medicines use in pregnancy and breastfeeding. Where stakeholders currently do not undertake active promotion of their data collection systems, we hope that the Toolkit can provide practicable and feasible guidance to initiate a new communications campaign.

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107217

The use of ondansetron in the first trimester: Any differences after the EMA PRAC recommendation to not use it?

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Introduction

Ondansetron is an antiemetic drug that is used off-label to treat severe nausea and vomiting during pregnancy. After reviewing the available literature, in 2019 the European Medicines Agency Pharmacovigilance Risk Assessment Committee (EMA PRAC) released a recommendation to update the Summary of Product Characteristics (SmPC) with the information to not use ondansetron in the first trimester of pregnancy. This recommendation was based on studies with conflicting results on cardiac defects and a study suggesting a slightly increased risk of oral clefts after use of ondansetron in the first trimester. The aim of this study is to determine whether first trimester ondansetron use had changed after the recommendation.

Methods

Data on medication use was obtained from the Dutch Pregnancy Drug Register. This register has a prospective cohort design, collecting data by web-based questionnaires. All women using ondansetron during pregnancy between 2014 and May 2022 were included. Ondansetron use in the first trimester was compared between women with a pregnancy start date before and after the EMA recommendation date of July 2019 using a Fisher exact test with a significance level of <0.05.

Results

A total of 106 women reported the use of ondansetron during pregnancy. Thirty-six of them had a pregnancy start date before July 2019 and 70 women after July 2019. In 22% and 20% of the women, the exact timing of use was unknown. The number of first trimester users was significantly higher before July 2019 compared to after July 2019 (92.9% vs 64.3%, $p = 0.007$). The median start of use in the first trimester before July 2019 was gestational week 8.7, compared to gestational week 9.9 after July 2019. Of the twenty women starting ondansetron use after the first trimester after July 2019, 9 started at a pregnancy duration of 13 or 14 weeks.

Conclusions

In our pregnancy registry, a decrease in women using ondansetron in the first trimester was seen if we compare the data before and after the EMA PRAC recommendation. It also seems that women start later in the first trimester or start right after the first trimester with the use of ondansetron, indicating the recommendation led to a change in the use of ondansetron in the first trimester.

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107218

Pregnancy outcome after erenumab treatment during early pregnancy: A case series

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Introduction

Migraine is one of the most common neurological disorders, often affecting women of childbearing age. The IgG_2 monoclonal antibody erenumab belongs to the newest class of substances used for migraine prophylaxis. It is an antagonist of the calcitonin gene-related peptide (CGRP) receptor and is administered once monthly as a subcutaneous injection due to its long half-life of 28 days. CGRP is a key mediator in the pathophysiology of migraine, acting as a nociceptive modulator and vasodilator. There is limited experience with the use of erenumab during pregnancy.

Methods

This case series includes all requests for erenumab exposure to TIS Berlin until February 2023 with a completed follow-up.

Results

We evaluated outcomes of 14 prospectively ascertained pregnancies, including one twin pregnancy. Median maternal age was 35 years and median BMI was 21. In the majority of pregnancies (92.9%), no cigarette or alcohol misuse was reported. More than half (57.1%) of the patients had at least one previous parity. Six women had already stopped treatment with erenumab in the preconception period, some however very shortly before conception. In the other cases treatment was discontinued after recognition of pregnancy at a median gestational age of 5 weeks after last menstrual period. The latest exposure was at week 12 + 4. Four women were treated with 70 mg/month, five with 140 mg/month. Dosage was unknown in five cases. Additionally, triptans were used frequently as on-demand medication, mostly sumatriptan. One woman discontinued her migraine prophylaxis with topiramate at 4 weeks after the last menstrual period. Five women additionally used amitriptyline as migraine prophylaxis. None of the 12 live-born infants presented with major birth defects. Six girls and six boys with a median birth weight of 3,160 g were delivered at a median gestational age of 39 weeks. Two spontaneous abortions occurred. One pregnancy was terminated electively due to personal reasons.

Conclusions

The results of our case series do not indicate an increased risk of adverse pregnancy outcome after erenumab exposure during the first trimester. However, data are still very limited and further studies are needed. Evidence from in-vivo and ex-vivo studies suggests that CGRP plays an important role in several physiological

processes, including development and adaptation of the vascular systems in the uterus, placenta and fetus. Based on the currently available information, the use of erenumab during pregnancy should be avoided. This work was supported by the German Federal Ministry of Health & Paul-Ehrlich-Institute (PEI).

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107219

I am a law student treated with amphetamines for Attention Deficit Hyperactive Disorder (ADHD): Can I breastfeed my child? A pilot study

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Introduction

In recent years, there has been a steady increase in ADHD prevalence and medication use by young adults, including women of childbearing age and during pregnancy and lactation. Currently, little information is available on the therapeutic use of amphetamine stimulants in nursing mothers. Most data on the safety of these medications are from recreational abuse of methamphetamine. Amphetamines are excreted into human milk and may be found in the urine of nursing infants. Poor sleeping and irritability have been reported in some nursing infants, but long-term developmental effects were not described.

Methods

A prospective pilot study of women who approached the TIS Zerifin between the years 2017–2022 for information on the safety of the use of amphetamine stimulants – lisdexamphetamine or mixed racemic amphetamine salts (Adderall®) during breastfeeding. A telephone follow-up interview was conducted to assess the outcome and the neurodevelopment of the children by using Pediatric Quality of Life (PedsQL), and Denver Developmental Scale.

Results

Thirteen women were included in the analysis, 6 (46%) exposed to lisdexamphetamine, and 7 (54%) to mix racemic amphetamine salts. Mean maternal age at the time of the first contact was 32 ± 5.8 years. Most of the women had a high academic education (11/13, 85%). Seven women used amphetamines during pregnancy, and 4/13 (31%) were exposed throughout pregnancy. Three (23%) women used concomitant psychotropic medications. Median (IQR) age of the child at the follow-up was 18 (5.25–34) months. Nine (69%) children were fully breastfed. Adverse effects were reported among five (38%) children: somnolence (1, 8%), crying/restlessness (3, 23%), GI effects (colic/constipation) – (4, 31%).

All children were reported to have normal gross motor development, based on Denver developmental scale. Neurodevelopment, as measured by PEDsQL, was also normal with PEDsQL score (median, IQR): total 97.16 (91.48–100), Psychosocial Health 99.33 (94.83–100), Physical Health 98.75 (87.8–100).

Conclusions

Exposure to amphetamine stimulants during breastfeeding was not associated with negative neurodevelopment of the offspring. However, due to the small sample size, further studies are needed in order to conclude on the effect of prolonged exposure to amphetamine stimulants during breastfeeding.

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107220

Identifying safety concerns related to antiseizure medication use in breastfeeding women with epilepsy by reviewing questions to the Norwegian drug information and pharmacovigilance centres

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Introduction

Breastfeeding has well-established health benefits for the child and the mother. Women with epilepsy (WWE) have lower breastfeeding rates compared to healthy women. We aimed to identify the type of safety concerns among health care professionals related to antiseizure medication (ASM) during breastfeeding in WWE by reviewing questions to the Norwegian drug information and pharmacovigilance centres (RELIS).

Methods

Question-answer pairs (QAPs) related to breastfeeding, epilepsy, and ASM identified by the drugs' ATC-numbers were retrieved from a searchable database containing over 55,000 QAPs using a combination of indexed and Boolean database searches and manual inspection. The QAPs were analyzed using descriptive statistics.

Results

In total, 112 QAPs were included. Most questions were from physicians, predominantly from hospitals, followed by nurses/midwives and other health care workers, in that order. Lamotrigine and levetiracetam were the ASM most frequently asked about, and antidepressants were the most prevalent co-medication. The majority of questioners called for general information about the compatibility of a specific ASM with breastfeeding. Other questions were raised due to concerns about polypharmacy or adverse effects in breastfed infants, while some questions, predominantly posed by physicians, were related to the fact that breastfeeding was not recommended in the product information. At least half of the questions were posed after the women had given birth, of which half were asked after initiation of breastfeeding, partly motivated by suspected adverse events in the infants. In most cases RELIS recommended continued breastfeeding, but with specific recommendations.

Conclusions

Health care professionals with acknowledged high competence and skills in the field were uncertain about the prevailing safety

information of ASM during breastfeeding possibly leading to avoidance of breastfeeding or non-optimal medical treatment of breastfeeding WWE. Future information strategies should aim to reach these professions, encourage planning of medication use with respect to breastfeeding before birth and support the professions' information needs on this topic.

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107221
Vitamin D macro dosing in pregnancy: A case report of D hypervitaminosis in pregnancy according to non-conventional Coimbra protocol and perinatal toxicity

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Introduction
Vitamin D3 (cholecalciferol) is a prohormone metabolized in various tissues to the biologically most active vitamin D hormone 1,25(OH)2D3 (calcitriol). Vitamin D has a modulating role in the immune system via interaction with the vitamin D receptor (VDR). Vitamin D is increasingly utilized not only within prophylaxis, but also within therapy of various diseases. In 2013, the group of Cicero Coimbra reported the clinical efficacy of the so-called "Coimbra protocol" (CP), of high dose of vitamin D3 in patients suffering from autoimmune skin disorders. The necessity of high doses of vitamin D_3 can be explained by the concept of an acquired form of vitamin D resistance. There is no clinical evidence on the efficacy of Vitamin D macro doses on ulcerative colitis even though the gut microbiota could be positively influenced by it.

