Faculty of Medicine

Master's study programme „Biostatistics"

MASTER'S THESIS

Drug Utilization Study: Prescription Medication Use in Pregnant Women in Latvia 2020–2023

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Abstract (in Latvian)

Medikamentu lietošana grūtniecības laikā ir plaši izplatīta visā pasaulē, taču Latvijā līdz šim nav veikts visaptverošs nacionāla līmeņa zāļu patēriņa pētījums par recepšu zāļu izrakstīšanas un izsniegšanas tendencēm, kā arī zāļu drošuma profilu. Pētījuma mērķis bija novērtēt zāļu izrakstīšanas un izsniegšanas biežumu grūtniecēm Latvijā, kuras dzemdēja laika posmā no 2020. līdz 2023. gadam, kategorizēt izrakstītās zāles balstoties uz starptautiskām riska klasifikācijas sistēmām un identificēt, vai pastāv mātes raksturlielumi, kas saistīti ar potenciāli kaitīgu zāļu izrakstīšanu.

Dati par izrakstītajām un izsniegtajām zālēm, grūtnieču sociāldemogrāfiskajiem un veselības raksturlielumiem, kā arī grūtniecības iznākumiem tika iegūti no Jaundzimušo reģistra informācijas sistēmas un nacionālās e-Veselības sistēmas, vēlāk tie tika sasaistīti individuālā līmenī. Zāles tika klasificētas pēc to ietekmes uz augli, attiecīgi Austrālijas TGA un Zviedrijas FASS riska klasifikācijas sistēmām, kur „potenciāli kaitīgi" medikamenti tiek definēti kā D kategorijas zāles. Izrakstīšanas un izsniegšanas biežums tika aprēķināts katram gadam un visam pētījuma periodam kopumā. Riska klasifikācijas sistēmu savstarpējā atbilstība tika novērtēta izmantojot *Koena kappa* koeficientu. Saistības starp mātes faktoriem un potenciāli kaitīgu zāļu izrakstīšanu tika analizētas ar loģistiskās regresijas palīdzību.

Laikā no 2020. līdz 2023. gadam Latvijā tika identificētas 58 844 dzemdētājas un 64 506 dzemdības. 2020. gadā 50,9% grūtnieču tika izrakstītas zāles arī 50,9% no tām zāles izņēma, savukārt 2023. gadā šie rādītāji paaugstinājās līdz aptuveni 64%, liecinot par vidēji augstu zāļu lietošanas izplatību grūtniecības laikā. Visbiežāk izrakstītās zāļu grupas bija antibakteriālie līdzekļi, progestogēnu kombinācijas un zāles hronisku slimību ārstēšanai. Potenciāli kaitīgu zāļu lietošana svārstījās robežās no 2% līdz 10,4% (attiecīgi 2020. un 2023. gadā) atkarībā no izmantotās riska klasifikācijas sistēmas. Biežāk sastopamie šīs kategorijas medikamenti bija flukonazols, doksiciklīns un magnija sulfāts. Statistiski nozīmīgas asociācijas tika novērotas starp potenciāli kaitīgu recepšu zāļu izrakstīšanu un mātes vecumu, apaugļošanās terapijas izmantošanu, plānotu ķeizargriezienu, kā arī ar noteiktiem sarežģījumiem grūtniecības un dzemdību laikā. Modeļa sniegums tika izvērtēts pēc *laukums zem līknes* vērtības (AUC), kas bija 0,591 un norāda uz ierobežotu modeļa spēju atšķirt klases.

Pētījuma rezultāti apstiprināja vidēji augstu zāļu lietošanas izplatību Latvijā un ievērojamu daļu grūtnieču, kas pakļautas potenciāli kaitīgu medikamentu iedarbībai. Tika konstatēta nepieciešamība pēc starptautiski vienotas riska klasifikācijas sistēmas, uzlabotas grūtniecības uzraudzības un mērķtiecīgām veselības politikas intervencēm. Iegūtie rezultāti

sniedz vērtīgu ieguldījumu nākotnes farmakoepidemioloģiskajos pētījumos un var tikt izmantoti valsts zāļu politikas pilnveidošanā, lai uzlabotu mātes un bērna veselību.

