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Inivited speakers

The teratogenic risk of caffeine in pregnancy

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Introduction: Caffeine, a methylxanthine alkaloid, is the most widely used stimulant substance in the world. Tea, coffee, cola and cocoa are the main sources for caffeine; it is also added to soda and energy drinks. Many over-the-counter medications also contain caffeine. Caffeine exerts pharmacological and physiological actions at different sites such as stimulation of the central nervous system and cardiac muscle, and relaxation of smooth muscle. In addition, caffeine has effects on physical and cognitive performance, as well as mood, memory, and alertness. In adults, caffeine is principally metabolized in the liver by the cytochrome P450 oxidase enzyme system, through $CYP1A_2$ enzyme. During pregnancy, the $CYP1A_2$ is downregulated so the rate of caffeine metabolism decreases from the first to the third trimester of pregnancy. At the end of pregnancy, the half-life of caffeine is three to four times longer than in the non-pregnant state. Because of the caffeine rapidly crosses the placental barrier and is not metabolized by the fetus, its clearance depends on the maternal rate metabolism.

Methods: In order to identify, the current topic was searched in EMBASE and MEDLINE. Searches were executed using Ovid search engine and were limited to the English language, animal and human studies.

Results: Numerous studies on animals have shown that caffeine exposure can cause birth defects, premature labor, preterm delivery, reduced fertility, and increase the risk of low-birth-weight offspring. In the last decades, many studies have been conducted addressing the risk of caffeine exposure during human pregnancy. Considering the risk of spontaneous abortion from exposure to caffeine, two recent systematic reviews reported an increased risk respectively by 14%, in a linear fashion with every 100 mg/day increase in caffeine consumption, and by 19%, for every increase in caffeine intake of 150 mg/day. Although observational and cohort studies reported conflicting data on the impact of caffeine on birth weight, two metanalyses found that maternal caffeine intake during pregnancy was associated with an increased risk of low birth weight as compared with the reference group (no or very low caffeine intake), with a dose-response of 7% increase for each 100 mg/day. A recent narrative review concluded that caffeine consumption was significantly associated with negative outcomes, including miscarriage, stillbirth, low birth weight, and small for gestational age. Negative outcomes were identified at lower levels of consumption and increased in a dose-dependent manner. Even moderate caffeine consumption (200 mg per day) was alleged to be unsafe.

Conclusions: Assessing consequences of caffeine exposure during pregnancy is extremely difficult in light of biologic and epidemiologic considerations. Overall, low levels of caffeine consumption are not consistently associated with any fetal adversity. Furthermore, more rigorous research with prospective designs is needed to mitigate some of the methodologic weaknesses in the current body of evidence.

Cobalt exposure due to metal on metal hip prosthesis in pregnancy: Toxicological risks

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Introduction: Systemic toxic manifestations associated with metallic alloys used for hip prosthesis have been related mainly to cobalt and cases of toxicity related to metal release have been described in literature. However very few reports involve clinical effects due to cobalt release from hip implants in pregnant women.

Methods: Published data on cobalt exposure due to hip implant in pregnancy have been evaluated with particular focus on cobalt levels (maternal, cord and infant) and clinical outcome of the mother and the infant.

Results: Among human data, successful pregnancies have been reported with maternal, cord and infant cobalt blood levels (mcg/L) that vary from low/normal concentrations of 0.4 (infant) and 0.8 (mother) up to high levels of 143 (mother), 75 (cord) and 13 (infant). The only anomaly reported in a pregnant woman with hip implant was a first-degree hypospadias. In that case, asymptomatic maternal levels were 103 μg/L, with fetal levels of 20 μg/L at 3 weeks of age. The authors point out that hypospadias is relatively common and causality could not be determined. A case of spontaneous abortion was described in a woman at 10-weeks' gestation with high blood cobalt (136 μg/L). The authors concluded that the role of metal could be questionable considering the advanced age and the voluminous uterine fibromatosis condition.

Conclusions: Published data from literature, even if very limited, describe successful pregnancies either with low and high maternal/fetal cobalt concentrations. Nowadays metal hip replacement does not seem to increase the reproductive risk. However, no conclusive data are available and the experience is still limited. Individual conditions, such as clinical manifestations of toxicity arising during the time span after implantation, should be taken into account. Metal monitoring may be indicated in pregnant metal implanted patients and a chelating approach could be evaluated in those cases presenting progressively increasing cobalt maternal blood levels during pregnancy. The Expert Advisory Group of the British Committee on the Safety of the Devices recommends women with metal hip replacements should be advised to postpone pregnancy for at least two years post hip implantation.

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Probably this approach is because the clinical experience is still limited and further investigations are required in order to evaluate pregnancies clinical outcome and offspring physical and mental development. At present metal hip-implants and the detection of increased cobalt levels without maternal adverse effects do not constitute a reason to terminate a pregnancy. However it is something the surgeon and a woman of childbearing age should be aware of when selecting a joint replacement.

Oral presentations

Neonatal morbidity after fetal exposure to antipsychotics - a national register-based study

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Introduction: Data on neonatal outcomes after fetal exposure to antipsychotics are scarce. The objective of this study was to analyze neonatal morbidity and admission rate to neonatal care in infants exposed to antipsychotics *in utero*.

Methods: The rate of admission to neonatal ward and separate neonatal outcomes were compared between infants exposed to antipsychotics *in utero,* infants born to mothers using antipsychotics before or after but not during the pregnancy and the non-exposed population. All singleton births in Sweden between July 2006 and December 2017 were included. Data on prescription drugs, deliveries and infants' health were obtained from the Swedish Medical Birth Register, the Prescribed Drug Register, and the Swedish Neonatal Quality Register. Risk ratios (RR) were calculated with modified Poisson regression.

Results: Among 1,307,587 infants, 2677 (0.2%) were exposed to antipsychotics during pregnancy and 34,489 (2.6%) had mothers who were treated before/after pregnancy. Of the exposed infants, 19.3% were admitted to neonatal care compared with 7.8% in the population (adjusted risk ratio [aRR]: 1.7; 95% confidence interval [CI]: 1.6–1.8), with a further increased risk after exposure in late pregnancy. The adjusted number needed to harm (NNH) was 18. There was no difference in admission rate to neonatal care between first and second generation antipsychotics. The highest risks were seen for withdrawal symptoms (aRR: 17.7; 95% CI: 9.6–32.6], neurological disorders (aRR: 3.4; 95% CI: 2.4–5.7) and persistent pulmonary hypertension, aRR: 2.1; 95% CI:1.4–3.1) when compared to the population. The absolute risks for these outcomes were however low. The risk increases were lower when exposure during pregnancy was compared to treatment before/after pregnancy than when compared to the non-exposed population.

Conclusion: Treatment with antipsychotic drugs during pregnancy is associated with an increased risk for neonatal morbidity. This study indicates that the causes are multifactorial, where the drug exposure is one factor. The neonatal disorders seem transient and predominantly mild, and do not warrant discontinuation of a necessary treatment but rather an increased monitoring of these infants postpartum. The finding of an increased risk for persistent pulmonary hypertension needs to be studied further.

COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry

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Introduction: Pregnant individuals with coronavirus disease 2019 (COVID-19) are at increased risk of severe disease, prematurity, and stillbirth. In March 2021, vaccination for at risk pregnant women was recommended in Switzerland, expanding this to all pregnant women in May 2021. Our aim was to assess the safety of mRNA COVID-19 vaccines in pregnancy.

Methods: This multicentre prospective cohort study evaluated pregnant women who received at least one dose of mRNA vaccine between March and December 2021 in Switzerland, using the COVI-PREG registry. Pregnancy and neonatal outcomes were collected from medical records.

Results: Of 1012 vaccinated women, 894 (88.3%) received both injections during pregnancy, with BNT162b2 ($n = 271$) or mRNA-1273 ($n = 623$) vaccines. Local events (mainly local pain) were reported in 81.3% and 80.5% after the first and second doses. Rates of systemic reactions (mainly fatigue and headache) were similar after the first dose and most frequent after the second dose of mRNA-1273. Of the 1012 women, four severe early adverse events occurred: pulmonary embolism, preterm premature rupture of membranes, isolated fever with hospitalisation, and herpes zoster. Of 107 patients vaccinated before 14 weeks, two miscarriages were reported (8 and 16 weeks). Of 513 women exposed before 37 weeks, 6.4% delivered preterm. Among 530 patients exposed in pregnancy, no stillbirth was reported. Neonatal intensive care unit admission was 4.7%.

Conclusion: Exposure to mRNA vaccines during pregnancy was associated with frequent local and systemic effects, but rare severe events. Women vaccinated during pregnancy did not experience higher adverse pregnancy or neonatal outcomes than in the general obstetric population.

Antiseizure medication use during pregnancy, trends over time and individual treatment pattern: An evaluation of the German Embryotox Cohort

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Introduction: Due to their developmental toxicity, some antiseizure medications (ASM) should be avoided during pregnancy. Concerns about adverse fetal effects may lead to discontinuation or switching of ASMs after recognition of pregnancy. Overestimating prenatal drug risk followed by unnecessary changes of medication may also compromise seizure control. Data on ASM treatment changes during the 1st trimester of pregnancy are still scarce.

Methods: The German Embryotox Pharmacovigilance Institute prospectively ascertained 3763 pregnancies exposed to ASM at conception between 2000 and 2018. These were analysed for trends in ASM use and treatment indication. In addition, treatment pattern during the 1st trimester in women with epilepsy ($n = 2395$) including the proportion of recommended (lamotrigine/levetiracetam) versus non-recommended (valproate/phenobarbital/phenytoin/topiramate) ASMs were evaluated.