Methods
Case report.

Results
We report the case of a 31-year-old pregnant woman affected by ulcerative colitis treated with the CP: cholecalciferol 100.000 IU/day; magnesium 200 mg/day; vitamin B2 150 mg/day; vitamin K 100 μg/day; Omega 3500 mg/day; low-calcium diet (500–600 mg/day), 2.5 l of low-calcium water per day and daily exercise. She was 8 weeks pregnant when referred to our TIS, reporting a good clinical control of the ulcerative colitis. The patient was informed on the lack of evidence of such treatment and the potential dangers of D hypervitaminosis during pregnancy. 25OH vit D in her serum resulted to be far above toxicity with 566 ng/ml (30–100 ng/ml). Despite the indication of the gastroenterologist to stop the CP the patient continued it throughout pregnancy and gave birth to a baby girl at week 40. The baby showed a very high value of 25OH vit D (250 ng/ml), total calcium was 10.3 mg/dL (8.5–10.3), phosphorus 7.4 mg/dl (2.5–4.5 mg/dL), creatinine 1.23 mg/dl (0.44–0.95). The mother 25OH vit D was still very high at 560 ng/ml. 25OH vit D in breast milk was 7.59 ng/ml *vs* < 4 of pooled human milk. Therefore, a human milk-based diet from the Children's Hospital milk bank was provided to the baby, while IV fluid therapy was carried out together with diuretic therapy to promote adequate hydration and avoid a further increase in calcium and vitamin D levels. Renal and cerebral echography showed no anomalies while echocardiography showed microcalcifications at the papillary muscles of the left ventricle, not confirmed on a second examination. The baby was discharged on day 10 with a 25OH vit D value of 174 ng/ml. She was then sent to day hospital during the first month. The growth was regular during the first 3 months and 25OH vit D slowly decreased to normal.

Conclusions
As far as we know this is the first well documented case of a baby born by a mother on the CP and the first documented mother's milk D hypervitaminosis. We can conclude that despite a long afterbirth hospitalization the baby had only mild toxic effects and is now healthy.

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107222
Breastfeeding exposure to agomelatine – Preliminary findings from an Australian observational cohort study

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Introduction
Agomelatine is a melatonin receptor (MT_1 and MT_2) agonist and $5HT_{2C}$ receptor antagonist used for the treatment of major depressive disorder and generalised anxiety disorder. There is currently a limited number women exposed to agomelatine during pregnancy, as it is a third-line antidepressant. The cost of the medication also limits its use as it is currently not covered by the Pharmaceutical Benefits Scheme (PBS) in Australia. The main objective of this study was to follow-up women who had contacted the MotherSafe telephone counselling line with queries regarding the use of agomelatine during pregnancy and/or breastfeeding.

Methods
Women who called MotherSafe with queries regarding agomelatine during breastfeeding or pregnancy were given a follow-up call by a MotherSafe counsellor. Data were collected on women calling between 2013 and 2023.

Results
Data on breastfeeding were collected on 14 breastfeeding women about 16 babies (including two women who breastfed two of their babies while taking agomelatine). Average maternal age was 37 years (range 26–44 years) and doses of agomelatine ranged from 25 mg twice weekly to 50 mg daily with a mean dose of 25 mg (one of the doses was unknown). All women had taken agomelatine and breastfed their babies from birth until a maximum age of 21 months with a mean of 7.38 months. All fourteen women had called MotherSafe during pregnancy or planning a pregnancy and thirteen of the women had taken agomelatine throughout their pregnancy. Four out of the fourteen women were taking concurrent antidepressants or mood stabilisers (duloxetine, mirtazapine, sodium valproate, pregabalin). One women reported chronic use of cannabis and tobacco smoking with agomelatine and mirtazapine during pregnancy and breastfed her baby until 4 months of age with no

reported adverse effects. Only one mother reported a possible adverse reaction of drowsiness in her baby in the first few weeks after birth which she attributed to agomelatine. She was taking agomelatine with duloxetine 90 mg daily and continued breastfeeding her baby until 9 months of age. She reported some developmental concerns of speech and low muscle tone in her baby who was 9 months of age at the time of follow-up. The other thirteen mothers did not report any short term or longer term adverse effects in their babies. The age of the babies at the time of follow-up ranged from 3 months to 21 months.

Conclusions

This small study demonstrated that the majority of babies exposed to agomelatine via breastmilk did not experience any serious or clinically significant adverse effects.

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107223
Breastfeeding during lithium therapy is safe in healthy full-term infants when monitored

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Introduction

Previous studies of breastfeeding during lithium therapy have shown conflicting results regarding the safety for the infant. Different approaches to this question are practiced across the European Teratology Information Service-centers. The aim of this study was to evaluate the safety of breastfeeding in a real-life setting, when practicing a thorough follow-up of the infants.

Methods

This retrospective study focused on breastfed infants to mothers treated with lithium born between 2006 and 2021 in Stockholm, Sweden. Information on serum lithium concentrations in breastfed infants and their mothers as well as infant clinical status was collected from medical records.

Results

In total, 30 infants exposed to lithium through mother's own milk, 21 girls and 9 boys, were included. The median age at follow-up was 40 days (range 8–364 days). The median lithium serum concentration was 0.10 mmol/L in the second week of life (range < 0.05–0.7 mmol/L), 0.08 in week 2–4 (range < 0.05–1.2), 0.06 in the second month of life (range < 0.05–0.2) and 0.07 after 2 months of age (range < 0.05–0.2). The mean infant-mother ratio of serum lithium concentrations was the highest in the second week of life (0.37, range 0.08–1.17), whereafter it stabilized at a mean level of 0.1 (range 0.05–0.35). Half of the included infants were exclusively breastfed. Unexpectedly high lithium serum concentrations, 0.7 and 1.2 mmol/L were found in the first month of life in two partly breastfed infants. The lithium concentrations decreased when the breastfeeding was discontinued. One of these infants was born at 35 weeks of gestation and had an initial weight loss of over 10% and the other one had experienced an apparent life-threatening event in the second day of life, but both were without any clinical symptoms at the time of the measured high concentrations. Apart from poor weight gain, no adverse effects were found in the breastfed infants.

Conclusions

Serum lithium concentrations in breastfed infants were stabilized at barely measurable levels after the first weeks of life. Before that, concentrations higher than the maternal ones were found. The two infants with notably high, but not toxic, lithium concentrations at follow-up were either preterm or experienced serious symptoms at birth, which supports that breastfeeding during lithium therapy should be limited to healthy full-term infants. However, lithium treatment during breastfeeding can be considered safe for healthy full-term infants under strict follow-up. The size of the cohort presented by this study is the largest to date, but the generalizability of these results is limited to mentally and socioeconomically stable mothers and their infants. Also, further studies are needed to confirm the potential negative effect of mild prematurity on infant outcomes after exposure to lithium through human milk.

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107224
NSAIDs exposure during late pregnancy: Trends in prescriptions and reporting fetal adverse effects

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Introduction

In France, non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated beyond 24 weeks of pregnancy. Two reminders on the harmful effects of NSAIDs during pregnancy were released by the ANSM in 2003 and 2017. Our aim was to evaluate trends in reporting fetal adverse effects (FAE) of NSAIDs and NSAIDs dispensation in late pregnancy.

Methods

FAE resulting from maternal NSAIDs exposure were identified in the French pharmacovigilance database (FPD) for the period 2004–2022. Inclusion criteria were NSAIDs exposure after week 12 of pregnancy and FAE likely due to these drugs. Reimbursed NSAIDs dispensations (excluding low dose acetylsalicylic acid) after 6 months of pregnancy were identified for all pregnancies between 2018 and 2021 from the French national health data system (SNDS).

Results

Of 133 cases retrieved in the FPD, 33 were included (20 between 2004 and 2017, 13 between 2018 and 2022). Systemic and topical administration were involved in 25 and 7 cases (both routes in 1). Cases were mainly exposed to NSAID through self-medication ($n = 18$) and for a short duration (≤2 days for 14 cases). Renal, cardiopulmonary or both FAE were reported in 13, 10 and 2 cases, respectively. Intrauterine growth retardation and isolated fetal death occurred in 3 and 5 cases, respectively. FAE were reversible in 14 cases, 3 were complicated by fetal/neonatal death and 4 neonates still had medical consequences after delivery (outcome unknown in 7). Among the 2.8 millions of pregnancies identified in the SNDS, the frequency of dispensation of NSAIDs after 6 months of pregnancy decreased from 0.7% to 0.5% between 2018 and 2021 (5117 and 3710 pregnancies respectively, i.e. -27%). Less than 5% of them had more than one dispensing during this late pregnancy period. Ibuprofen and ketoprofen were the most dispensed (55% and 19%). General practitioners, midwifes and gynaecologists were the most frequent prescribers (48%, 11% and 9% respectively).

Conclusions

Despite repeated ANSM communications on the contraindication of NSAIDs in late pregnancy, these drugs are still prescribed and delivered beyond 6 months of pregnancy. As exemplified by spontaneous reports, self-medication may be also an important source of avoidable exposure. Although the number of reported FAE after prenatal exposure to AINS is low its remains unchanged over years. Prescribers and patients need to carefully consider this risk after 6 months of pregnancy.