Keywords (in Latvian)

Zāļu patēriņa pētījums, iespējami kaitīgas zāles, droša medikamentu lietošana grūtniecības laikā, farmakoepidemioloģija, loģistiskā regresija, riska klasifikācijas sistēmas

Abstract (in English)

Medication use during pregnancy is widespread globally, however no comprehensive national level drug utilization study has previously been conducted in Latvia to analyze prescribing and dispensing patterns or medication safety profiles. The aim of this study was to assess the prevalence of prescribing and dispensing among pregnant women in Latvia who gave birth between 2020 and 2023, to classify the prescribed medications using international fetal risk classification systems and to identify whether maternal characteristics are associated with the prescribing of potentially harmful medications.

Data on prescribed and dispensed medications, maternal sociodemographic and health characteristics and pregnancy outcomes were obtained from the Medical Birth Register and the national e-Health system and were subsequently linked at the individual level. Medications were classified according to their potential impact on the fetus using the Australian TGA and Swedish FASS risk classification systems, where category D drugs were considered potentially harmful. Annual and overall (2020-2023) prevalence of prescribing and dispensing was calculated. Agreement between risk classification systems was assessed using *Cohen's Kappa*. Associations between maternal factors and the prescribing of potentially harmful medications were analyzed using logistic regression.

In total 58 844 birth givers and 64 506 deliveries were identified in Latvia during the 2020 – 2023 period. In 2020, 50.9% of women were prescribed at least one medication and 50.9% received dispensed medications, while in 2023 these figures rose to approximately 64%, indicating a moderate to high prevalence of medication use during pregnancy. The most frequently prescribed medication groups were antibacterials, progestogen combinations and treatments for chronic conditions. The proportion of women prescribed potentially harmful medications ranged from 2% to 10.4% (in 2020 and 2023, respectively) depending on the used risk classification system. The most common drugs in this category were fluconazole, doxycycline and magnesium sulfate. Statistically significant associations were observed between the prescribing of potentially harmful drugs and maternal age, the use of assisted reproductive therapy, planned cesarean section, as well as with certain pregnancy and delivery complications. Model performance was evaluated using the area under the curve (AUC), which was 0.591, indicating limited discriminatory ability.

The study confirmed a moderately high prevalence of medication use during pregnancy in Latvia and a substantial proportion of women exposed to potentially harmful medications. A need was identified for internationally harmonized risk classification systems, improved pregnancy surveillance and targeted public health policy interventions. The findings contribute

valuable insights for future pharmacoepidemiological research and may support improvements in national medication safety policies aimed at protecting maternal and fetal health.

Keywords (in English)

Drug utilization study, potentially harmful drugs, medication safety in pregnancy, pharmacoepidemiology, logistic regression, risk classification systems

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List of abbreviations

DUS – drug utilisation study

FDA – Food and Drug Administration

RCS – risk classification system

EMA – European Medicines Agency

SmPC – summary of product characteristics

ROC AUC – receiver operating characteristics area under the curve

SES – socioeconomic status

BMI – body mass index

ICD-10 – the International Classification of Diseases, Tenth Revision

NHS – National Health Service

ATC – Anatomical Therapeutic Chemical

WHO – World Health Organization

CDC – Centers for Disease Control and Prevention

INN – International Nonproprietary Name

NSAIDs – nonsteroidal anti inflammatory drugs

CI – confidence interval

NIR – no information rate

PPV – the positive predictive value

NPV – negative predictive value

AIC – Akaike's information criterion

SD – standard deviation

SE – standard error

OTC – over the counter

DHPCs – direct healthcare professional communications

RMMs – risk minimisation measures

GEE – generalized estimating equations

TGA – Therapeutic Goods Administration (Australia)

FASS – Farmaceutiska Specialiteter i Sverige (Swedish Medicines Information Portal)