Results: There was an increase in women using ASMs for non-epilepsy indications from 19% in 2000 to 39% in 2018. In women with epilepsy, analysis of treatment pattern over time showed a shift from non-recommended teratogenic ASMs to recommended ASMs. However, at

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the end of the study period (2017–2018), 13% of women still used non-recommended ASMs at conception. Despite limited evidence of their safety for the unborn, zonisamide, lacosamide, eslicarbazepine, and brivaracetam as newer ASMs with marketing authorization after 2004 were increasingly used, even shortly after their approval. Among women with livebirth and complete information on course of ASM use 90% (1361/1506) did not change ASM treatment during the 1st trimester, 7% discontinued, and 2% switched to other ASMs. Valproate, oxcarbazepine, and topiramate were more likely discontinued or switched than other ASMs. Focusing on women with ASM monotherapy, 4% discontinued anti-seizure medication, 2% switched to other ASMs, and 1% added an ASM during the 1st trimester. 16% of women with polytherapy at conception reduced the number of concomitantly used ASMs.

Conclusions: This first analysis of treatment pattern in ASM exposed pregnancies in Germany confirms a trend also observed in other countries towards less teratogenic and newer ASMs. However, it remains questionable whether women still using non-recommended ASMs with a teratogenic potential or insufficient evidence of safety are refractory to established low-risk ASMs or if pertinent treatment guidelines and risk minimization measures for women of childbearing age are disregarded.

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Development and validation of a machine-learning algorithm to predict the relevance of scientific articles in teratology

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Introduction: The Teratology Information Service (TIS) Lareb counsels healthcare professionals and pregnant and lactating women to optimize the use of drugs during pregnancy and lactation. In addition, TIS shares its information through a website. To keep the information up to date, employees at TIS have performed a standardized weekly PubMed query for many years. However, the selection of relevant articles is a labor-intensive manual process. We aimed to develop and validate a machine-learning algorithm to predict the relevance of scientific papers and evaluate its suitability as a tool to aid this manual selection process.

Methods: Based on the weekly PubMed query, we generated training data for our machine learning algorithm by downloading all abstracts and PubMed IDs over the last ten years. Articles were subsequently labeled as relevant based on TIS' previous manual rating. A same-sized set of abstracts was selected from the remaining articles and labeled irrelevant. We split the resulting case-control dataset of 15,540 scientific papers into train, test, and validation datasets. A language-model pretrained on a broad biomedical text corpus was fine-tuned to optimally discriminate relevant from irrelevant abstracts (SciBERT transformer, with dropout: 0.2, reshape: 2, learning rate: 1^{e-5}, epochs: 5, and a SoftMax layer). We performed an additional external validation to test our model in practice. This validation used an independent set of 1288 abstracts prospectively collected and labeled by an experienced human TIS rater (gold standard). In addition, a team of five human TIS raters independently labeled the same set of articles to assess the interrater agreement and compare human rater performance to our model's performance.

Results: Validation of our machine learning model on the retrospectively collected outheld dataset showed a balanced classification accuracy of 82% and an area under the receiver operating characteristic of 0.88 (i.e., 0.5 = coin flip, 1.0 perfect classification). In the prospective external validation of the model, our model classified relevant literature with a balanced accuracy of 84%, showing a 95% overlap in predicted and human gold standard classifications. Our model achieved higher sensitivity and specificity compared to the team of human raters (sensitivity of 0.97 vs. 0.96, specificity of 0.7 vs. 0.52). The team of human raters showed weak to moderate levels of agreement in their article classifications (κ range 0.40–0.64).

Conclusions: To keep the teratology information up-to-date, the human selection of the latest literature is indispensable. This important but labor-intensive work could be leveraged with the help of machine learning. We show that automatic pre-selection of relevant abstracts is possible without sacrificing the selection performance. With the cumulation of more training data, which will be gathered when the tool is used in daily practice, we expect an even higher model performance after retraining.

An overview of the UK COVID-19 antivirals pregnancy registry

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Introduction: In the UK, early intervention treatments for COVID-19 (CV-19), including neutralizing antibodies and antiviral medications, are routinely offered to symptomatic adults with CV-19 that are at high risk of developing severe illness. Novel CV-19 antiviral medications including molnupiravir and nirmatrelvir/ritonavir, and the antiviral remdesivir are authorised for such use. Due to the mechanism of action of molnupiravir and results of preclinical animal teratogenicity studies, use in pregnancy is not recommended in the UK, and women of childbearing potential are advised to use effective contraception for the duration of treatment, and for a short period afterwards. Preclinical animal teratogenicity studies have not suggested that nirmatrelvir, ritonavir or remdesivir may be harmful to the developing fetus, but human pregnancy exposure data are either lacking or highly limited. As such, a cautious approach towards use in pregnancy is advised in the UK.

Methods: The UK COVID-19 Antivirals Pregnancy Registry is being operated by UKTIS in collaboration with the Medicines and Healthcare products Regulatory Agency (MHRA) to gather fast real-world fetal outcome information following inadvertent CV-19 antiviral medication exposure in pregnancy. The registry also collects data on the outcomes of pregnancies with paternal exposure to CV-19 antiviral medications. Registration can be undertaken by medication users or healthcare professionals. The registry utilises an enhanced monitoring method, which includes additional follow-up requests than are routinely performed under the standard UKTIS protocol. These follow-ups are conducted after the standard 12 and 20 week prenatal ultrasound scans and at birth. Detailed information about CV-19 disease course, vaccination history, CV-19 antiviral medication adherence and maternal/paternal treatment adverse reactions are collected in addition to the routine data collected by UKTIS.

Results: In line with national recommendations, UKTIS have received minimal reports of inadvertent CV-19 antiviral medication exposure in pregnancy. Up to the end of February 2022, a single case of inadvertent molnupiravir exposure has been reported to the registry. The exposure occurred between four weeks and six days and five weeks and zero days. No maternal adverse effects occurred. Follow-up information is due to be collected in March, May and September.

Conclusions: Due to national recommendations advising against the routine use of CV-19 antiviral medications in pregnancy, it is unlikely that large numbers of exposed pregnancies will be reported to UKTIS. The combination of international data, such as those collected by ENTIS affiliated organisations, will likely be required to collect a large enough sample of exposed pregnancies to provide a timely assessment of fetal safety for CV-19 antiviral medications.

Risk of miscarriage following exposure to NSAIDs during early pregnancy: A systematic review and meta-analysis

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Introduction: Analgesics, including non-steroidal anti-inflammatory drugs (NSAIDs), are widely used medications among childbearing and pregnant women. The data regarding NSAIDs exposure during early pregnancy is still controversial and inconclusive.

We aimed to evaluate if exposure to NSAIDs during early pregnancy increases the risk of spontaneous abortions.

Methods: The systematic review was performed using multiple medical literature databases, including MEDLINE (PubMed), EMBASE, Cochrane Library, and Scopus, using Emtree and MeSH terms. The search included various keywords, and no language or date restrictions were applied. The search included randomized controlled trials and observational studies in which pregnant women were exposed to NSAIDs.

The primary outcome was a spontaneous miscarriage, defined as a miscarriage up to the 20th week. Results analysis was conducted through CMA software using random-effects models. The review protocol was registered at the PROSPERO registry of systematic reviews in October 2019 (CRD42019145150).

Results: Thirteen studies involving 11,182 pregnant women exposed to NSAIDs were analyzed. Risk of spontaneous abortion was not increased following NSAIDs exposure (OR, 1.29; 95% CI, 0.77–2.15 for studies reporting OR, HR, 1.05; 95% CI, 0.90–1.23 for studies reporting HR) with considerable heterogeneity across the studies ($I^2 = 85\%$ and $I^2 = 54\%$, respectively). Further sensitivity and subgroup analyses corroborated these results, including high-quality studies, typical NSAIDs, and one study removed analysis.

Conclusions: This systematic review and meta-analysis did not observe a significantly increased risk of spontaneous abortion following NSAIDs exposure during early pregnancy. Shedding light on this topic can help health care providers in the counseling process and settle the concern regarding NSAIDs' safety during early pregnancy.

Sildenafil and bosentan quantification in human milk: A case report from the ConcePTION project

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Introduction: Sildenafil and bosentan are used to treat pulmonary arterial hypertension (PAH). Published data on the extent of human milk transfer are currently lacking for bosentan, while only one single case-report exists on sildenafil levels in human milk (1.64–4.49 μg/L). Peak plasma concentrations of sildenafil and bosentan at steady-state were 113 μg/L and 333 μg/L. Transfer of these medicines into human milk is expected to be low due to the high protein binding of these medicines. The aim of the case presented here was to quantify human milk levels of both sildenafil and bosentan, and to report on the health of the nursing infant.

Methods: A 43-year-old woman using sildenafil (20 mg, 3×/day) and bosentan (125 mg, 2×/day), and breastfeeding her 21-month-old infant ~ three times a day collected milk samples during steady-state therapy over 24 h on two sampling days (with a 14 days interval). Sildenafil and bosentan levels were determined with a bioanalysis method based on liquid chromatography with tandem mass spectrometry (LC-MS/MS). Information on the health of the infant until sampling was reported in a questionnaire by the mother. Approval from the Ethics Committee Research UZ/KU Leuven (S64702) and written informed consent were obtained prior to milk sampling.

Results: The average steady-state human milk concentrations of sildenafil (2.84 μg/L) and bosentan (49.0 μg/L) were low. On sampling day 1 and 2, the estimated infant doses via human milk were 0.02 and 0.03 μg/kg/day for sildenafil and 0.29 and 0.60 μg/kg/day for bosentan. The relative infant dose (RID) values were 0.003% and 0.005% for sildenafil, and 0.01% and 0.02% for bosentan. For an exclusively breastfed infant with an average milk intake of 150 mL/kg/day, the estimated infant doses via human milk were 0.43 μg/kg/day for sildenafil and 7.43 μg/kg/day for bosentan, corresponding to RID values of 0.06% and 0.24%, respectively. No adverse effects in the breastfed infant were reported since the start of maternal medication use.