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107225

Consensus panel recommendations for management of pregnant women affects by anxiety and depressive disorders

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Introduction

The initiative of a consensus on the topic of antidepressant and anxiolytic drugs use in pregnancy is developing in an area of clinical uncertainty. Although many studies have been published in recent years, there is still a paucity of authoritative evidence-based indications useful for guiding the prescription of these drugs during pregnancy and the data from the literature are complex and required expert judgment to draw clear conclusions.

Methods

For the elaboration of the consensus, we have involved the scientific societies of the sector, namely the Italian Society of Toxicology, the Italian Society of Neuropsychopharmacology, the Italian Society of Psychiatry, the Italian Society of Obstetrics and Gynecology, the Italian Society of Drug Addiction, and the Italian Society of Addiction Pathology. An interdisciplinary team of experts from different medical specialties (toxicologists, pharmacologists, psychiatrists, gynecologists, neonatologists) was first established to identify the needs underlying the Consensus. The team, in its definitive structure, include all the representatives of the aforementioned scientific societies; the task of the team was the evaluation of the most accredited international literature as well as, using the methodology of the "Nominal Group Technique" with the help of a systematic review of the literature and with various discussion meetings, to arrive at the drafting and final approval of the document.

Results

Five areas of investigation were identified: 1. Importance of management of anxiety and depressive disorders in pregnancy, identifying the risks associated with untreated maternal depression in pregnancy 2. Assessment of the overall risk of malformations with the antidepressant and anxiolytic drugs use in pregnancy 3. Evaluation of neonatal adaptation disorders in the offspring of pregnant antidepressant/anxiolytic-treated women 4. Long-term development: infants' cognitive development or behavior after in-utero exposure to antidepressant/anxiolytic medicines 5. Evaluation of pharmacological treatment of opioid abusers pregnant women with depressive disorders.

Conclusions

Considering the state of the art, it is therefore necessary in the first instance to frame the issue of pharmacological choices in pregnant women who need treatment with antidepressant and anxiolytic drugs on the basis of data currently available in the literature. Particular attention must be paid to the evaluation of the risk/benefit ratio, understood both in terms of therapeutic benefit with respect to the potential risks of the treatment on the pregnancy and on the fetal outcome, and of the comparative risk between the treatment or the absence of treatment: in the choice prescription, the specialist needs to be aware of both the potential risks of pharmacological treatment and the equally important risks of an untreated or inadequately treated disorder.

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107226

Fertility treatment in Norway - What about breastfeeding during treatment?

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Introduction

In our service, SafeMotherMedicine (tryggmammamedisin.no) in Norway, we have observed an increased number of inquiries about fertility drugs while still breastfeeding. However, medical literature and research addressing breastfeeding during fertility treatment are very scarce. Furthermore, we do not know what policy the Norwegian fertility clinics have regarding breastfeeding during

fertility treatment. Medically, the question of whether it is advisable to breastfeed during fertility treatment has three associated issues; 1) Some fertility drugs could potentially pose a risk to the breastfed child or 2) reduce milk production. 3) Lactation is a physiological state of hyperprolactinemia that could theoretically influence the success rate of the fertility treatment. Thus, the purpose of this project was to prepare a report with practical advice on these three issues.

Methods

We conducted a structured literature search in PubMed, lactation databases and textbooks. We also contacted the Norwegian fertility clinics (14 clinics in total) about their breastfeeding policy. To get an overview of the women's breastfeeding situation in general, we reviewed relevant inquiries to our internet service SafeMotherMedicine (from January 2012 to Mars 2023).

Results

In the relevant inquiries to SafeMotherMedicine ($n = 142$), 94% and 79% of the children were over 6 and 12 months of age, respectively. The majority of medications commonly used in fertility treatment seems to be acceptable during partial breastfeeding of an older infant/toddler, with exception of letrozole and possibly clomiphene, used for ovulation stimulation. Several of the hormones and hormone analogues used in fertility treatment (e.g. GnRH agonists and antagonists, FSH, LH and choriogonadotropin) have a polypeptide structure and large molecular weight that make it unlikely that the drugs will enter human milk in significant amounts. Additionally, such medications are not orally well absorbed. Some of the medications, like estradiol, can potentially decrease breastmilk production. However, as the vast majority of the children are >6 months old, the breastmilk production is likely well established, and not a cause of concern. We did not locate any published evidence/research that breastfeeding could interfere with fertility treatments, only claims of theoretical nature. In most cases, the women undergoing a new fertility trail for siblings will however have resumed regular ovulation and menstruation.

Conclusions

Updated guidelines are necessary to provide healthcare personnel with evidence-based recommendations. Limited documentation is available, however, with the exception of letrozole, medications used during fertility treatment do not appear to pose any significant risk to breastfed infants over 6 months of age. There are also good reasons to question that partial breastfeeding of an older infant/toddler should influence the success rate of fertility treatment. In our opinion, weaning or not before undergoing fertility treatment should therefore be a personal decision in the vast majority of cases.

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107227

Profile of calls and activities of the first Teratogen Information Service in Latin America through 32 years

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Introduction

In 1990, the first Teratogen Information Service was implemented in Latin America, the SIAT: *Sistema Nacional de Informação Sobre Agentes Teratogenicos* in Porto Alegre, Brazil. SIAT is free-of-charge and open to health professionals and lays people, especially pregnant or planning pregnancy women.

Methods

To present the activities of SIAT in its initial years (1990–2006: P1), compared to those in the last years (2007–2019: P2) and the Pandemic Period (2020–2021).

Results

From 1990 to 2021, SIAT received 11,329 calls (6503 in P1). Medication use was the main reason for calls in both periods (75%). When analyzing only medications, there was an increase in calls referring to CNS-acting, particularly in the pandemic years 24% in P1, 47% in P2 and 75% in the Pandemic Period. Maternal infectious diseases didn't change much (5%), but there was a marked difference in the infectious agent. Rubella and rubella vaccine were common in P1 and disappeared in the subsequent years; zika was the main question in P2 and, expectedly, Covid-19 in the Pandemic Period. It's interesting that during the Pandemic Period, CNS-active drugs (antidepressants, mood stabilizers and tranquillizers) represented 78.9% of all questions about pharmaceutical drugs, compared to 38.7% in the 15 years before the Covid-19 pandemic. SIAT had a prominent role in identifying two new human teratogens: misoprostol in the 1990s and Zika virus in 2015/16. SIAT also was involved in the investigation of recent cases of thalidomide syndrome in Brazil and acted with governmental regulatory agencies to better regulations to prevent further pregnancy exposures. For all calls, we address additional risk factors, such as alcohol, smoking, chronic diseases, nutritional status, and maternal age. SIAT provides written answers for all doctors with an educational part on prevention and prenatal screening of congenital anomalies. As for the training of health professionals, SIAT trained more than 330 undergraduate and graduate students. More recently, SIAT expanded the research scope to experimental teratogenesis, investigating the molecular mechanisms of teratogens and their interaction with developmental gene networks.

Conclusions

SIAT shows the importance of a Teratogen Information Service in middle or low-income countries since the nature of pregnancy risk factors and exposures are distinct from high-income countries.

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107228

Pregnancy outcomes of anti-TNF-alfa treatment during pregnancy: A mixed case series

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Introduction

Anti-TNF drugs like adalimumab, infliximab, certolizumab, golimumab, and etanercept are immunological agents that are frequently used in the treatment of rheumatological diseases. Limited literature regarding the teratogenicity of anti-TNF drugs is

available. We aimed to show the pregnancy outcomes of the pregnant women who admitted to Marmara University Teratology Information Service between 2012 and 2022.

Methods

The follow-up interviews of the patients were performed by phone calls and data regarding the exposure period, the development of complications, the exacerbations of the chronic diseases during pregnancy, and the outcomes of pregnancies were collected.

Results

There were eleven pregnant women who exposed to adalimumab (mean age: 33; median exposure period: 7 weeks; min-max: 4–38 weeks). Six patients experienced exacerbations of their diseases where two had spontaneous and three had elective abortions. The remaining six patients gave birth at term. Premature closure of the anterior fontanelle was observed in one infant at four months of age and the others were healthy. In our database, there were sixteen pregnancies that were exposed to certolizumab (median exposure period: 27 weeks; min-max: 4–38 weeks). Certolizumab medication was ceased in the last trimester in seven pregnant women. One infant was hospitalized for dyspnea at three months of age. Seven pregnant women received etanercept, while four exposed to golimumab (mean age:36; median exposure periods were seven and five weeks for etanercept and golimumab, respectively). Spontaneous abortion occurred during the fourth week only in one pregnant woman receiving golimumab together with isoniazid. The rest of the infants born to mothers that used golimumab and etanercept had no congenital abnormalities. In one infant golimumab exposure occurred within the first four weeks of pregnancy and the infant lactated for thirty months and was diagnosed with developmental delay, and the need for special education emerged. Allergic asthma was detected in a five year old whose mother used etanercept between 4 and 38 weeks of pregnancy. There were six pregnant women receiving infliximab (mean age:25.7; median exposure period four weeks). One neonate was hospitalized to the intensive care unit because of neonatal asphyxia. Another infant was hospitalized for low birth weight, and the other for neonatal urinary tract infection.