OR – odds ratio

LMP – last menstrual period

Introduction

Understanding medication use during gestation period is vital, as it impacts the wellbeing of both mother and fetus. Drug utilization studies (DUS), characterized as the "quantification, understanding and evaluation of the processes of prescribing, dispensing and consumption of medicines" (Elseviers *et al.*, 2016), offer a useful model for determining medication safety and effectiveness. One of the aims of DUS is to encourage as harmless as possible and effective use of medicines among populations. This kind of study requires expertise in biostatistics to succesfully conduct research and interpret it's results, enhancing quality for evidence based research. The theoretical context for this study is rooted in the understanding that while medications can provide significant health benefits to pregnant women, they also can pose potential risks to the fetal development. Although such statement would suggest minimizing or avoiding pharmacotherapy during gestational period, such an option is not possible and realistic for women with serious health conditions. In particular, those diagnosed with psychiatric disorders, epilepsy and hematological diseases, often require continuous medical treatment to manage their conditions and prevent complications that could endanger both maternal and fetal health (Slimību profilakses un kontroles centrs, 2022). Safety profile of medications can be altered by different factors, one of such factors are physical changes during pregnancy, which can potentially shift drug pharmacokinetics, alongside the potential of placental transfer of active substances, that is why such physical modifications require cautious evaluation during pregnancy (Mao and Chen, 2022). From practical context, drug utilization research advises clinical guidelines, regulatory policies and public health campaigns towards optimizing medication use during pregnancy. By determining patterns of medicine use, assessing prescribing practices and impacts from certain active substances on maternal and fetal outcomes, this research contributes to evidence based decision making in prenatal healthcare.

Risk classification systems for medication use in pregnancy are designed to help clinicians to evaluate potential harm to the developing fetus. Several international risk classification systems exist, each with its own structure and criteria. The most widely referenced are from the United States (FDA) (U.S. Food and Drug Administration, no date), Australia (TGA) (*Australian Government Department of Health. Australian categorisation system for prescribing medicines in pregnancy,* no date), Sweden (FASS) (*Läkemedelsindustriföreningen. FASS for vårdpersonal*, no date) and the Netherlands (Lareb) (Netherlands Pharmacovigilance Centre Lareb, no date). These systems typically divide drugs into categories based on available data from human and animal studies, refer to Appendix 3.

for more detail. For example, the former FDA system used five categories (A, B, C, D, X), ranging from medicines with no evidence of risk (A) to those contraindicated in pregnancy (X) (Leek JC, 2025). The Australian system is similar, but includes additional subcategories (B1, B2, B3) to reflect varying levels of animal and human data and the Dutch Lareb system uses a nuanced approach that distinguishes between drugs requiring monitoring, those to avoid temporarily and those with unknown risk (Leek JC, 2025). Their goal is to guide safer prescribing, but despite that, these classification schemes have notable limitations and inconsistencies. Medicines may be placed in different categories across systems due to differences in how evidence is interpreted or weighted, as well as the availability of local medicines. For example, only about a quarter of medications common to the FDA, Australian and Swedish systems are classified in the same risk group (Addis, Sharabi and Bonati, 2000). This variability can create confusion for prescribers and patients, which sometimes leads to conflicting recommendations. Furthermore, these systems often do not account for factors such as timing of exposure, dosage or the clinical context in which a drug is used, nor do they always reflect updated evidence as new data emerge (Addis, Sharabi and Bonati, 2000; Leek JC, 2025). Recognizing these challenges, the FDA replaced its letter category system in 2015 with a different narrative format that provides more detailed information about risks, benefits and available data, but other countries continue to use categorical systems. Overall, while risk classification systems are valuable for summarizing complex information, their limitations underline the need for individualized clinical judgment and up-to-date, evidence-based counseling when prescribing medications during pregnancy. In Latvia and other EMA countries, information about medicine use during pregnancy is primarily based on the Summary of Product Characteristics (SmPC), which outlines known or potential risks based on available data from preclinical and clinical studies. Recommendations are made on a medicine specific basis and healthcare professionals are encouraged to rely on clinical judgment and the latest evidence when prescribing during pregnancy. In practice, Latvian prescribers may also consult external sources such as the Swedish FASS or the Netherlands' Lareb database to support decision making.

Research from multiple countries show that most pregnant women are exposed to at least one medication, whether prescribed or over-the-counter. In large European studies, the proportion of women using any medication during pregnancy ranges from about 70% to over 90% depending on the country and data source (Trønnes, Lupattelli and Nordeng, 2017; Fortinguerra *et al.*, 2023; Subramanian *et al.*, 2023) Various research methods have been used to study this topic, including population based cohort studies using prescription or pharmacy databases to track medication use across pregnancy and postpartum periods (Houben *et al.*,

2020; Blotière *et al.*, 2021; Fortinguerra *et al.*, 2023). Some research studies were based on population surveys and self report studies to capture both prescribed and non prescribed over-the-counter medicine use (Basgül, Akici and Uzuner, 2007; Trønnes, Lupattelli and Nordeng, 2017). Most of the publications include risk classification systems (RCS) that categorize medications by fetal risk using systems such as the FDA (U.S. Food and Drug Administration, no date), Swedish FASS (*Läkemedelsindustriföreningen. FASS for vårdpersonal*, no date) and Australian TGA (*Australian Government Department of Health. Australian categorisation system for prescribing medicines in pregnancy*, no date). These studies often analyze medication use by trimester, maternal age, health status and other demographic factors. They also assess the prevalence of exposure to drugs considered potentially harmful or teratogenic.