Conclusions: In this case-report, the human milk concentrations of sildenafil and bosentan were low, with RID values below 1%. Based on a milk intake of 150 mL/kg/day, the estimated infant dose via human milk for sildenafil (0.43 μg/kg/day) and bosentan (7.43 μg/kg/day) are 2–3 orders of magnitude below the therapeutic infant dose of sildenafil (1500 μg/kg/day) and bosentan (4000 μg/kg/day). Nevertheless, further studies are needed to confirm these results.

Pregnancy outcome following first-trimester exposure to mirtazapine: An observational comparative cohort study

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Introduction: Untreated depression in pregnancy has been associated with various health concerns for both the infant and the mother. Mirtazapine is an effective and well-tolerated tetracyclic antidepressant. Data on mirtazapine in pregnancy are relatively limited. The objective of this study was to evaluate the rate of major congenital anomalies following 1st trimester exposure to mirtazapine compared to two groups: 1st trimester exposure to Selective Serotonin Reuptake Inhibitors (SSRIs) & non-teratogenic exposure (NTE). Secondary endpoints were pregnancy outcome, prematurity rate, gestational age at delivery, birth weight, mode of delivery, and neonatal complications.

Methods: This is an observational comparative cohort study that was conducted in the Israeli Teratology Information Service, Ministry of Health. Callers who were counseled between 2002 and 2020 were prospectively followed-up. The time-frame was similar between the groups.

Results: Follow-up was obtained in 248 pregnancies exposed to mirtazapine in the 1st trimester, compared with 248 SSRI exposed pregnancies and 744 pregnancies in the NTE group. The risk of overall major anomalies in the mirtazapine group compared to the NTE was not significantly different [OR_{crude} 1.48; 95% CI (0.69–3.18) and OR_{adj} 1.33; 95% CI (0.60–2.97)]. A similar finding was observed in the SSRIs vs. NTE [OR_{crude} 1.45; 95% CI (0.67–3.11) and OR_{adj} 1.46; 95% CI (0.66–3.23). After excluding genetic/cytogenetic anomalies, the rate of major anomalies was not significantly different in the mirtazapine vs. NTE groups [OR_{crude} 1.78; 95% CI (0.65–4.88) and OR_{adj} 1.81; 95% CI (0.63–5.21)], nor in the SSRIs vs. NTE comparison [OR_{crude} 2.02; 95% CI (0.77–5.28) and OR_{adj} 1.80; 95% CI (0.67–4.84)]. The HR_{adj} for miscarriages in the mirtazapine vs. NTE group was 1.31; 95% CI (0.93–1.96) and 1.41; 95% CI (0.97–2.07) in the SSRIs vs. NTE comparison. The rate of major anomalies without genetic/cytogenetic for mirtazapine monotherapy vs. NTE was not significantly different between the groups. Similarly, there were no significant differences between the groups in other pregnancy outcomes of interest.

Conclusions: This is the first study in Israel to assess the risk of major anomalies after exposure to mirtazapine. Mirtazapine does not appear to be associated with an increased risk of major anomalies. However, larger studies are needed before definitive conclusions can be drawn. Pregnancy outcomes after mirtazapine exposure in this study were reassuring and similar to those observed in the SSRIs group.

Potential sources of bias in the analysis of COVID-19 vaccine

safety during pregnancy: How the embryotox study plans to avoid them by design and analysis methods

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Introduction: Many studies are currently investigating the safety of COVID-19 vaccines in pregnant women. Primary endpoints focusing on pregnancy outcomes are often major birth defects and spontaneous abortions. However, many studies report crude proportions and therefore do not account for most types of biases in the analyses of those endpoints.

Methods: The types of bias include a) reporting bias by combining prospectively and retrospectively collected data, b) length bias when not accounting for a delayed study entry, i.e., left-truncation, c) immortal time bias when neglecting the time-dependency of the vaccination, d) competing risk bias when censoring competing events. Furthermore, an adequate comparison cohort and adjustment for covariates are essential prerequisites. Multistate survival models and an appropriate study design can account for these sources of bias in the analysis of spontaneous abortions. Furthermore, they distinguish between the different doses and vaccine types. For the analysis of major birth defects, vaccinations in the first trimester are of interest. Logistic regression with adjustment of covariates by inverse probability of treatment weighting is planned to be used in our analysis.

Results: The study period of the study investigating the safety of the COVID-19 vaccination during pregnancy is from January 2021 until the end of September 2023. In 2021, Embryotox received over 6400 inquiries with COVID-19 vaccination during pregnancy, for which the follow-up was initiated. Although the follow-up is not complete for a large part of these prospectively ascertained data, the response rate so far shows that the sample size will be sufficiently large to apply complex statistical models. Furthermore, retrospective pregnancy case reports are also collected and will be analyzed separately. The standardized procedure of data collection also enables to separately consider pregnancies exposed to teratogens or fetotoxicants to avoid overestimating the risk.

Conclusions: By design and advanced statistical methods, the Embryotox study on the COVID-19 vaccination during pregnancy avoids certain kinds of biases. Applying these methods, more precise estimates of pregnancy outcome data are obtained.

Pregnancy outcomes after maternal exposure to trazodone in pregnancy: Preliminary results of a comparative ENTIS cohort study

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Introduction: The aim of this study was to assess the risks linked to trazodone exposure during pregnancy for which limited safety data is available.

Methods: This multicentre, observational prospective cohort study compared pregnancy outcomes in women exposed to trazodone in early pregnancy compared to a reference group of women exposed to a SSRI (sertraline, citalopram or escitalopram). Data were collected between 1996 and 2021.

Results: The sample included 221 trazodone and 869 SSRI exposed pregnancies. Exposure to trazodone in the first trimester was not associated with a difference in the risk of major congenital anomalies (trazodone (1/169, 0.6%), SSRI (18/730, 2.5%), crude odds ratio 0.2; 95% [confidence interval (CI) 0.03–1.8]. The cumulative incidences of live birth were 61% and 73% in the trazodone and reference group respectively (HRadj 1.1 [95%CI 0.9–1.3]. Trazodone exposure was not associated with a significantly increased risk of termination of pregnancy (HRadj 1.6 [95%CI 0.9–2.7]) and spontaneous abortion (HRadj 1.4 [95%CI 0.9–2.2]). There was a trend toward a higher preterm birth rate (13.5% versus 8.3%, $p = 0.05$) and earlier gestational age at birth (median 39 weeks, interquartile range (IQR) 37–40 versus median 39, IQR 38–40, $p = 0.03$) in the trazodone group compared to the SSRI group. Birthweight (median 3125 g, IQR 2800–3500 versus 3162 g, IQR 2880–3500, $p = 0.64$) did not differ between the groups.

Conclusions: This study did not reveal a significant difference in the risk of major birth defects after first trimester exposure to trazodone, compared with SSRI exposure. Even though this study is the largest comparative evaluation of teratogenic effects of trazodone so far, its sample size is still limited and the results call for confirmation through further studies.

Posters

Development of a process for collaborative management of the IMI ConcePTION Knowledge Bank

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Introduction: Mums Using Medicines Safely (MUMS) is an EU centralised digital knowledge bank (KB) which is being developed as part of the IMI ConcePTION project (www.imi-conception.eu). The KB aims to provide up to date, evidence-based information to healthcare professionals and members of the public on the use of medicines during pregnancy and breastfeeding. The content of the KB will be collaboratively developed by experts in the area of medicine use in pregnancy and breastfeeding, including ENTIS affiliated teratology information services (TISs). Here we describe the development and testing of procedures which will be used to collaboratively create and maintain information pages and other content on the KB. This work has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking ConcePTION grant no. 821520.

Methods: IMI ConcePTION subtask 5.2.4 group members included representatives from several ENTIS affiliated TIS and a medication use in breastfeeding advice service from the UK. Group members met regularly to plan and design KB processes and content. Development of the KB content benefited from expertise of ENTIS members and previous work with similar systems. The structure and functioning of the KB was agreed through an iterative process of testing and review. A Standard Operating

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Procedure (SOP) was developed to ensure content written for the KB is accessible, comprehensive and of high-quality. Feedback was obtained from potential end-users and other stakeholders. Considerations for sustainability of the KB were explored through a joint meeting of ENTIS and ConcePTION partners.

Results: A Standard Operating Procedure (SOP) to guide the production of content for the EU KB has been developed and agreed by participating ENTIS members. This SOP sets out; a process for collaborative working and work sharing between KB contributors throughout Europe, the proposed structure and content of individual information page and a detailed 8-step procedure for the development and update of individual information pages. This process is now being tested in the creation of the initial knowledge pages.

Conclusions: This SOP outlines the collaborative process for writing content for the European-wide KB on medication use in pregnancy and breastfeeding, which is being developed within WP 5.2 of the IMI ConcePTION project. The KB presents a unique opportunity for collaboration between TISs to provide accessible, trustworthy and consistent information to a wide audience across Europe. Processes outlined in this SOP will inform and support further development and sustainable, collaborative maintenance of the KB in the future.

Which elements do we include, and how do we present them, in answers on use of medications during breastfeeding? A descriptive pilot study

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Introduction: Most medications can be used while breastfeeding. To avoid unnecessary discontinuation or refrainment from use of medications, or avoidance of breastfeeding, access to well-balanced information is crucial. Health care professionals use several elements in the assessment of safety of medications during breastfeeding. However, international literature is scarce on which elements that should be included, and how they should be presented, in written information to breastfeeding women. The objective of this pilot study was to systemize and describe how a Norwegian web-based medicines information service directed at breastfeeding women present answers concerning use of medications during breastfeeding.