Conclusions

Although we do not have age- and year-matched controls, we state that reporting the outcomes of exposures to anti-TNF-alfa drugs may be critical. We observed that adalimumab use had a higher miscarriage rate, but our results should be verified with further studies.

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107229
Iohexol exposure in the first trimester of the pregnancy, a case report

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Introduction

Iohexol, an iodinated and non-ionic radiocontrast agent administered commonly during computerized tomography (CT) investigations. Iohexol use during pregnancy may be associated with abnormal thyroid functions in the newborn, but little is known about the outcome of the early pregnancies in its use.

Methods

We report a case of a 38-year old pregnant exposed to iohexol who admitted to our teratology information service (TIS). The data was collected by face to face interview and a written consent was taken. She reported that she was given metoprolol for her chest pain and palpitations and she had underwent a cardiac CT investigation with contrast agent iohexol. The patient became aware of her pregnancy in the 6th week after her last menstrual period and admitted to our TIS for the safety of her pregnancy. Metoprolol was used during the 5th and 6th weeks. Radiology consultation was also asked for checking the safety of the dose of radiation she was exposed. During the follow up, she reported that her pregnancy ended as a miscarriage in the 10th week.

Results

Metoprolol is a $beta_1$-selective adrenergic receptor blocker and the data to date showed that its use may be associated with low-birth weight but not with major malformations. In cardiac tomography procedure, the amount of radiation that the fetus will be exposed usually ranges between 1 and 6.6 rad and this dose range is not expected to increase the risk of spontaneous abortion and produce major malformations according to *American Committee on Obstetric and Gynecology Report (2004)*. The knowledge about the teratogenic effects of radiocontrast agent iohexol is scarce but the iodine levels of the iohexol may alter the thyroid functions in the later trimesters. *The European Society of Urogenital Radiology* recommended that thyroid function should be assessed in the neonates if iodinated contrast media was given during pregnancy (2005).

Conclusion

As cardiac disease, metoprolol and X-ray remain as confounding factors in the formation of spontaneous abortion, the embryotoxic effects of iohexol in the first trimester should not be disregarded until the results of controlled studies were collected.

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107230
Evaluation of paternal drug use in a teratology information service

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Introduction

While maternal drug use accounts for the majority of admissions to teratology information services (TIS), it should be noted that paternal drug use also carries known risks, mainly genotoxicity and infertility. Unfortunately, data regarding the effects of paternal drug use are limited. In this context, we aimed to analyze the details of paternal drug use cases in our database of teratology information service (TIS).

Methods

We examined the admissions to Marmara University TIS for paternal drug use between 2012 and 2022. A total of 53 cases were

included, which comprised of 32 cases that were directly consulted for paternal drug use and 21 cases that were detected during comprehensive investigations of maternal referrals. The most common diagnoses of the cases and the most frequently consulted drugs to our service were evaluated. The drugs were also grouped by the first level of Anatomical Therapeutic Chemical (ATC-1) classification. In addition, the decisions on the consultation reports were analyzed.

Results

The cases referred for paternal drug exposure of the fetus constituted 50.9% ($n = 27$), while the remaining 49.1% ($n = 26$) were consulted to evaluate the suitability of paternal drug use for pregnancy planning. The mean age at admission was 37.4 ± 5.1 years (range: 29–48 years). The three most commonly encountered diagnoses were ankylosing spondylitis (14.6%), chronic myeloid leukemia (9.8%), and rheumatoid arthritis (9.8%). The mean number of drugs consulted per case was 2.0 ± 1.3. Among the consulted drugs, 44.2% were classified as "L-Antineoplastic and immunomodulating agents" per ATC-1. The three most commonly consulted drugs were azathioprine (6.7%), methotrexate (4.8%), and adalimumab (3.8%). Three cases (7.3%) involved illicit drug use, with two of those reportedly sharing with their partners. For 48.2% of the paternal drug exposure cases, our counseling report was inconclusive due to limited data in the literature. No major increment in baseline teratogenicity risk was expected in 29.6%, while 22.2% showed a potential increase in risk. Twenty-two of the cases referred for pregnancy planning were evaluated for teratogenicity, and in 30.7% of those, the current drug treatment regimen was considered as appropriate only if the expected benefits outweighed the potential risks. Among the 17 cases evaluated for infertility risk, 70.6% showed an increase in the risk of potential adverse outcomes regarding fertility.

Conclusions

The high mean age of the male patients seeking counseling may be linked to the growing incidence of chronic diseases and the consequent use of medications in later years of life. Many of the drugs consulted in our TIS for paternal use belonged to the antineoplastic / immunomodulator (group L) category, which points out the need for increased awareness for those. The study also stresses that whenever an illicit drug use was reported, the partner should also be investigated accordingly for the possibility of sharing.

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107231
Isotretinoin cases in the Finnish TIS database

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Introduction

Isotretinoin is a known teratogen and causes malformations in up to 25–35% of exposed fetuses. The organs affected include the central nervous system, the heart, and facial structures. To prevent fetal exposure, several pregnancy prevention measures have been introduced by regulating authorities over the years. The latest measure was introduced by the European Medicines Agency, EMA in March 2018, and passed as a law in July 2018 by the European Commission. This law is legally binding in all EU member states. The commission also required the manufacturers to follow up the efficacy of the latest pregnancy prevention programs by following the amount of isotretinoin exposures during pregnancy.

Methods

We performed a search of isotretinoin related calls in the Finnish TIS database. The search covered a period between June 1st 2006-Jan 31st 2023.

Results

The annual number of calls related to isotretinoin exposure varied between 8 and 19. Most of these calls concerned pregnancy planning and length of the washout period. During the study period, there were a total of 23 cases where isotretinoin use had continued until a positive pregnancy test or until a suspicion of pregnancy. Approximately two cases per year included isotretinoin exposure continuing into the period of organogenesis. There were 14 cases in which isotretinoin use continued into the washout period i.e. isotretinoin was used after LMP but stopped before ovulation. The number of exposures during pregnancy have been constant during the study period in our data set. In several of these cases contraception was not used despite having been prescribed. The reason for non-use of contraception was often a perceived infertility leading the mother to believe that she was unable to get pregnant.

Conclusions

Despite the tightened pregnancy prevention programs, isotretinoin exposures extending into the washout period and organogenesis still occur. Pregnancies are usually discovered at an early stage, and the Finnish legislation allows termination of pregnancy based on social grounds until 12 weeks of gestation with no further authority permissions needed. Pregnancy terminations on social indications are not recorded in the National Register of Congenital Malformations, which collects data on pregnancy terminations performed on fetal indications, and it is possible that these terminations are therefore not recognized by the authorities. To prevent isotretinoin exposures, the knowledge and understanding of the risks with isotretinoin use needs to increase.

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107232
Bisoprolol during breastfeeding: A prospective case series

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Introduction

Lately, the prevalence of cardiovascular diseases in women of child-bearing age has increased. Beta-blockers are one of the most common pharmacological groups for treatment cardiac morbidity.

While the information regarding the safety during pregnancy and breastfeeding of "old" non-selective beta-blockers is available (labetalol, propranolol, etc.), the data for bisoprolol, a beta-1 adrenoreceptor selective antagonist, is lacking. We aimed to evaluate the physical and psychomotor development of children exposed to bisoprolol during breastfeeding.

Methods

A prospective pilot study. Women who contacted TIS Zerifin between the years 2016–2022 seeking for information on the safety of bisoprolol during breastfeeding were followed-up. A telephone interview was conducted to assess children's outcome and neurodevelopment by using age-adjusted Pediatric Quality of Life (PedsQL) questionnaires, and Denver Developmental Scale.

Results

Eleven women were enrolled for the analysis. The dose range of bisoprolol was between 1 and 5 mg per day, the median dose was 2.5 mg. The mean maternal age at the time of the telephone consultation was 35.2 years. Eight women used bisoprolol during pregnancy, and 6 of them were exposed throughout pregnancy. Five women (45%) used concomitant medications as propafenone, omeprazole, colchicine etc. The median (IQR) age of the child at the time of follow-up was 49 (25.5–58.5) months. Eight children (73%) were fully breastfed. Adverse effects were reported among 2/11 (18%) infants: somnolence ($n = 1$) and poor weight gain ($n = 1$). No abnormal results were found by Denver developmental scale. Psychomotor development according to PEDsQL score (median, IQR) was: total 97.5 (95.96–100), Psychosocial Health 97.9 (95.55–100), Physical Health 100 (100–100). These results represent normal physical and psychomotor development.

Conclusions

Exposure to bisoprolol during breastfeeding was not associated with negative physical and psychomotor offspring development. Further studies are needed in order to strengthen the conclusion of our case series.

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107233

Don't cry over spilt milk: Women treated with medications CAN (in many cases) donate milk to a Human Milk Bank

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Introduction

Human breast milk is the recommended nutrition for newborns and premature neonates according to the World Health Organization. Breastmilk is of utmost physiological importance for neonates and is crucial for the survival of premature newborns, preventing necrotizing enterocolitis and other medical conditions. Recently, the National Israeli Human Milk Bank was established by the emergency medical service - Magen David Adom (MDA). Around 10% of women willing to donate milk to the milk bank are taking medications. The Drug Consultation Center at Shamir Medical Center provides guidance regarding dilemmas related to these milk donations. Our aim is to set criteria for milk donations designated for premature newborns, from women treated with medications.