Several controversies are noted in this field, for example inconsistencies between RCS. Different systems may classify the same medication differently, leading to varying estimates of potentially harmful exposure. For example, in France, the prevalence of potentially harmful drug prescribing during pregnancy ranged from 2.2% according to Swedish system to 3.9% according to Australian system, and up to 9.2% when including medicines that are contraindicated nationally (Blotière *et al.*, 2021). While it is stated that some medicines are necessary for chronic maternal health conditions, the use of medications with known or suspected teratogenicity remains debated, especially when safer alternitives exist or evidence of benefit is lacking (Basgül, Akici and Uzuner, 2007; Blotière *et al.*, 2021; Fortinguerra *et al.*, 2023). There is also the controversy of polypharmacy during pregnancy, meaning the use of multiple medications, which is increasing, particularly among women with multiple chronic conditions. In the UK, 58.7% of pregnancies involved two or more medicine prescribtions during entire pregnancy period and 24.6% during the first trimester. Among women with multimorbidity, these rates rose to 80.3% and 49.8%, respectively. However it is important to note that the implications for fetal safety and drug interactions are not fully understood (Trønnes, Lupattelli and Nordeng, 2017; Subramanian *et al.*, 2023). Nevertheless, certain supplements are recommended during different stages of gestational period, like folic acid before conception and early in pregnancy, yet their consumption often remains lower than optimal, potentially missing opportunities for birth defect prevention (Basgül, Akici and Uzuner, 2007; Subramanian *et al.*, 2023). There are ongoing discussions about the possible risk factors associated with polypharmacy and potentially harmful drug use– higher maternal age, chronic illnesses, lower socioeconomic status, non-majority ethnicity, smoking and higher number of previous pregnancies are all associated with polypharmacy and potentially harmful drug use (Trønnes, Lupattelli and Nordeng, 2017; Houben *et al.*, 2020; Blotière *et al.*, 2021; Subramanian *et al.*, 2023).

General prevalence of medication use differs in European countries. In the Netherlands, 73% of pregnancies involved any medication use and 34% involved drugs classified as potentially harmful (Houben *et al.*, 2020). In France, 91% of pregnancies involved at least one reimbursed medication with up to 9.2% exposed to potentially harmful drugs depending on the classification system (Blotière *et al.*, 2021). In Italy, 70% of pregnant women received at least one prescription with the highest use in the first trimester which was 51.5% (Fortinguerra *et al.*, 2023)

These findings underline the public health significance of medicine use during pregnancy. Despite some progress, a substantial proportion of pregnant women are still exposed to medicines with known or uncertain risks. Ongoing debate over risk classification and limited safety data for many drugs highlight the need for continued research and improved evidence based guidance.

Study hypothesis– maternal factors are associated with the prescribing of potentially harmful medicines during pregnancy

Study aim– to determine the prevalence of prescribing and dispensing medications to pregnant women in Latvia who gave birth between 2020 and 2023, and to assess the safety profile of the prescribed medications

Study objectives:

1. Assess the prevalence and temporal trends in prescribing and dispensing of medications to women who gave birth between 2020 and 2023.
2. Determine the risk category for each risk classification system of prescribed medications at ATC 5th level among women who gave birth between 2020 and 2023.
3. Determine the proportion of women who gave birth between 2020 and 2023 and were prescribed at least one potentially harmful medication during pregnancy.
4. Characterize the association of maternal factors with the prescribing of potentially harmful medicines.
5. Assess the agreement level between the two risk classification systems.
6. To assess medication availability and patient compliance based on the comparison between prescribed and dispensed medications.

1. Drug utilization research

Drug utilization studies (DUS) during pregnancy require careful methodological considerations to ensure valid and reliable results. These studies face unique challenges related to defining the timing of exposure, ensuring correct maternal and newborn data linkage, population selection and confounding control that directly impact the statistical validity of findings.