Methods: Answers to questions received through SafeMotherMedicine's web-based service for pregnant and breastfeeding women are stored full-text in a database. From at total number of more than 35,000 question-answer pairs, 50 question-answer pairs from January 1st to December 31st 2021 regarding use of medications during breastfeeding were randomly selected from the database. The answers were analyzed using text inspection, examining for the presence of several pre-defined elements, and assessment of their qualities. The predefined elements were chosen by the authors based on more than ten years experience with SafeMotherMedicine. Descriptive statistics were used for analysis.

Results: In the majority of the answers (86%), it was concluded that the medication could be used during breastfeeding. In 12%, caution or avoidance was advised, and in 2% of the answers, there were no conclusion with regard to use during breastfeeding. Inclusion of predefined elements, and how they were presented, was: Transfer of medication into breast milk was addressed in 92% of the answers. The degree of transfer was exclusively presented using verbal expressions, with no use of numeric expressions. Other pharmacokinetic principles relevant for the exposure of the breastfed child, such as bioavailability, were mentioned in 52% of the answers. In 70% of the answers, possible side effects in the breastfed child was discussed, and in more than half of these answers, the parents were recommended to observe the breastfed child for possible side effects during maternal use of medication. The age of the breastfed child was mentioned as a principle for safety assessment in 44% of the answers.

Conclusions: This pilot study has identified frequently used elements, and their presentation, in written answers to spontaneous questions on use of medications from breastfeeding women. The findings could motivate discussions among health care professionals providing information on medications. The results represent a preliminary foundation to further explore written risk communication on use of medications during breastfeeding.

Use of prescribed drugs to treat chronic diseases during pregnancy in outpatient care in Switzerland between 2014 and 2018: Descriptive analysis of Swiss health care claims data

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Introduction: Evidence on the use of drugs during pregnancy in Switzerland is lacking. We aimed to evaluate the utilization of drugs to treat chronic diseases during pregnancy in Switzerland.

Methods: We identified all pregnancies (excluding abortions) in Swiss Helsana claims data (2014–2018). In those, we identified all claims for drugs to treat a chronic disease, which typically affect women of childbearing age. Potentially teratogenic/fetotoxic drugs were evaluated during specific risk periods. Results were demographically weighted relative to the Swiss population.

Results: We identified claims for ≥1 drug of interest during 22% of 369,371 weighted pregnancies. Levothyroxine was most frequently claimed (6.6%). Antihypertensives were claimed during 5.3% (3.9% nifedipine in T3). Renin–Angiotensin–Aldosterone System (RAAS) inhibitors were dispensed to 0.3/10,000 pregnancies during trimester 2 (T2) or trimester 3 (T3). Insulin was claimed during 3.5% of pregnancies, most frequently in T3 (3.3%). Exposure to psychotropic drugs was 3.8% (mostly Selective serotonin reuptake inhibitors (SSRIs)) and to drugs for obstructive airway diseases 3.6%. Traditional immunosuppressants (excluding corticosteroids) were claimed during 0.5% (mainly azathioprine and hydroxychloroquine), biologic immunosuppressants (Tumour necrosis factor-alpha (TNF-alpha) inhibitors and interleukin inhibitors) during 0.2%, and drugs to treat multiple sclerosis during 0.09% of pregnancies. Antiretrovirals were claimed during 0.15% of pregnancies.

Conclusions: Patterns of drug claims were in line with treatment recommendations, but relatively rare events of in utero exposure to teratogenic drugs may have had severe implications for those involved.

Mental health of pregnant and postpartum women during the third wave of the Covid-19 pandemic – a European cross-sectional study

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Introduction: There is mounting evidence that the COVID-19 pandemic disproportionately affects pregnant and postpartum women's mental health compared to the general population, due to fear and concerns about the well-being of their unborn child and neonate. This study aimed to describe the mental health of pregnant and postpartum women in five European countries during the third wave of the pandemic and to identify risk factors related to depressive and anxiety symptoms among pregnant and postpartum women.

Methods: An online survey was performed in Belgium, Norway, Switzerland, the Netherlands, and the United Kingdom between 10th June and 22nd August 2021. The Edinburgh Depression Scale (EDS) and the Generalized Anxiety Disorder seven-item scale (GAD-7) were used to assess mental health status. Univariate and multivariate generalized linear models with logit and log link were performed to identify factors associated with poor mental health.

Results: 5210 women participated (including 3411 pregnant and 1799 postpartum women). The prevalence of major depressive symptoms (EDS $\geq$ 13) was 16.1% in the pregnancy and 17.0% in the postpartum group. Moderate to severe generalized anxiety symptoms (GAD $\geq$10) were found among 17.3% and 17.7% of the pregnant and postpartum women. Risk factors associated with poor mental health included having a chronic mental illness, a chronic somatic illness, having COVID-19 or its symptoms, smoking, having an unplanned pregnancy, and country of residence. Pregnant and postpartum women were most anxious about the thought of not having their partner present at the time of delivery, that their partner had to leave the hospital early and being separated from the newborn infant after delivery.

Conclusions: Approximately one in six pregnant or postpartum women in five European countries reported symptoms of major depression or anxiety during the third wave of the pandemic. These findings suggest that there is a continued need to monitor depression and anxiety in pregnancy and postpartum populations throughout the entire pandemic. Tailored support and counselling are essential to reduce the burden of the pandemic on perinatal and infant mental health.

Open issues in management of carbon monoxide poisoning in pregnancy: Practical suggestions

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Introduction: Carbon monoxide (CO) poisoning is still a challenging toxicology emergency worldwide. It may have potentially serious adverse effects for the mother and the fetus. As a result of intrauterine hypoxia, it may lead to fetal death or severe neurological sequelae. After exposure in the first trimester, several types of malformations have been reported. In this letter, in accordance with all Poison Control Centers and Hyperbaric Medicine Units in Lombardy, we report some practical suggestions for organizations wishing to develop their own protocols and/or initiatives.

Methods: In order to identify the current approaches to CO poisoning in pregnancy the topic was searched in EMBASE and MEDLINE. Searches were executed using Ovid search engine and were limited to the years 1969 to 2021, the English language, and human subjects.

Results: EMBASE and MEDLINE yielded 305 citations. Almost all authors indicate that oxygen treatment is imperative, and many of them recommend hyperbaric oxygen therapy (HBO) for pregnant patients. However, it was not possible to identify evidences nor agreed criteria. Some authors recommend HBO in every instance of alteration in consciousness' and others, once the maternal carboxyhemoglobin level is greater than 10% to 20%.

Conclusions: As evidence-based studies are lacking, based on the CO pathophysiology, we suggest that pregnant women acutely poisoned by CO should be treated with 100% oxygen via a tight-fitting face mask until the patient is transferred to the hyperbaric room. HBO should be performed if (i) the patient reveals any mild, moderate or severe sign or symptom of CO toxicity, not limited to neurological effects and including myocardial injury, or (ii) the maternal carboxyhemoglobin levels are greater than 5% in non-smokers and $>$ 10% in smokers, even if the patient presents no symptoms, or (iii) any signs of fetal compromise occur. Obstetric evaluation should be performed in emergency room before HBO treatment. HBO therapy should be repeated 6 to 12 h following the first HBO administration if the fetus shows signs of distress. Finally, it should be offered a detailed fetal ultrasound scan and a fetal echocardiography 24 to 48 h after CO poisoning, to be repeated 15 to 30 days later. In our opinion, the different timing of CO elimination from the maternal and fetal compartment can cause errors in clinical management, if the poisoning is assessed on maternal parameters alone, thus requiring to adapt the usual criteria for adult patient treatment. It should be noted that low CO levels in the mother do not exclude ongoing poisoning in the fetal compartment that requires its own proper treatment.

Can topical NSAIDs be used by pregnant women in the third trimester? A review of the literature and practical recommendations

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Introduction: Over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) are available in all parts of the world. Review of enquiries to the Web-based service for pregnant and lactating women in Norway (Safe Mother Medicine) shows that several pregnant women are asking about the safety of topical NSAIDs during pregnancy. Topical NSAIDs are generally thought to result in very low blood levels. However, even single doses of oral NSAIDs in the third trimester may lead to clinically significant constriction of the ductus arteriosus (DA). The objective of our work was to assess the risk of topical NSAIDs exposure during late pregnancy, aiming to prepare practical advice about use of topical NSAIDs in this population.

Methods: Literature search of medical databases. The search strategy involved three separate components: 1) topical NSAIDs and pregnancy, 2) systemic absorption of topical NSAIDs and 3) systemic adverse effects of topical NSAIDs.

Results: Our literature search resulted in three case reports where short term maternal exposure to topical NSAIDs during late pregnancy (week 26–35) was suspected to result in antenatal closure of the DA. We also found a case series with three cases of prenatal constriction of the DA after maternal benzydamine local therapy (3 mg lozenges) in third trimester pregnancies. The summary of product characteristics state that NSAIDs gels are contraindicated during the third trimester, but standard sources, with the exception of Swedish Janusinfo, do not give any information or advice on the topic. Topical therapies avoid first-pass metabolism of oral drugs, and the systemic exposure is probably highly variable. The manufacturer of diclofenac gel states that systemic absorption of the 1% concentration applied on healthy skin reached 6 to 7% in healthy individuals. However, we have also found data that

systemic exposure after application of 4 g of 1% diclofenac gel to each knee and 2 g to each hand 4 times daily for 7 days equated to an AUC of 19.7% of the values obtained after use of oral diclofenac sodium 50 mg 3 times daily. Although topical NSAIDs are clearly safer than oral NSAIDs, there are indications of systemic adverse events with topical agents in the literature.