Methods

In order to maximize the potential of milk donations, we assess the safety of the donation by evaluating the Relative Infant Dose (RID) and other pharmacokinetics (PK) parameters: molecular weight, protein binding and oral bioavailability of the medication. Possible undesirable effects on the premature newborn are also being taken into consideration. The attitude toward medication compatibility with breastfeeding differs between a mother breastfeeding her own child versus milk donation intended for premature newborns. Upon the safety assessment, recommendation regarding the milk donation are provided: decline, accept donation, or accept the donation-but, with dilution. In the latter case, the milk amount will not exceed 10% of the total batch. Other donations from the same batch should not contain other medications from the same pharmacological group.

Results

Around 65 consultations were performed. 30% of the queries were regarding anti-depressant and anti-anxiety medications, 14% regrading anti-thrombotic and anti-platelet therapy and 10% - treatment for allergic conditions. Five percent of donations were declined due to potentially hazardous medications (e.g. doxorubicin), 21% of donations were accepted (e.g. loratadine). In 74% of the queries, the recommendation was to accept the milk donation with dilution (e.g. fluoxetine).

Conclusions

The human milk bank is a lifesaving service. In the near future, milk donations' samples will be transferred to our unit in order to measure the concentration of the medications. This collaboration enables to use donated human breastmilk "up to the last drop".

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107234

The risk of miscarriage or preterm labor after COVID-19 vaccination before and during pregnancy

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Introduction

Pregnant women have a higher risk of severe illness and adverse pregnancy outcomes due to a SARS-CoV-2 infection, which can be prevented by COVID-19 vaccination. Observational studies are needed to ascertain safety of COVID-19 vaccination during pregnancy. This study aimed to assess whether COVID-19 vaccination before or during pregnancy is associated with the risk of miscarriage or preterm labor (PL).

Methods

In this cohort study, we included pregnant women (mean age: 33.0 ± 3.7 years) from the Dutch Pregnancy Drug Register. Information on COVID-19 vaccinations, miscarriage, PL, and confounders were self-reported using web-based questionnaires. The hazard ratio on miscarriage was estimated in a set of 4640 women, comparing those who received ≥1 COVID-19 vaccine between week 2 and 20 of pregnancy, to those who did not. The hazard ratio (HR) on PL was estimated in a set of 5910 pregnant women, comparing those who received ≥1 COVID-19 vaccine during any moment of pregnancy to those who did not, was estimated using survival analyses with vaccination as time-varying exposure. Additionally, we estimated the risk of PL after COVID-19 vaccination prior to pregnancy, and after COVID-19 vaccination during trimester 1, 2, or 3 of pregnancy.

Results

For the analyses on miscarriage risk, a total of 3202 pregnant women (69%) received ≥1 COVID-19 vaccine in gestational week 2–20. We observed no association of vaccination during pregnancy with the risk of miscarriage (adjusted HR of 1.29 (95%CI = 0.93;1.74)). Vaccination prior to pregnancy, however, was associated with a decreased risk of miscarriage (adjusted HR = 0.69, 95%CI = 0.48;0.99). For our analyses on PL, we observed a total of 5227 (88%) participants received ≥1 COVID-19 vaccine between gestational week 2 and 37. We observed no statistically significant association of COVID-19 vaccination during pregnancy (adjusted HR = 0.93, 95%CI = 0.59;1.45) nor of COVID-19 vaccination prior to pregnancy (adjusted HR = 1.09, 95%CI = 0.70;1.71) with the risk of PL. Moreover, we observed no association between the risk of PL and COVID-19 vaccination in any trimester of pregnancy.

Conclusions

We demonstrated that COVID-19 vaccination prior to or during pregnancy is not associated with an increased risk of miscarriage or PL. These results add to the growing evidence supporting safety of COVID-19 vaccination during pregnancy.

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107235

Paternal smoking and maternal secondhand smoke (SHS) exposure: Results from the EHF (Environmental Health Fund) Birth Cohort

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Introduction

The World Health Organization has classified the tobacco epidemic as one of the biggest public health threats worldwide. Second-hand smoke is a mixture of the smoke from the burning tobacco product and the smoke exhaled by a smoker. It is also called environmental tobacco smoke (ETS). This study aimed to measure ETS exposure in pregnant women using urinary cotinine measurements and to evaluate the association between paternal smoking and maternal urine cotinine, and birth outcomes in a birth cohort of Israeli mothers and children.

Methods

The EHF-Assaf-Harofeh-Ichilov cohort includes 263 mothers-newborns dyads. We retrieved data on 96 non-smoking mothers. Half of the partners were smoking according to the self-reported smoking status in the questionnaires, and half of the partners were nonsmokers. Maternal urinary cotinine measurements were obtained at birth. Women as exposed or non-exposed to secondhand smoke based on urinary cotinine below or above the Limits of Quantification (LOQ).

Results

Ninety-six mother-father-newborn triads were included in the final analysis. In our study, 94.1% of women with a smoking partner and nearly 60% of those with a non-smoking partner had urine cotinine levels above the LOQ. Furthermore, paternal smoking was a significant predictor for maternal urinary cotinine levels above the LOQ (aOR 7.83 95%CI [2.01–30.57], p-value = 0.003). Maternal urinary cotinine levels were inversely associated with newborns' birth weight (beta estimate −281.39, p-value = 0.048). In male newborns, maternal urinary cotinine was inversely associated with newborns' birth weight, (beta estimate 470.22, p-value = 0.014), but not in females.

Conclusions

Among participants in our study, 94% of non-smoking pregnant women with a smoking partner had urinary cotinine levels above the LOQ. Maternal urinary cotinine levels at birth are associated with lower birth weight, male newborns might be more affected than females. Because one of the main sources of maternal secondhand smoke is the partner's smoking, our findings have emphasized that partners have a central role in the creation and maintenance of a smoke-free environment.

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107236
Olmesartan-induced reversible transaminase elevation in a breastfed newborn. A case report

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Introduction
The drug-induced liver injury (DILI) is a challenging disease in clinical practice, both in adults and children. Many drugs have been suspected or confirmed to cause DILI, and for many of them, the underlying mechanisms are yet unknown. It is far more problem-posing when hepatotoxicity in a breastfed child is caused by a drug taken by the lactating mother. We describe a case of a hepatic injury in a newborn induced by Olmesartan taken by his mother because of acute postpartum hypertension.

Methods
Teratology Information Service was consulted to investigate drug involvement in hepatic injury of a newborn; demographic and clinical data were collected in a dedicated online database. Follow-up was conducted for 20 days.

Results
A 6-days-old healthy newborn was exposed to Olmesartan, prescribed to his breastfeeding mother. He was born at 41 weeks by eutocic delivery, 15-h observation in a neonatal intensive therapy unit was undertaken because of respiratory distress caused by umbilical cord around his neck. His birth weight was 3400 g; weight progression was regular during the first two weeks of life, but at the pediatric checkup on the 17th day since birth, an abrupt decrease in body weight was recorded. He was hospitalized on the 21st day, and mixed feeding with milk and formula was started. Biochemical examinations showed aspartate-aminotransferase (AST) 250 mg/dl, and regular urinalysis. The virologic and metabolic causes of hypertransaminasemia were ruled out. The baby started to regain weight and his AST gradually normalized to 50 mg/dl by the 24th day. Olmesartan intake was interrupted and the child was dismissed at his 24th day of life.

Conclusions
Olmesartan is an Angiotensin II AT1 Receptor Blocker, suspected to cause an immune-mediated enteropathy; recently some reports of hepatic injury associated with the drug have been published. An immune-mediated mechanism has been hypothesized for some cases, reversible following drug interruption; immunosuppressive therapy was occasionally required. Breastfeeding pharmacokinetic data on Olmesartan is scarce: its protein-binding capacity is high and the milk/plasma ratio is low but it is nevertheless not recommended during breastfeeding, specially in prematures and newborns. This is the first case report describing a hypertransaminasemia episode due to Olmesartan exposure in a breastfed newborn. Further investigation will be needed.

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107237
Safety of Covid-19 vaccination during pregnancy – The Finnish TIS experience

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Introduction
Covid-19 mRNA vaccines use novel technology. Data on safety during pregnancy were scarce in the beginning of the pandemic but have accumulated. In Finland, vaccination for special risk groups began in Dec 27th 2020, not excluding pregnant women. Health care authorities gave a general recommendation for vaccinating pregnant women in Aug 5th 2021, and pregnant women were considered a high-risk group for serious coronavirus disease in Jan 18th 2022. The available vaccines in Finland have been mRNA based (Comirnaty®, Spikevax®). The adenovirus-vector based vaccine (Vaxzevria®) has not been given to fertile-aged women after March 19th 2021.

Methods
We prospectively followed up pregnancies where the mother was exposed to one or more Covid-19 vaccine doses during pregnancy or within three months before pregnancy. The follow up period extends from Feb 10th 2021 until Jan 31st 2023.