Defining the timing of medication exposure during pregnancy is critical, as different stages of fetal development show varying sensitivities to pharmacological agents. The embryonic period, especially the first trimester when organ formation occurs is particularly vulnerable to teratogenic effects. Accurate dating of gestation period is essential for exposure classification. Often, the first day of the last menstrual period (LMP) is used as the gestational start point, this is typically estimated by subtracting gestational age from the delivery date. However, this may lead to misclassification, because LMP can differ from conception based dating by around two weeks. While many administrative datasets do not contain direct LMP records, validated algorithms have been used to derive gestational timing and trimester classification (U.S. Food and Drug Administration, 2005).

When infant outcomes are studied, linking maternal records to newborn data is essential. Linkage can be performed using deterministic methods (based on exact identifiers) or probabilistic approaches (based on matching characteristics such as shared insurance, timing of delivery and hospital data). Healthcare databases often lack explicit family identifiers, requiring researchers to develop matching algorithms (Huybrechts, Bateman and Hernández-Díaz, 2019). In one example a linkage algorithm applied to United States insurance data connected 73.6% of mothers to 49.1% of newborns, with most birth dates closely aligning with the recorded pregnancy end dates(Weaver *et al.*, 2023).

Choosing the appropriate study population involves a trade-off between internal validity and external generalizability, so by applying strict exclusion criteria, it can help to reduce bias, but may limit applicability to broader populations. Restrictions might include maternal age ranges, continuous insurance coverage or exclusion of pregnancies involving assisted reproductive technologies or multiples (twins, triplets) (Lopez-Leon *et al.*, 2024). Longer lookback windows provide more data on baseline health and medication use but may reduce eligible sample sizes due to enrollment criteria. The choice of this window must balance between completeness of covariate information and maintaining statistical power. Ideally, enrollment should begin before pregnancy to capture preconception exposures. While the LMP

is commonly used as the start of pregnancy for defining drug exposure, some pregnancies are only identified later, which can result in missing data for exposures occurring early in fetal development (Lopez-Leon *et al.*, 2024).

Clearly identifying the analysis unit whether it is the woman, delivery, or the infant, is vital for interpreting results. Including more than one pregnancy per woman raises the issue of correlated data and potential clustering. Special consideration is also needed for multiple gestations, where assumptions of independence do not apply (Fortinguerra *et al.*, 2023).

One of the main statistical concerns in DUS is unmeasured confounding. Administrative data often lack information on OTC medication use, lifestyle behaviors like smoking or alcohol use and psychosocial factors. These missing variables can introduce residual confounding that may distort results. For congenital outcomes, covariates ideally should be measured before conception or early in pregnancy to ensure temporal precedence. For other outcomes like preterm birth, mid-pregnancy covariates might still be appropriate (Wood *et al.*, 2018). Common statistical strategies for addressing confounding include the use of propensity scores to balance baseline characteristics across exposure groups. This can involve matching, weighting or stratification methods. Where unmeasured confounding is suspected, sensitivity analyses and external validation studies can provide context and test the robustness of findings. Some large-scale applications of these methods have assessed hundreds of medications simultaneously. For example, one study found 58 drugs significantly associated with preterm birth after adjusting for relevant maternal and pregnancy related variables using propensity scores(Wood *et al.*, 2018; Hwang *et al.*, 2024).

1.1. Commonly prescribed medications during pregnancy

Medication use during pregnancy is a routine component of prenatal care aimed at managing existing conditions, treating pregnancy related complications and ensuring optimal maternal and fetal outcomes. While prescribing practices vary between countries and healthcare systems, certain therapeutic groups consistently appear across national datasets and studies. Globally, pharmacological management during pregnancy prioritizes medications with well established safety profiles while addressing maternal health needs (Leek JC, 2025).

Genito-urinary system and sex hormones therapies– ATC code “G”– particularly progesterone and dydrogesterone, are commonly prescribed in the first trimester, often for threatened miscarriage or other gynecological indications. These medications represent a substantial share of prescriptions in early pregnancy. Patterns suggest higher use among women of advanced maternal age and those with a history of pregnancy complications (Palmsten et al., 2015).

Antimicrobials are among the most commonly prescribed medications during pregnancy. Amoxicillin and its combinations are frequently used, particularly in the first trimester. Other antibiotics such as azithromycin and fosfomycin show variable use with some studies indicating higher rates among younger pregnant women or those with specific infections (Różańska *et al.*, 2020). Overall, anti-infective agents account for a significant portion of prescriptions with usage during pregnancy. Antifungal agents like butoconazole and econazole are commonly used to manage vulvovaginal candidiasis, a condition exacerbated by hormonal changes (Różańska *et al.*, 2020).