Conclusions: The literature does clearly not provide enough evidence to draw definite conclusions on the safety of topical NSAIDs during the third trimester. To be on the safe side we recommend that pregnant women in the third trimester should only use topical NSAIDs under medical supervision and only when strictly necessary. Further discussion by the ENTIS members are warranted.

Why did the Magdalena study- an RCT on the effects on infants born to women with treatment of depression in pregnant women-fail?

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Introduction: Depression and its treatment during pregnancy are well studied, however, there is still a lack of knowledge on the long-term outcome in the children born to mothers with depression and/or treatment with antidepressants during pregnancy. We aimed to study the outcome at 2 years of age in two randomized groups of children exposed to sertraline or placebo during fetal life. However, we failed and we aim to describe and discuss possible factors causing the failure and suggest future directions.

Methods: A randomized placebo-controlled trial (RCT) of 200 women with moderate depression during pregnancy, and no on-going antidepressant drug treatment. All women received internet-based cognitive behaviour therapy (I-CBT), 100 were supposed to be randomized to treatment with sertraline and 100 to placebo. All women were assessed by a psychiatrist. The women were closely monitored during pregnancy by the study midwife and a specialist nurse in psychiatry. The infants were assessed in the newborn period, at three months and two years of age. Recruitment area was the Stockholm region, with around 29,000 births/year and a 10% rate of depression during pregnancy, 2% of all pregnant women receive treatment with SSRI, which means that about 50 women should have been eligible each year.

Results: The women were recruited through maternity clinics, advertisements, and social media, where we had an active campaign. In total, 51 women performed the depression screening, 19 fulfilled the criteria for inclusion. Only 16 women participated in the study, 12 infants were examined at birth and one child was evaluated with Bayley Scales of Infant Development® at 2 years of age. The participation rate to the I-CBT was low in both groups. However both groups showed decreasing signs of depression evaluated by Montgomery Asberg Depression Scale (MADRS®) during follow-up.

Conclusions: It is urgent to find methods to evaluate long-term outcomes in children exposed to drugs during fetal life. RCTs should be the golden standard. However, there is great difficulty in recruiting pregnant women with depression to RCTs. We witnessed a general fear of drug treatment during pregnancy from the women, the depression itself may make it difficult for the women to seek help and participate and there are difficulties connected to clinical studies with long-term follow-up. These were some of the obstacles during the study, despite the fact that we had very dedicated and skilled staff working with the study. How to design an optimal study on long-term outcome in children exposed to antidepressants during pregnancy is a discussion that needs to take place amongst experts in the field. Are register-based studies enough or do we think that a clinical trial with another design could satisfactorily answer the question?

Neonatal outcome and adherence to drug therapy in bronchial asthma in pregnancy

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Introduction: During an acute asthmatic attack, embryo and fetus may be affected by lack of oxygen. Women with asthma tend to worry about how pregnancy will affect their breathing and if asthma medicines will harm the baby. Asthma is common among pregnant women and if not controlled can lead to complications. For this reason, it is of paramount importance that asthmatic mothers, do not stop asthma treatments and perform regular and targeted checks during pregnancy.

The aim of the research was to compare neonatal outcome in a population of asthmatic patients and a control group of non-asthmatic women.

Materials and methods: We conducted a retrospective cohort study on data collected by the Teratology information Service of Careggi University Hospital between 1 January 2009 and 31 December 2018, analyzing a population of asthmatic patients divided in 3 groups (one with regular inhalation treatment, one with on-demand inhalation therapy, and one with no therapy) compared to a control group of non-asthmatic women. Demographic characteristics of women enrolled in the study included: age, body mass index, education level, smoking habits, alcohol and/or substance abuse. The presence of hereditary diseases in personal or family history, as well as history of any previous pregnancies and their outcomes were investigated. Regarding the characteristics of asthmatic patients during pregnancy, the following variants were considered: pneumological specialist examinations and the number of acute asthmatic attacks during the gestational period. Neonatal outcomes were: live-born pregnancy outcomes, miscarriages, elective and therapeutic termination of pregnancy and fetal death. Type of delivery, weeks of gestation, the initial weight assessment, length and cranial circumference at birth, APGAR score were recorded. Eventually, we observed the incidence of major congenital malformations.

Results: Asthmatic patients with regular background therapy were 789, asthmatic patients with therapy on demand 206, asthmatic patients without therapy 285. The cohort of non-asthmatic patients consisted of 4408 women. We found that there was no increased risk of malformation for anti-asthmatic therapies and that uncontrolled asthma may increase the frequency of: caesarean section delivery, low birth weight and preterm birth. This last neonatal outcome was found to be statistically significant in the logistical regression and therefore poor adherence to therapy can be considered a risk factor for preterm delivery in older asthmatic patients.

Conclusions: Our study confirms that good adherence to asthma therapy, good prenatal counselling and good control of the underlying chronic disease are fundamental conditions for the success of pregnancy.

Feasibility assessment and validation of the prototype of the Belgian data registration system on medication use during pregnancy and mother-infant outcomes ('BELpREG')

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Introduction: Prospective data collection and pharmacoepidemiologic research on medication safety during pregnancy is lacking in Belgium. Therefore, in 2021, we developed a prototype of the Belgian registration system 'BELpREG', allowing comprehensive data collection on maternal medication use and mother-infant outcomes through online questionnaires. After 'in-house' testing, the feasibility and validity of data collection by the BELpREG prototype will be assessed during a pilot study.

Methods: The 18-month pilot study will kick-off in Spring 2022 by launching data collection in five purposively sampled primary care regions in Flanders, Belgium. All Dutch-speaking pregnant women, ≥18 years, are eligible for data registration. After the 'intake' questionnaire, women will receive a follow-up questionnaire each four weeks, with a maximum of ten questionnaires during pregnancy and two postpartum. Ethical approval is pending. Informed consents will be obtained prior to the first questionnaire.

Results: The goal is to recruit 750 women during the pilot period (±10% of the population). Feasibility and validity will be assessed in four complementary stages. First, completeness of the collected data will be evaluated, both within questionnaires (i.e., missing variables) as at consecutive timepoints (i.e., loss to follow-up). Second, the 'reach' or representativeness of the BELpREG pilot sample will be examined by comparing women's characteristics to population statistics. Third, to assess data correctness and the sensitivity of BELpREG to collect reliable outcome data, the outcome data registered by women will be compared to data available in medical and obstetric records. Finally, women's experiences with data registration through questionnaires will be repeatedly investigated using surveys and interviews; HCPs' experiences with informing and motivating women to enroll in BELpREG will be assessed during interviews and focus groups. This iterative mixed-methods approach aims to result in optimal recruitment, accessibility, and ease of use of the registration system.

Conclusions: This dynamic process of pilot testing followed by system modifications and improvement strategies will eventually result in a robust, patient-friendly and 'fit-for-purpose' research instrument, ready for large-scale implementation in Belgium and within the ENTIS network.

Experiences and perspectives of pharmaceutical industry towards the monitoring of medication safety during pregnancy: A qualitative analysis on a pan-European level

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Introduction: Marketing authorization holders (MAHs) are involved in monitoring medication safety through post-marketing spontaneous reporting or product-specific registries. However, it is unclear how MAHs experience their role and current activities with regard to pregnancy. Therefore, the aim of this study was to gain insight into the experiences and perspectives of MAHs towards the monitoring of medication safety during pregnancy.

Methods: A qualitative study using online focus group discussions with purposively sampled MAHs and the Belgian umbrella organisation of MAHs was conducted in June–July 2021. Focus groups were organized until data saturation was reached. Data were analysed using an inductive thematic analysis. Ethical approval (SMEC KU Leuven; G-2021-3245; 23/04/2021) and informed consent of participants was obtained.

Results: In total, 38 representatives of nine organisations participated in the focus groups. Participants reported several difficulties with data collection on medication use in pregnancy: underreporting of exposure and outcome data by patients and healthcare professionals (HCPs), collection of incomplete information and loss to follow-up. MAHs acknowledged that their current monitoring activities regarding medication safety in pregnancy result in poor returns compared to the invested resources, illustrated by the limited high-quality data collected, the unknown denominator and the lack of available comparator data. These obstacles complicate MAHs' data processing activities, preventing them from providing decisive statements in the pregnancy label. Based on the experiences reported by MAHs, three 'conflicts' inherent to their specific role and position were identified, explaining their difficulties with providing timely evidence on medication safety in pregnancy. The first 'conflict' relates to the concept of (mis)trust. While patients and HCPs are the main actors to provide data, participants indicated that both actors often show suspicion towards data reporting to MAHs. The second 'conflict' is related to MAHs' legal obligations and constraining factors inherent to the regulatory framework. As third 'conflict', MAHs' position outside the healthcare context was seen as a barrier as proximity to patients and HCPs was considered a prerequisite for successful data collection. MAHs suggested that data registration should ideally occur in close collaboration with patients and HCPs, organized within the healthcare context and performed using a user-friendly system.

Conclusions: MAHs jointly acknowledged experiencing multiple obstacles regarding data collection, processing, and communication of evidence in the pregnancy label, perpetuating the existing lack of safety evidence on this topic. The identified conflicts highlight the need for more effective, preferably collaborative strategies to prospectively collect real world data to fill the current information gap on medication safety in pregnancy.

Information needs and preferences of pharmacy staff regarding safe compounding of medicines during pregnancy and lactation: Results from a cross-sectional survey in Belgium

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Introduction: Pharmacy staff can be exposed to medicines when compounding. Exposure during pregnancy or lactation may hold a risk to the unborn or nursing infant. In the absence of up-to-date information, this may raise safety questions. Still, the extent and type of questions among pharmacy staff in Belgium has not been thoroughly studied. Therefore, the aim was to gain insight into the information needs and preferences of pharmacy staff regarding safe compounding of medicines during pregnancy and lactation. The findings also provide evidence on the type of medicines that are considered to pose a risk.