Results
The TIS received 536 calls related to Covid-19 vaccines and pregnancy during the follow-up period. A total of 288 women exposed to Covid-19 vaccines consented to participate in the follow-up study. The majority (over 94%) of exposures concerned mRNA vaccines. Altogether 175 (61%) women reported any vaccine-related adverse effects, and 64 (22%) reported generalized symptoms. A total of 147 women (51%) (mean age 33.3 years; age range 23–46) returned their follow-up information. Of them, 87 had received only one Covid-19 vaccine dose and 59 had received one or more additional booster shots. The mean BMI before pregnancy was 25.2 and 33 women (22%) had gestational diabetes. A total of 135 (92%) pregnancies ended in a full-term live birth and 43 (32%) of these infants showed symptoms in the neonatal period, mostly mild and related to hypoglycemia or jaundice. There were no major malformations among the 75 pregnancies with exposure during the period covering three months before pregnancy or first trimester.

Conclusions
Our sample size was small and included mostly women who were pregnant in spring 2021. At that time, pregnant women in Finland were only vaccinated if they belonged to a specific risk group based on their chronic illness or high-risk work environment. Nevertheless, our results are in line with the results from previous research suggesting that mRNA-based Covid-19 vaccines are safe during pregnancy.

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107238
Quetiapine intake and milk ejection reflex in a breastfeeding woman: A case report

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Introduction
Quetiapine is an atypical antipsychotic medication blocking dopamine receptors in addition to its antagonism of histamine, adrenergic, serotonin, and muscarinic receptors. By enhancing prolactin excretion, quetiapine could lead to galactorrhoea. To date, the SmPC does not contain information on the likelihood or frequency of quetiapine intake and subsequent oxytocin secretion, and hence, stimulation of the milk ejection reflex in (breastfeeding) women. We describe a single case report of a breastfeeding woman using quetiapine and experiencing a milk ejection reflex, each time after she had taken the medicine.

Methods
The Netherlands Pharmacovigilance Centre Lareb received a spontaneous report from a psychiatrist in 2022. Informed consent of the patient was obtained to report the case.

Results
The case involves a 28-year old woman who had given birth to a male infant at 42 weeks of gestational age. Four weeks after childbirth, the exclusively breastfeeding mother started using 50 mg quetiapine a day (at 11 PM, after the last nursing event of the day), to treat psychotic intrusive thoughts. The woman did not use any other medication and had not used quetiapine before. About 30–40 min after the intake of quetiapine, the mother experienced a milk ejection reflex each time, starting from the day after quetiapine initiation. She described this as a tingling sensation in her breasts, after which the milk ejection started. The mother reported that it felt similar to what happened when she started breastfeeding her son. She did not report having experienced leaking breasts in between feeds. At the time of quetiapine intake, her breasts were almost empty, and her baby had stopped suckling. The mother reported having experienced the adverse effect after quetiapine intake during a period of six months. Importantly, the one time she did not use quetiapine, i.e., when she did not have the medication, the milk ejection reflex did not occur. When restarting the medicine the next day, the effect occurred again (i.e., a positive rechallenge). No hormone or drug levels of quetiapine and/or its metabolites were analyzed in breast milk or blood.

Conclusions
Although a clear relationship cannot be established based on this single case, the observation of quetiapine intake followed by a milk ejection reflex in a breastfeeding woman is interesting given 1) its continuous and long-term appearance over a 6-months period; 2) the positive rechallenge; 3) the plausible timing of appearance of the side effect since quetiapine intake (Tmax = 1.5 h) and 4) the limited likelihood of spontaneous milk leakage in this case. Hence, this observation requires further investigation, and we therefore encourage clinicians and researchers to share their experiences and to explore a plausible biologic mechanism.

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107239
Pregnancy and neonatal outcome following agomelatine and pipamperone exposure during pregnancy: A case series from the Netherlands

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Introduction
Antidepressants and antipsychotics are regularly used in pregnancy, although the amount of available safety data varies across substances. This study aimed to provide evidence on the safety of agomelatine (antidepressant) and pipamperone (antipsychotic) in pregnancy for which no cases have been published in the literature.

Methods
The prospective pregnancy registries within the Lareb TIS were screened for cases with available outcome data from inception until February 2021. The study obtained ethical approval (MP017801).

Results
For agomelatine, two cases were identified. Both women were exposed during the 1st trimester (at 50 mg/day and unknown dose), in addition to other psychotropic co-medication. Hyperemesis gravidarum and gestational diabetes were reported as pregnancy complications, each in one of the pregnancies. Two live births with no congenital malformations, prematurity, low birth weight or abnormal Apgar scores after 5 min were noted. One neonatal complication was reported, but no specific information was available. For pipamperone, 15 cases were identified. Of them, eight women were only exposed during the 1st trimester and three during each pregnancy trimester. Only for two cases, information about the used dose was available (between 20 and 80 mg/day). Overall, 13 live births and two elective pregnancy terminations were noted (one due to unplanned pregnancy, while the reason was unknown for the 2nd termination). Pregnancy complications were reported for three pregnancies: 1) an intra-uterine infection and premature rupture of membranes; 2) pre-eclampsia; and 3) abnormal maternal weight gain (in a woman with pre-existent diabetes). No congenital malformations were observed; one infant had a short neck but no

chromosomal abnormalities. Prematurity occurred in three pregnancies (at 30, 33 and 34 weeks). The single neonate with a birth weight of <2500 g (i.e., 969 g) was born at 30 weeks from a woman with preeclampsia who had smoked 12–30 cigarettes/day. The Apgar score after 5 min was normal for all neonates. The following neonatal complications were reported for four of the 13 neonates: 1) circulation problems, hyperbilirubinemia and anemia (in the neonate born at 30 weeks); 2) oxygen deficiency due to prolonged labor; and 3–4) unknown.

Conclusions

This case series presents the first data following agomelatine and pipamperone exposure during pregnancy. Due to a lack of available evidence, further investigation is needed to allow a correct benefit/risk assessment of these medicines in the future.

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107240
Brivudine exposure during pregnancy and infant outcomes: Two case reports

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Introduction

Brivudine is a nucleoside thymidine analogue antiviral drug that blocks the action of DNA polymerases used to treat herpes zoster and herpes simplex type-1 epithelial keratitis. It is approved for first-line antiviral treatment of herpes zoster in many European countries. However, its use during pregnancy is not recommended due to insufficient data. This case study presents two cases of pregnant women who were exposed to oral brivudine in the first and second trimesters and their outcomes.

Methods

Two pregnant women without significant medical history and taking folic acid (400 μg/day) were referred to TERAFAR for risk assessment.

At week four, the first case (27-year-old, 6-weeks pregnant) received brivudine tablets (125 mg/day) for seven days for herpes zoster, fusidic acid topically for four days and a single dose of vitamin D3 oral solution (300,000 I.U./day). The second case (19-year-old, 16-weeks pregnant) used brivudine tablets (125 mg/day) for 7 days for herpes zoster at the 15th week of her pregnancy. The patient also used topical 1% diphenhydramine HCl lotion, paracetamol, and oral ferrous fumarate. After receiving teratological counselling, both women continued their pregnancies with perinatology follow-up and gave birth to healthy babies.

Results

No birth defects were diagnosed in the first case, and the baby's physical and neurological development was normal at the twelfth month. The infant's medical history was unremarkable except for mild allergy. After immunologic evaluation, general recommendations were given, and no treatment was recommended.

Similarly, no birth defect was diagnosed in the second case. The neurodevelopmental evaluation performed at age one, detected a delay in the personal-social domain with the Denver Developmental Screening Tests. A control test will be performed during the clinical follow-up of the baby.

Conclusions

This case study is the first report in the literature on first and second-trimester brivudine exposure during pregnancy. It highlights the importance of careful risk assessment of medication exposure during pregnancy, close follow-up, and monitoring of maternal and infant health after delivery. Although the findings in this report are consistent with other nucleoside analogues in terms of not increasing the risk of major malformations, there is insufficient data to establish a link between brivudine exposure and the mild atopic condition observed in the first infant or the partial delay in personal-social parameters observed in the second infant. These case reports may be useful for the clinical teratologists in conducting risk assessment of pregnant women exposed to brivudine during pregnancy. Further human data and observational studies are needed for more definitive conclusions.

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107241
Comparison of the safety of atypical antipsychotics used during pregnancy: A systematic review and network meta-analysis

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Introduction

Atypical antipsychotics are increasingly used in pregnant women. Although there are a few reviews that provide information on the risks of atypical antipsychotics when used in pregnancy, to date, no study has compared them between each other. The aim of this study is to compare the relative safety of atypical antipsychotics used during pregnancy and, if possible, to rank the molecules. We undertook a systematic review and a network meta-analysis.

Methods

Systematic literature search in PubMed and Web of Science was performed up to March 2022, using a proprietary collaborative WEB-based meta-analysis platform (metaPreg.org). All comparative case–control and cohort studies were included. The network meta-analysis was performed using R software, to compare amisulpride, aripiprazole, clozapine, olanzapine, quetiapine and risperidone/paliperidone. Only, outcomes reported in at least 3 studies were included. Risk of bias of each included study was assessed using the ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool.

Results

24 studies were included in our network meta-analysis. 17 had at least one risk of bias item assessed as “critical”. 7 outcomes met the inclusion criteria: “major congenital malformations”, “gestational

diabetes", "early intrauterine death (<22 weeks)", "elective termination of pregnancy", "preeclampsia", "preterm (<37 weeks)" and "small for gestational age (weight)". Comparisons for all molecules were only available for major congenital malformations. For the risk of major congenital malformations, risperidone was associated with a significant increase in risk (OR = 1.30, 95% CI = [1.08; 1.57]), while the other molecules moderately increased this risk, but not significantly. Other outcomes had results, except for preeclampsia and prematurity, where atypical antipsychotics had a protective effect compare to control group. Control groups were therefore invalidate.