Methods: A cross-sectional, anonymous web survey (Dutch/French) was distributed between September–November 2021 among pharmacists and pharmacy technicians (PTs) in Belgium, in community as well as in the hospital setting. The survey explored personal characteristics, individual safety questions and information preferences, and was promoted via newsletters and social media of professional organizations and companies commercializing compounding ingredients. Ethical approval (MP018096) and online consent of participants were obtained. Results were descriptively analyzed.

Results: In total, 153 community pharmacists, 82 hospital pharmacists and 26 PTs employed all over Belgium participated ($N = 261$); the majority was female (90%) and Dutch speaking (87%). Overall, 98% had already questioned the risks to pregnancy or lactation in women compounding medicines; 32% questioned safety for men. With regard to compounding by women, 60% had reflected upon the likelihood of 'specific' risks, including congenital anomalies (97%), miscarriage (83%), developmental disorders (78%), and infertility (74%). Most frequently questioned medicines here were tretinoin (82%), metronidazole (74%), finasteride (71%), corticosteroids (69%) and methadone (66%). With regard to compounding by men, 41% had reflected upon

the likelihood of 'specific' risks, including reduced semen quality (85%) and congenital anomalies in the offspring (80%). The medicines most frequently considered by pharmacy staff to pose a risk were metronidazole (35%), vitamin A derivatives (35%), 5α-reductase inhibitors (31%), anticonvulsants (18%), corticosteroids (15%) and antibiotics (13%). All respondents (99%) agreed that safety information on manipulating medicines during pregnancy or lactation should be available. Respondents were mainly interested in concrete advice ('manipulate it or not') (97%) – if possible per trimester (73%), specific protective precautions (86%) and information on 'specific' risks (71%), preferably accessible online (79%), as a poster (78%) or integrated in the pharmacy software (51%).

Conclusions: Despite the overrepresentation of female pharmacy staff of reproductive age, information needs towards safe compounding of medicines during pregnancy or lactation were ubiquitous. Besides, one-third had already questioned pregnancy-related risks of paternal exposure during compounding. These findings highlight the importance of up-to-date safety information on this topic, which needs to be provided to pharmacy staff in Belgium soon.

Psychomotor development of children exposed to Ondansetron during pregnancy: A prospective cohort study

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Introduction: Nausea and Vomiting in Pregnancy (NVP) is a very common phenomenon, affecting up to 85% of pregnant women. While mild to moderate NVP is not associated with a high risk for the mother and fetus, it has an impact on the quality of the mother's life. Severe NVP and Hyperemesis Gravidarum (HG) are both hazardous for the mother and can endanger the normal development of the newborn. Ondansetron's safety in pregnancy is controversial. Some studies reported an increased risk of congenital defects, while others reported no increased risk. The data regarding the psychomotor development of children following ondansetron use during pregnancy is scarce. We aimed to evaluate the psychomotor development of children exposed to Ondansetron in pregnancy.

Methods: A prospective cohort study. Mothers who suffered from NVP and contacted TIS Zerifin seeking information regarding NVP treatment were prospectively followed up. The psychomotor development was assessed by using Pediatric Quality of Life (PedsQL). We also used Denver milestone scale for baby's gross motor development.

Results: A total of 260 women were included in the analysis, 137 women exposed to Ondansetron and 123 women exposed to other (non-teratogenic) medications for NVP. There were no differences between the groups in respect to newborn malformations or newborn weight. Children exposed to Ondansetron and those in the control group both had very high PedsQL scores with no statistical significance in the subcategories. The only statistically-significant finding was in emotional function category. The median score of emotional function in the study group was 95, while non-exposed had the median score of 90 ($P = 0.04$). No statistical significance between the groups was found in Denver development scale. Regression models adjusted to maternal age and education, PUQE score and other psychotropic medications failed to show increased risk for negative PedsQL score – psychosocial health: aOR 0.89, 95%CI (0.47,1.67), $p = 0.7$, physical health: aOR 1.08, 95%CI (0.46, 2.54), $p = 0.9$. There was a trend in Cognitive functioning below 90: aOR 1.99, 95%CI (0.95, 4.22), $p = 0.07$.

Conclusions: Exposure to Ondansetron during pregnancy was not associated with negative psychomotor offspring's development. Due to the small sample size in this study, further studies are needed in order to conclude on the effect of exposure to Ondansetron on the child's development.

Neurodevelopmental outcome of children exposed to Selective Serotonin Reuptake inhibitors (SSRI's) or Attention Deficit Hyperactivity Disorder (ADHD) stimulant medications during pregnancy: A prospective cohort study

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Introduction: The use of stimulant drugs and SSRIs has increased in recent years. There are studies examining the association between SSRIs exposure and neurodevelopmental and behavioral disorders in children. However, due to the conflicting data and the paucity of existing information, it is important to investigate this field. The aim of the study was to assess the neurodevelopment of children exposed during pregnancy to SSRIs or to stimulants, versus a control group.

Methods: A prospective cohort study of pregnant women who applied to the TIS Zerifin between the years 2015–2018 for information on the safety of the use of stimulants, SSRIs (study group) or pharmacological therapy for nausea and vomiting during pregnancy (control group). Telephone follow-up was conducted to assess pregnancy outcomes and the neurodevelopment of the children.

Results: Stimulants, SSRIs and control group included 34, 159 and 109 cases, respectively. Multivariate analysis found that exposure to stimulants increases the probability of maternal complications at birth compared to the control group (OR = 3.00, 95% CI 1.05–8.61, $P = 0.04$). Exposure to stimulants increases the probability of an equal to or lower than 90 PEDsQL (Pediatric Quality of Life) score in the cognitive function category (OR = 3.50, 95% CI 1.00–12.24, $P = 0.05$). Exposure to SSRI's increases the probability of complications in the newborn after birth (OR = 4.13, 95% CI 1.92–8.92, $P < 0.01$). In addition, exposure to SSRI's increases the probability of an equal to or lower than 90 PEDsQL score in physical function (OR = 3.26, 95%CI 1.38–7.66, $P = 0.007$) and in the physical health summary (OR = 2.61, 95%CI 1.14–5.99, $P = 0.02$). The probability of speech delay according to mother's report (OR = 9.07, 95% CI 1.14–71.93, $P = 0.04$) and according to the DDST (Denver Developmental Screening Test) (OR = 7.25, 95% CI 1.56–33.70, $P = 0.01$) increased in the exposed group. The overall score of the development rate according to DDST was lower in the study group compared to the control group (B = 5.29, 95% CI 2.48–11.28, $P < 0.01$).

Conclusions: There appears to be an association between exposure to stimulants or SSRI's to negative birth and neurodevelopmental outcomes. However, the sample size in the stimulant exposure group was small and further studies are needed to strengthen the study conclusion.

Pregnancy outcomes of Favipiravir

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Introduction: Favipiravir (Favicovir®, Favimol®) is a pyrazinecarboxamide-derived antiviral drug that inhibits RNA-dependent RNA polymerase. Effectiveness of favipiravir against RNA

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viruses such as Ebola and Influenza has been shown. SARS-CoV-2 is also a RNA virus. Although it wasn't approved by FDA and EMA for the treatment, during the COVID-19 pandemic, favipiravir has been widely used in Turkey, as in many countries such as Russia, India, Japan. There are inadequate data on whether favipiravir causes major congenital anomalies or not in humans. In animal experiments, it has been shown that favipiravir increases teratogenicity and early embryonic death. Based on animal reproduction studies, it is contraindicated for use during pregnancy and both in patients planning pregnancy. In this study, women treated with favipiravir for COVID-19 infection without being aware of their pregnancy were evaluated for teratogenicity.

Methods: Pregnant women who applied to Trabzon-TIS between November 2020 and December 2021 using favipiravir due to COVID-19 infection were evaluated. Histories of the women were recorded in registration forms. Risk assessment was made for each pregnant woman, and they were followed up. Postnatal information about congenital anomalies of the babies were obtained.

Results: 38 pregnant women were consulted by the KTU-TIS. The data of 23 women who gave birth were evaluated. All pregnant women were considered at risk. All of the pregnant women used favipiravir within the first eight weeks. The ages of the pregnant women ranged 21–43 years. The total dose of favipiravir used was between 1600 mg and 8000 mg. Eighteen of 23 women had multiple drug use (1-8drugs). No spontaneous abortion, stillbirth or preterm labour was observed. Of the 23 pregnancies, 21 resulted in live-birth and two elective terminations; in one, methotrexate use four months before conception and thiocolchicoside use during pregnancy with a history of radiation exposure, the other a hepatitis B carrier, anhydramnios and polycystic kidney disease were reported in the fetus and terminated at 20 weeks. Postnatally, among 21 live-newborns respiratory distress developed in one, meconium aspiration in one, and hypoglycemia in two. These four newborns were followed-up in the NICU for 4-7 days. Jaundice developed in six, and all recovered. Hydronephrosis, which did not require intervention after birth, was observed in one fetus at the intrauterine 20th week. No major congenital malformation was observed in any of the 21 live-newborns.

Conclusions: In animal studies on favipiravir, it has been reported that favipiravir increases teratogenicity and early embryonic death. There are inadequate data on whether favipiravir causes major congenital anomalies or not in humans. In a case series, no major malformations were reported using favipiravir, but foramen-ovale was detected only in one case. Hydronephrosis was observed in only one fetus in our study. These early results are not sufficient for interpreting the safety of the drug and further studies are needed.

Evaluation of pregnancy using mirabegron in terms of teratogenity

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Introduction: Mirabegron is a beta-3 adrenergic receptor agonist drug used to treat overactive bladder. Beta-3 receptor stimulation increases the bladder's storage capacity by relaxing the detrusor muscle. Animal studies of mirabegron have not shown a teratogenic effect. There are no published human data on mirabegron. In our case, we wanted to present a case exposed to mirabegron, which has the wider potential to be used in treatment.

Methods: The registration form of a 34-year-old pregnant woman who applied to Karadeniz Technical University Teratogenicity Information Service (KTU-Trabzon-TIS) in 2020 with exposure to mirabegron was filled. The registration form included demographic information, risk factors during pregnancy (history of Rh incompatibility, consanguineous marriage, smoking and alcohol use, radiation exposure), obstetric history, drugs used during pregnancy, periods and doses. Risk assessment was performed on the pregnant woman. After delivery, birth information in terms of congenital anomalies was obtained by phone, and the newborn's development was followed.

Results: The patient used 50 mg Mirabegron (Betmiga®) tablet 6 tablets between 2 weeks 3 days and 3 weeks 6 days according to USG. In addition to Mirabegron, the pregnant woman also has additional drug (cefixime + clavulanic acid, etodolac, famotidine; not attributable to teratogenicity) use and radiation exposure (1 rad). The pregnant woman delivered a healthy infant.

Conclusions: In this case report, no teratogenic effect was observed. In animal studies, much higher doses did not cause any teratogenicity. However, more human studies are needed to predict the safety of using mirabegron during pregnancy.

Outcomes of 5-nitroimidazoles exposure in pregnancy

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Introduction: Nitroimidazoles are a class of antimicrobial widely prescribed for protozoa, anaerobic gram-positive and gram-negative bacterial infections. Inhibition of energy metabolism, DNA and RNA synthesis, is suggested to be the mechanism of action. They are prescribed in several pharmaceutical formulations. Metronidazole is not a major teratogen in humans; however, when used intravaginally in combination with miconazole in the first trimester, hydrocephalus, cleft lip/palate and polydactyly/syndactyly were observed. We aimed to evaluate our data about this drug class and its combined use.

Methods: Between 1999 and 2021, counseling was given to 267 pregnant women exposed to 5-nitroimidazoles by Trabzon-TIS. We performed a risk assessment, depending on additional risk factors. We received delivery information of the infants and followed-up their development.

Results: This study included 267 pregnancies, (150, 154 and 18 exposures, metronidazole, ornidazole and tinidazole, respectively). 83 cases were lost to follow-up and were excluded. Age range was 17–45 years. There were 55 pregnant women who concomitantly used two different nitroimidazole drug in different pharmaceutical forms. 57 of the metronidazole and all of ornidazoles were in the form of oral tablets and ampoules (only metronidazole ones), the rest are in the form of combined ovule and creams. All exposures were in the first trimester, except 2 in the second and third trimesters. Depending on birth outcome records there were 148 healthy babies, 12 spontaneous, 15 therapeutic, 2 elective abortions, 5 intrauterine deaths and 2 anomalies (hydronephrosis, atrial/ventricular septal defect) among 184 pregnancies.

Conclusions: Hydrocephalus, cleft palate/lip, and polydactyly/syndactyly mentioned in previous studies were not seen in our study. One of the babies with anomaly had only bilateral hydronephrosis, while the other one had hydronephrosis and atrial/ventricular septal defect. Both pregnant women received combined metronidazole and miconazole vaginal ovule treatment in the first trimester and also with different drugs. The pregnant woman with an atrial/ventricular septal defect in her baby also used sertraline, which is considered by many authors to be associated with an increased risk of cardiac defects. While no congenital anomaly is observed when metronidazole or other nitroimidazoles are used alone, their combined use with other drugs may increase the risk of anomaly, not attributable 5-nitroimidazoles. Based on experimental animal studies, it has been reported that increased risk of adverse effects is not expected in pregnancies inadvertently exposed tinidazole. In a case-control surveillance study including 6 pregnant women exposed to tinidazole in the first trimester, no increase in the prevalence of birth defects was reported.

Outcomes of olanzapine exposure in pregnancy

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Introduction: Olanzapine is an atypical antipsychotic drug that acts on the serotonin-5HT$_{2A}$ and dopamine-D$_2$ receptors used in the treatment of psychotic disorders, especially schizophrenia. Olanzapine did not increase the risk of major congenital malformations (MCM) in animal studies. Although previous studies for the first trimester did not report increased risk of MCM, a cohort study conducted in 2021 reported that use of olanzapine in the early stages of pregnancy was associated with an increased risk. We aimed to reevaluate our outcome data since 2008 in light of this cohort study.

Methods: Between 2008 and 2021, 74 pregnant women exposed to maternal olanzapine were consulted by the Trabzon-TIS. The demographic information of the pregnant women, risk factors during pregnancy, obstetric history, drugs used during pregnancy, exposure period, and doses were obtained and the registration form was filled. Risk assessment was carried out and pregnant women were followed up. Postnatal information was obtained in terms of congenital anomalies and infant development was monitored.

Results: The ages of our pregnant women ranged from 20 to 45. 71 of 74 pregnant women were exposed to olanzapine in the first trimester, three in the second and third trimesters. Olanzapine doses were ranging from 2.5 to 10 mg/day. No information was available on pregnancy outcomes for 34 of 74 pregnant women after delivery. Among those with birth outcomes there were 24 healthy babies, 4 spontaneous abortions, 5 therapeutic abortions, 2 postpartum exitus, 1 intrauterine death, 1 ectopic pregnancy, 3 births with anomalies (hydronephrosis/encephalocele/Down Syndrome with hip dysplasia) among 40 pregnancies. Among the 4 pregnancies women who resulted in spontaneous abortion, 2 had smoking and 1 had paroxetine use as risk factors.

Conclusions: Previous studies indicated that olanzapine was safe in pregnancy. Ellfolk et.all. (2021) showed that olanzapine exposure in the first trimester increases congenital malformations, especially musculoskeletal malformations (dislocation of hip). Case reports of olanzapine exposure in the literature during pregnancy include meningocele/encephalocele, developmental hip dysplasia, Down Syndrome, clubfoot and atrioventricular septal defect. In our study, one of the babies with anomaly had encephalocele while the other one had Down Syndrome with hip dysplasia. Olanzapine exposure of both pregnant women lasted for the first 6 weeks and the dose was 2.5–5 mg. Even with the limited number in our study, this finding supports the last cohort. These results don't show the safety of olanzapine use during pregnancy and further studies are needed to assess this issue.

Case report: Sitagliptin in a pregnant woman

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Introduction: Type 2 Diabetes is a common disease. Dipeptidyl peptidase 4 inhibitors play an essential role in treatment by increasing insulin secretion. Sitagliptin is one of the drugs in this family. In some cases, it is also among the first line drugs for newly diagnosed diabetes patients. However, no information has been found on the teratogenicity of this drug, which is widely used. We aimed to present a case report about a newly diagnosed pregnant patient with diabetes using sitagliptin.

Method: The case was consulted from the obstetrics clinic to Karadeniz Technical University Teratogenicity Information Service (KTU-Trabzon-TIS). The patient's medical history is recorded and evaluated by a council consisting of a pharmacologist, histologist, radiologist, and perinatologist. After delivery, a doctor contacted the patient, received information about the birth and baby, and inspected medical records.

Result: A 34-year-old female patient was admitted to our TIS with obstetrics consultation. The obese patient with a body mass index of 33.87 was diagnosed with Type 2 Diabetes Mellitus three months before getting pregnant. She used Sitagliptin 50 mg + Metformin 1000 mg (Janumet 50/1000 mg®; 2 × 1) until the end of seventh week of her pregnancy. In addition, the patient used Hyoscine n-methyl bromide 10 mg (Buscopan 10 mg ®; 2 × 1) and Esomeprazole 20 mg (Nexium 20 mg®; 1 × 1) for four days due to gastrointestinal complaints in the first week of pregnancy. The patient is evaluated as a high-risk pregnancy due to obesity and is consulted to be followed up in the endocrinology outpatient clinic, administered insulin therapy. The patient gave healthy birth at 37 weeks by C/S. The newborn had physiological neonatal jaundice for two weeks and did not encounter any pathology.

Conclusion: This case report presented the result of sitagliptin use in a pregnant woman for the first time. In our case, no malformation was found in the baby whose mother used sitagliptin for the first seven weeks of pregnancy. However, this result does not show the safety of the drug in pregnancy. Further studies are required.

Queries on medication use during pregnancy: An analysis of data from the Swiss Teratogen Information Service

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Introduction: Limited information on medication safety may result in concerns on how to treat pregnant and breastfeeding patients. The Swiss Teratogen Information Service (STIS) provides information to healthcare professionals about medications during pregnancy and breastfeeding. Our objective was to describe the queries addressed to the STIS over the past two decades.

Methods: The STIS maintains a database of queries likely to provide information on pregnancy outcomes after exposures to various substances. We have initially analysed general characteristics of all queries. Thereafter, we focused on exposures to medications during singleton pregnancies and associated health-related aspects.