Conclusions

It is, to our knowledge, the first network meta-analysis evaluating the safety of atypical antipsychotics during pregnancy. The study has some strengths, as the ability to compare atypical antipsychotics that had never been compared before, and the meta-analysis that allowed us to improve the statistic power. However, there are some limitations. The main ones are the difficulty to assess hypotheses of network meta-analysis on observational studies, especially the transitivity, and the high presence of bias in the included studies. Regarding the objectives of our study, we were able to compare molecules, but it was not possible to rank and to find a potentially safer molecule to use during pregnancy. It is important to undertake solid studies to get better quality results, to provide the best possible care for pregnant women.

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107242

Safety of monoclonal antibodies targeting PCSK9 in pregnancy: Analysis of the WHO's global pharmacovigilance database

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Introduction

Safety data of monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) in human pregnancy are scarce. The objective of this study was to provide additional information on the safety of alirocumab and evolocumab in pregnancy by querying VigiBase®, the World Health Organization's global pharmacovigilance database of spontaneous safety reports.

Methods

Safety reports collected in VigiBase® as of 31.12.2022 reporting exposure to alirocumab and/or evolocumab (selected as active ingredients) in the peri-pregnancy period and eventually suspected of having caused pregnancy outcomes were retrieved for a case-by-case assessment. The standardized query "pregnancy and neonatal topics" from the Medical Dictionary for Regulatory Activities (MedDRA®) was used to select safety reports concerning pregnancy. Although disproportionality analyses for pregnancy outcomes reported in at least five safety reports were initially planned in the subgroup of female patients of childbearing age, these could not be carried out due to insufficient numbers of safety reports with complete information on patient's sex and/or age.

Results

There were 38 safety reports, 25 (65.8%) with evolocumab and 13 (34.2%) with alirocumab. Most of safety reports originated from Europe ($n = 22$, 57.9%) and the United States of America ($n = 9$, 23.7%), and more frequently were reported by health-care professionals ($n = 30$, 78.9%). Patients of female sex were involved in 32 (84.2%) safety reports with a median age of 36 years (interquartile range 31–41 years, $n = 18$, 47.4%). Exposure to PCSK9 inhibitors occurred during pregnancy in 31 (81.6%) safety reports, via father in three (7.8%) safety reports, and during lactation in two (5.3%) safety reports. 20 (52.6%) safety reports consisted only of drug exposure, while 18 (47.4%) additionally reported pregnancy outcomes. Of these, 4 (10.5%) safety reports reported only maternal toxicities (without specific patterns), one safety report reported both maternal toxicities and foetal death, and 13 (34.2%) safety reports reported only foetal/neonatal outcomes including spontaneous abortion ($n = 8$), normal new-born ($n = 2$), foetal death, premature baby and congenital central nervous system anomaly (all $n = 1$). Four safety reports of spontaneous abortion had confounding factors among which maternal age > 35 years (n = 1) and co-reported drugs ($n = 3$), including atorvastatin (n = 2) or rosuvastatin (n = 1), ezetimibe (n = 3), elasomeran and fluoxetine (both in one safety report).

Conclusions

Given the paucity of information available to date, no conclusions can be drawn at present on the safety of PCSK9 inhibitors in pregnancy. Future pharmacoepidemiological studies on different real-world data, such as those from pregnancy exposure registries, are warranted to precisely assess exposure to PCSK9 inhibitors during the peri-pregnancy period and to further characterise relevant outcomes.

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107243

Monotherapy treatment of epilepsy in pregnancy: Congenital malformation outcomes in the child

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Introduction

A Cochrane Systematic Review was undertaken to investigate major congenital malformation (MCM) outcomes following prenatal exposure to antiseizure medications (ASMs).

Methods

Searches were undertaken in MEDLINE (Ovid), SCOPUS, and Cochrane Central Register of Controlled Trials. Prospective cohort studies and studies using routine health record data were included. Participants were women with epilepsy taking ASMs. The two control groups were women without epilepsy and women with untreated epilepsy. Data were analysed in RevManWeb.

Results

Fifteen cohort studies and eight routine health record studies included pregnancies exposed to lamotrigine, with eleven cohort studies and one routine health record study identified for levetiracetam. Across all studies, the prevalence of MCM was 2.9% (95% CI 2.3 to 3.7) and 2.8% (95% CI 1.8 to 4.3) for lamotrigine and levetiracetam, respectively. There was no significant difference in MCM risk between levetiracetam or lamotrigine exposure from either cohort studies ($n = 1223$ vs 4389, RR 0.90, 95% CI 0.58 to 1.39) or routine health record studies ($n = 248$ vs 2068, RR 0.78, 95% CI 0.37 to 1.69). MCM risk was significantly higher for carbamazepine exposure compared to lamotrigine from cohort studies ($n = 4018$ vs 4550, RR 1.37, 95% CI 1.06 to 1.77), but not from routine health record studies ($n = 2001$ vs 1906, RR 1.21, 95% CI 0.88 to 1.67). Similarly, MCM risk was significantly higher for carbamazepine exposure compared to levetiracetam from cohort studies ($n = 3814$ vs 1242, RR 1.51, 95% CI 1.01 to 2.26), while data from routine health record studies was not significantly different ($n = 1000$ vs 248, RR 1.73, 95% CI 0.78 to 3.83). Exposure to lamotrigine had lower MCM risk compared to topiramate from cohort studies ($n = 4275$ vs 505, RR 0.59, 95% CI 0.36 to 0.96), but data were limited for routine health record studies. MCM risk was not significantly different for levetiracetam exposure compared to topiramate in cohort studies ($n = 1124$ vs 505, RR 0.57, 95% CI 0.32 to 1.04). There was no significant difference in MCM risk between lamotrigine and oxcarbazepine for cohort studies ($n = 2208$ vs 333, RR 0.73, 95% CI 0.33 to 1.62) or routine health record studies ($n = 2158$ vs 377, RR 1.24, 95% CI 0.67 to 2.30). Similarly, there was no significant difference between levetiracetam and oxcarbazepine for cohort studies ($n = 833$ vs 333, RR 1.04, 95% CI 0.51 to 2.09) or for routine health record studies ($n = 248$ vs 373, RR 1.17, 95% CI 0.45 to 3.06).

Conclusions

Lamotrigine and levetiracetam exposure were associated with comparable MCM risks and tended to have a lower risk than carbamazepine and topiramate exposures. Data were limited in comparison to oxcarbazepine and other exposures.

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107244
An observational study on safety of COVID-19 vaccines in pregnancy – Current status and preliminary data based on the Embryotox cohort

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Introduction

Pregnant women with COVID-19 infection are at increased risk for severe disease, stillbirths and prematurity. Since September 2021, vaccination against COVID-19 is recommended for pregnant women after 1st trimester in Germany. The primary aim of this study is to assess pregnancy outcome after exposure to COVID-19 vaccines in pregnancy.

Methods

This surveillance study is based on observational data and includes pregnant women who were vaccinated with any COVID-19 vaccine during pregnancy or at least 30 days prior last menstrual period. Eight weeks after the expected delivery date a standardized follow-up is used to obtain details about pregnancy and neonatal outcomes. To assess potential risks, pregnant women exposed to COVID-19 vaccines will be compared to an unexposed control cohort.

Results

In 2021 and 2022 a total of 10,176 prospectively ascertained pregnancies with 17,063 vaccinations could be included in the study cohort. Most women ($n = 9910$) have received at least one mRNA vaccine (16,409 vaccinations; 14,864 Pfizer-BioNTech and 1545 Moderna). 539 doses of an adenovirus vector vaccine (Oxford-AstraZeneca and Janssen) have been used in 523 pregnancies. For 112 vaccinations, the exact vaccine was unknown or other vaccines were used ($n = 3$). More than half of the vaccine doses were administered after 1st trimester (preconception $n = 2258$; 1st trimester $n = 2714$; 2nd trimester $n = 6708$; 3rd trimester $n = 5383$). In the course of the pandemic, the number of women reporting a vaccination changed constantly. Immediately after approval of the vaccines, only few pregnant women have been exposed. In the further course of 2021, and especially after vaccination was officially recommended for pregnant women numbers increased. Later, most women have already been vaccinated before becoming pregnant and fewer vaccinations during pregnancy have been reported. At the beginning of 2023, the follow-up has been completed for 5646 pregnancies.

Conclusions

The uneven distribution of exposure over time leads to methodological challenges. Initially, there were predominantly women in the control cohort with inadequate protection against COVID-19. From mid-2022 onward, the control group increasingly included pregnant women who had achieved full vaccination protection prior to pregnancy. Additionally, it is a challenge to compare different vaccination regimens. There are heterologous vaccinations, basic immunizations as well as boosters in the exposed group. This also applies to vaccines that have rarely been used (vector vaccine and other vaccines). An analysis of study data on pregnancy outcome (pregnancy loss, birth defects) will be carried out in 2023. This work was supported by the German Federal Ministry of Health & Paul-Ehrlich-Institute (PEI).