Results: From 2000 to 2019, 7148 queries were entered into the database. An increasing number of queries was recorded over the study period, with an average of 357 queries entered into the database per year. Most of the callers were physicians; more specifically, gynaecologists/obstetricians (2389/7148; 33.4%) and psychiatrists (1007/7148; 14.1%). Two-thirds (4747/7148; 66.4%) of the queries addressed drug intake during pregnancy; the next most frequent queries concerned a planned medication in the context of pregnancy (928/7148; 13.0%) or drug use during breastfeeding (873/7148; 12.2%). In more than 50% (3795/7148) of cases, women were treated with more than one drug; a total of 16,513 drugs (taken alone or in combination) were identified. The most frequent queries concerned drugs for the nervous system (ATC-group N, $n = 7042$), with selective serotonin reuptake inhibitors (N06AB, $n = 1271$) in the leading position, followed by benzodiazepine derivatives (N05BA, $n = 1102$) and other antidepressants (N06AX, $n = 780$). The next most frequently mentioned drug classes were anti-infectives for systemic use (J, $n = 1586$) and drugs for the alimentary tract and metabolism (A, $n = 1205$). Analysis of follow-up information on cases of medication exposure during singleton pregnancies ($n = 2672$) revealed an offspring malformation rate of 4.2%. The organ system most often affected was the musculoskeletal system, followed by the circulatory system; congenital malformations of the nervous system as well as chromosomal abnormalities were seen as well. The three most frequently documented congenital diagnoses were malformations of cardiac septa, the brain and major arteries.

Conclusions: Pregnant women are often in need of (multiple) medications and prescribing physicians require professional counselling in

this area. A variety of drugs is mentioned in queries addressed to the STIS, whereby psycholeptics and psychoanaleptics are the most frequent ones. Proper guidelines on their use during pregnancy appear particularly urgent.

Renal pathologies and mesalazine use in pregnancy

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Introduction: Mesalazine is used in the treatment of various inflammatory conditions. Previous data regarding use in pregnancy have not shown an increase in malformations. However, renal disorders were reported in a limited number of studies, including a boy with microcystic disease and tubulointerstitial changes, whose mother used mesalazine throughout pregnancy. We aimed to examine neonatal outcomes after mesalazine use during pregnancy.

Methods: We evaluated admissions of pregnant women using mesalazine which were consulted to Marmara University Teratology Information Service between the years 2012 and 2021. Gestational history and drug information were questioned during consultation. Follow-up of patients included several phone calls before and after their expected delivery dates. Neonatal history regarding delivery outcomes and diagnosis of any chronic conditions were recorded.

Results: We identified 12 pregnant women using mesalazine in our records. One pregnancy was still ongoing, and only four of the mothers whose pregnancies were assumed to be concluded could be reached during follow-up calls. Two of the babies were born healthy without complications. One of them was exposed to mesalazine within the first four weeks of the pregnancy at a dose of 1 g/day, and the other newborn's mother reported to use the drug at least 3 g/day throughout pregnancy. One newborn, which was exposed to 2 g/day for the first 5 weeks, was incubated after birth due to being small for gestational age. The fourth baby was delivered at term (3200 g), whose mother used mesalazine throughout her pregnancy due to Crohn's disease at a dose of 3 g/day and received infliximab until the 18th week. Urinary tract infection was detected in the baby at birth and later, bilateral vesicoureteral and renal reflux were diagnosed. The infant was still being followed up by the pediatric nephrology unit. The mother fed the baby with breast milk for three months before returning to her previous therapy.

Conclusions: We have rarely encountered renal disorders in children of mesalazine using mothers. Although the existing data did not point out any association with an increase of malformations, given prostaglandin inhibitory mechanism of action of the drug, further studies are warranted which are specifically focused on occurrence of potential renal disorders in neonates, along with the details of their characteristics. We must also consider the adverse effect of lactation that may superimpose to teratogenicity.

Bilateral renal agenesis following in utero first trimester exposure to gadobutrol

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Introduction: Exposure to gadolinium contrast media during pregnancy has not been linked to adverse fetal development. Recommendations to avoid its use in pregnant women are based mostly on the lack of sufficient safety data. The total number of published reports is limited although reassuring.

Methods: We report a case of exposure to gadobutrol during pregnancy, which resulted in induced abortion due to a fetal anomaly.

Results: A 28-year old primigravida presented with bilateral ovarian cysts revealed during the ultrasound scan. Her physical examination and laboratory tests were normal. There was no history of any prior chronic disease. Due to suspected malignancy she was sent to MRI with 50 mM gadobutrol as contrast enhancer. She was 6 weeks pregnant at the time of exposure. At pregnancy week 12 left-sided laparoscopic adnexectomy was performed. The pathology analysis revealed low grade mucinous carcinoma in situ. The ultrasound scan showed normal fetal development. Based on the lack of major risks and in accordance with the patient's decision the pregnancy was prolonged. The next ultrasound scan was performed at week 18. It revealed oligohydramnios and fetal cardiomegaly. MRI revealed bilateral renal agenesis with the absence of the urinary bladder. The pregnancy was terminated with the combination of mifepristone and misoprostol. Fetal autopsy confirmed the diagnosis. Evaluation of genetic abnormalities in the fetus was not performed at the time of the report. All drug exposures during this pregnancy were short-term and consisted of ibuprofen and nasal drops during the first trimester; ketoprofen, ampicillin/sulbactam, indomethacin, hydroxyzine (preoperatively), omeprazole, fentanyl, sodium thiopental, rocuronium in relation to the surgery; vaginal progesterone, enoxaparin, vaginal metronidazole and miconazole during the second trimester. She also took regular doses of folic acid, vitamin D and iodine.

Conclusions: This is to our knowledge the first report of a congenital anomaly after the first trimester exposure to gadolinium-based contrast. Our report lacks genetic information and may not rule out a causal association. We believe, however, that this report should be taken into consideration until larger studies prove or disprove teratogenic potential of gadobutrol. This is particularly important for the women with pregnancy and new cancer diagnosis.

Evolution of the national guidelines on the medicines used to treat COVID-19 in pregnancy: A historical review

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Introduction: Since COVID-19 was declared a pandemic in March 2020, there has been a lack of active inclusion of pregnant women in clinical trials evaluating the effectiveness of medicines to treat COVID-19, because of theorical concerns related to the safety of therapeutical agents in pregnancy. This made it more difficult to establish specific guidelines for pregnant women. Our aim was to provide an overview of the evolution of the national guidelines on medicines used in pregnant women with COVID-19 throughout the pandemic.

Methods: We searched for the national guidelines and their updates published by the obstetrician and gynecologists' societies from countries participating in the CONSIGN group (Belgium, Canada, France, Italy, Norway, Saudi Arabia, Spain, Switzerland, The Netherlands, United Kingdom and United States) from March 2020 to December 2021 on Pubmed and official websites.

Results: In two years, the national online guidelines on COVID-19 during pregnancy were updated up to 14 times, and 42 times for the NIH recommendations, including a specific section for pregnant women. Since spring 2020, antibiotics such as amoxycillin or azithromycin, are not recommended, unless additional bacterial pulmonary infection is suspected. Hydroxychloroquine was initially prescribed in pregnant women in some countries and only in research settings. After the results of the RECOVERY trial in June 2020, hydroxychloroquine has been shown to be ineffective and all the national societies recommended against. Remdesivir can be considered for compassionate use in the US since June 2020. After a reluctance to use steroids because of concerns with the infection progression, results of the RECOVERY trial have enabled to recommend dexamethasone in case of severe COVID-19 since mid-2020. Some national societies still prefer non-fluorinated

corticosteroids to minimize fetal exposure. Regarding tocilizumab, some societies prescribe it to pregnant patients with hypoxia and evidence of systemic inflammation since June 2021. On May 2021, the US-FDA expanded the emergency use authorization to include pregnancy as a qualifying condition for monoclonal antibodies. It is thus offered in seronegative patients, after a detailed counseling about benefits and risks in some countries.

Conclusions: Since March 2020, our knowledge of COVID-19 and treatment modalities has evolved significantly. Comparison of the different guidelines published in spring 2020 revealed a lack of uniformity and consistency, resulting in potentially challenging decisions for healthcare providers. The recommendations became more homogeneous in 2021.

Agomelatine for the treatment of depressive episodes - preliminary data on the use in pregnancy

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Introduction: Agomelatine is a metabolically stable analogue of melatonin with high affinity for melatonin receptors. The drug was approved in Europe in 2009 for the treatment of depressive episodes in adults. The available evidence concerning the safety of agomelatine use in pregnancy is highly limited. Animal studies performed by the manufacturer have not identified adverse effects on embryo/fetal, pre- or postnatal development. However, no 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 agomelatine between 2010 and 2020. Our Teratology Information Service (TIS Ulm/Germany) was contacted by physicians or patients after conception during female treatment with agomelatine (25–50 mg/d).

Results: 58 mostly unplanned pregnancies were included in the analysis. Six patients decided to terminate their pregnancy between week 6 and 10 because of the lack of experience with the drug. Forty-six pregnancies were continued to term, with agomelatine medication being maintained until term in 11 cases. The other patients stopped the medication after their pregnancy was diagnosed in the first trimester. In addition to 42 healthy newborns, four children with congenital anomalies were registered: accessory kidney on the left (agomelatine 25 mg/d up to wk. 5), hydronephrosis (agomelatine 25 mg/d up to birth together with venlafaxine 300 mg/d and doxepin 100 mg/d), syndactyly on both feet (agomelatine 50 mg/d up to wk. 6), hypotonia (agomelatine 50 mg/d up to birth together with sertraline 150 mg/d and lithium 16.2 to 27.0 mmol/d). There were neither major malformations nor a homogeneous pattern of abnormalities. 18 girls and 28 boys were born between wk. 34/2 and wk. 41/5 (median wk. 39/1) with a median birth weight of 3240 g (range 2050–4125 g).

Conclusions: These preliminary data on the use of agomelatine in pregnancy do not indicate a severe teratogenic effect of the drug, but given the limited data, use during pregnancy should be avoided if possible. If a pregnancy occurs on agomelatine, a detailed sonographic diagnosis is recommended, as long as there is no sufficient experience.