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107245
Pharmacists' experiences of using knowledge bases on medicines in pregnancy and breastfeeding

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Introduction

To facilitate access to reliable information on medicines in pregnancy and breastfeeding, Region Stockholm provides the knowledge bases *Janusmed Drugs and Birth Defects* and *Janusmed Breastfeeding*. They are freely accessible on the internet (https://janusmed.se, available in Swedish) and integrated into Electronic Health Record systems. In September 2021, the knowledge bases were also integrated into the Electronic Expert Support (EES), a clinical decision support system used when dispensing prescription medicines, available at almost all Swedish pharmacies. The EES is provided by the Swedish eHealth Agency and financed by the government. This study is a preliminary evaluation of the pharmacists' perceptions of using the two knowledge bases via EES.

Methods

A web-based questionnaire was distributed via e-mail or intranet six months after the launch of the databases in EES, to approximately 5000 pharmacists working at Swedish pharmacies. The questions focused on use and perceptions of the knowledge bases and were multiple-choiced, scaled, or open-ended. A survey tool provided by Questback Essentials® was used to set up and collect the data.

Results

In total, 403 pharmacists responded to the questionnaire (response rate approximately 8–10%). They represented all regions in Sweden, most of them (95%) worked at community pharmacies. Around 38% received questions every week from pharmacy customers regarding medicines in pregnancy or during breastfeeding. When asked how they handle these questions, Fass (the Swedish Physicians' Desk reference) was the most common information source, used by 94% of the respondents. The majority (77%) were aware of the two new knowledge bases *Janusmed Drugs and Birth Defects* and *Janusmed Breastfeeding* in EES, and more than half of the respondents had used them. On a scale from 1 to 5, where 5 is the best rating, the information scored above 4 for being reliable, timesaving, for increasing patient safety and facilitating that pharmacy customers receive the same information from pharmacy staff as from other health care professionals. Six percent reported that they had experienced difficulties when using the Janusmed knowledge bases. One obstacle was differences in the assessments between Janusmed and Fass. The respondents also pointed out that questions regarding medicines in pregnancy and breastfeeding were most common in connection with self-care advice and over the counter medicines.

Conclusions

This study shows that pharmacists rate the two knowledge bases as reliable and supportive when dispensing prescription medicines. The positive results are in line with previous evaluations of the databases among physicians, midwives/nurses, and pregnant women. If pharmacists and other health care professionals use the same information source, this most likely facilitates communication and ensures that pregnant and breastfeeding women receives consistent, professional advice.

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107246

Clinical quality of information of primary pregnancy pharmacovigilance data sources – A ConcePTION project

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Introduction

Clinically well-documented reports of adverse events concerning exposure to medicinal products are more likely to support a reliable assessment of potential safety signals. An assessment tool for clinical quality, based on the presence and relevance of information elements, has recently been developed and validated to quantify the suitability of information for the purpose of safety assessment of medicinal product exposure during pregnancy. Detailed information on the clinical quality of various primary pregnancy pharmacovigilance (PV) data sources is currently lacking, but is important to highlight strengths and limitations of individual sources. The objective of this study was to assess the differences in clinical quality of various sources of pregnancy PV data, and to study characteristics of the nature of information collected by the different sources.

Methods

A random selection of 50 case reports of exposures to medicinal products during pregnancy was collected from each of the following data types: spontaneous reports and reports based on cases described in literature selected from EudraVigilance, European Network of Teratology Information Services (ENTIS), the Dutch Pregnancy Drug Register, enhanced PV programmes (EPV), and industry-sponsored patient support programmes (PSP). Reports were standardized and anonymized in order to blind for details that may have revealed the data source and then assessed using the new method. A score of <45% was considered poor, 45–65% intermediate, and ≥ 65% excellent clinical quality. The mean quality score was calculated per data source and compared using ANOVA (analysis of variance test). An analysis of scores for each section of the quality assessment tool was undertaken to assess for patterns in reporting of specific information that might compromise the quality of a report.

Results

Mean clinical quality scores for the various sources were 89.0% (SD 10.1%) for the Dutch Pregnancy Drug Register, 77.1% (SD 13.3%) for ENTIS, 64.7% (SD 20.5%) for EPV, 49.5% (SD 16.2%) for PSP, 40.9% (SD 21.6%) for spontaneous reports, and 38.6% (SD 18.0%) for literature reports. All were statistically significantly different ($p \leq 0.02$) except for spontaneous reports versus literature reports (mean difference 2.2%, $p = 0.99$) and spontaneous reports versus reports from PSPs (−8.6%, $p = 0.14$).

Conclusions

Data sources specifically designed for pregnancy data collection (the Dutch Pregnancy Drug Register and ENTIS) contain on average better clinical quality reports compared to sources designed for all clinical situations (EPV, PSP, spontaneous reports and literature reports). Also, EPV methods improve general spontaneous reporting data collection for pregnancy PV.

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Follow-up of breastfed infants exposed to maternal flecainide treatment

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Introduction
Flecainide is a class Ic antiarrythmic indicated in the treatment or the prevention of ventricular arrhythmia and supraventricular tachycardia. Low levels measured in few milk samples indicates that maternal doses of flecainide up to 200 mg daily would not be expected to cause any adverse effects in breastfed infants. However, there are no relevant published clinical data in breastfed infants of flecainide treated mothers.

Methods
All queries concerning breastfeeding wishes from women treated with flecainide and received by our pharmacovigilance center were assessed by a senior. Clinical follow-up of the babies was performed by telephone interviews with the mother and/or the pediatrician. An electrocardiogram (ECG) and a flecainide dosage in the infants were systematically proposed at day 15 of life in all breastfed infants.

Results
Since 2010, 18 queries were registered. After individual assessments, breast-feeding was allowed in 16 patients (contraindication in 2 due to co-medication). Of these, a complete follow-up was obtained in 8 who initiated breast-feeding. All women were treated throughout pregnancy with a median daily dose of 150 mg (IQR 100–175). Four also took another cardiotropic agent (betablockers in 3 and diltiazem/enalapril in one). Five newborns were fullterm and 1 was born at week 36 (unknown in 2). Breastfeeding was exclusive in 2 infants and mixed in 5 (unknown in 1). Serum flecainide concentrations at day 15 were below the lower limit of detection in all newborns and an ECG in 2 revealed no abnormality. In 8 infants, clinical examination at day 15 of life was normal and none developed adverse effect. Two children breastfed for 5 and 8 months, were healthy and developed normally at 1 and 2 years of age, respectively.

Conclusions
Our case series found low exposure in breastfed infants from mothers treated with flecainide and no short-term clinical repercussions in these infants. In addition, it is well known that milk or dairy products reduce the absorption of flecainide in neonates and infants. Taken together, these data suggest that breastfeeding during maternal flecainide treatment can be proposed safely.

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Medication use while breastfeeding – Are there problems to solve?

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Introduction
It is recommended that infants be exclusively breastfed for at least the first 6 months. There may be many reasons for breastfeeding cessation, including fears of medications use. We aimed at evaluating how medications compatibility with breastfeeding is accepted by women and how common it is ceased while in a healthcare institution.

Methods
Women who gave birth at the study hospital and stayed with their newborns were asked to participate in a structured interview. The questions included social status, health problems, breastfeeding status, prescribed medications, personal attitude to medications use during breastfeeding and related informational sources.

Results
By the time of the analysis 70 questionnaires were evaluated. Mean age of the women was 32 ± 5 years (17–44). Fifty-eight (84%) women had babies younger than 1 month. Ten women (14%) were not breastfeeding, three of them because of the medications: cyclosporine and antithymocyte globulin; amitriptyline, chlorprothixene, sulpiride; ciprofloxacin. Among breastfeeding women only 19 (32%) were not taking medications. Mean number of medications taken was 2 (1 to 6). The most common medications used while breastfeeding were non-steroidal anti-inflammatory drugs (11 women); paracetamol, oxytocine and ferrous preparations (9 women); low molecular weight heparins and methyldopa (7 women); vaginal antibiotics – 5; glycerin and ampicillin/sulbactam – 4; interferon alfa 2b – 3; thyroxine and nifedipine – 2. Other medications were used by one woman each (warfarin, metoprolol, acetylsalicylic acid, lactulose, sodium citrate). Nine women used herbal products (cranberries – 5; ginger – 2; seaberry – 1; leonurus – 1). The most common health related problems among breastfeeding women were constipation and skeletal pain (27% each), followed by headache and other pains. 78% (58 women) considered breastfeeding important for babies' health; 12% reported that it is not a big problem not to breastfeed; 10% reported that breastfeeding should be ceased as soon as possible for various reasons. Only one woman agreed that all medications are unsafe during pregnancy; 4 women thought that any medication may be harmful, but breastfeeding has more benefits. Only 13 women (19%) reported that they always have information sources to decide whether or not to take a drug while breastfeeding. 58% (40 women) thought that nobody including doctors knows for sure if a medication is safe during breastfeeding. 12 (17%) women would ask other women or relatives about medications safety; 21 (30%) would look for information on the internet. Only 33 (48%) would ask their doctor.

Conclusions
In our small, selected cohort we did not identify medications as a common reason for breastfeeding cessation while in maternity care hospital. Prevalence of medications use was 68%. Most women were positive towards breastfeeding, medications were not considered as a reason not to breastfeed. Still, there is an obvious problem of lack of information about medications safety. A high proportion of respondents would seek advice from non-professionals.

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