Nutritional supplements like colecalciferol (vitamin D), folic acid and ferric oxide polymaltose complexes (iron) are widely prescribed and routinely recommended during pregnancy to address deficiencies linked to fetal development and maternal anemia (Efendi *et al.*, 2023).

Nervous system medications– ATC code "N"– like analgesics, especially paracetamol, are the most frequently used drugs in this category with high rates of both prescription and self reported use, as these medicines are obtained over-the-counter and widely used for pain and fever management, with studies reporting prenatal exposure rates exceeding 50% in some populations (de Castro, Pereira and Dos Santos, 2022). Use of antidepressants and anxiolytics is lower but notable, particularly among women with mental health diagnoses or chronic illnesses. The choice of specific agents, such as selective serotonin reuptake inhibitors, reflects caution regarding fetal safety (Thunbo *et al.*, 2025).

Respiratory system medications– ATC code "R"– including short acting beta agonists and inhaled corticosteroids are regularly prescribed to pregnant women with respiratory conditions. These drugs are more common among women with preexisting asthma or allergies with some regional variation in the choice of specific agents (Suarez *et al.*, 2023).

Non-steroidal anti-inflammatory drugs, such as ibuprofen, are used during pregnancy but typically avoided in later trimesters due to concerns about fetal effects. Analgesic use is more common in women with chronic pain or musculoskeletal disorders (Suarez *et al.*, 2023). Antiemetics like promethazine and metoclopramide are prescribed for nausea, but their use requires careful risk and benefit evaluation due to potential neonatal effects (Starke, Weaver and Chowdhury, 2005). These prescribing trends align with international patterns, though regional variations exist, for example, nitrofurantoin and azithromycin are more prevalent in younger populations, while iron supplementation correlates strongly with antenatal care engagement (Palmsten *et al.*, 2015). The prioritization of these therapeutic classes underscores the focus on managing acute conditions and chronic comorbidities while minimizing fetal risk,

though disparities in prescribing practices highlight the need for standardized guidelines across demographic subgroups (Thunbo *et al.*, 2025).

2. Maternal characteristics and prescribing of potentially harmful medicines

Prescribing medications during pregnancy involves a complex balance between the health needs of the mother and the safety of the unborn child. While pharmacological treatment is often necessary for the management of both acute and chronic maternal conditions, certain drugs may pose developmental risks to the fetus. Therefore, identifying maternal traits that correlate with the use of medicines carrying a known or suspected fetal risk is essential for guiding safer prescribing behavior. This section reviews recent findings on the demographic, clinical and lifestyle factors that may influence the likelihood of such medications being used during pregnancy.

2.1. Demographic and socioeconomic characteristics

Maternal age and delivery history are among the most frequently examined variables in drug utilization during pregnancy. Women aged 35 years or older are more likely to require medication, including those with known risks due to age related health problems such as hypertension, gestational diabetes or autoimmune diseases. Older age groups also tend to have increased healthcare contact, potentially resulting in more prescriptions. Conversely, younger mothers under the age of 25 also show elevated medication exposure in some studies (Thunbo *et al.*, 2025). This may be linked to acute conditions, unplanned pregnancies or limited engagement with preconception care. Multiparous women– those with two or more previous pregnancies appear more likely to receive medicine prescriptions during gestation period. This may reflect some health challenges and a more pragmatic attitude toward drug use based on previous experience or a history of obstetric complications. Socioeconomic status (SES) further shapes medication patterns. Women with lower income or those who rely on social support systems are more frequently prescribed psycholeptics, including sedatives, antipsychotics, and pain management drugs. Employment status has also been shown to influence prescribing– working women may be more likely to receive antibiotics or hormonal treatments, while unemployment is associated with increased rates of polypharmacy (Verkerk *et al.*, 1993). These differences reflect broader health disparities as well as variable access to healthcare resources and specialist consultations. Educational attainment is another SES indicator with strong links to medication use. Lower levels of formal education are associated with greater exposure to medicines with higher fetal risk. This may be attributed to reduced health literacy, limited

awareness of safer alternatives or difficulty navigating complex treatment information. Conversely, women with higher education may be more likely to question their treatment options and request therapy that excludes drug interventions. Racial and ethnic disparities also contribute to variation in prescribing. For instance, in research conducted in United States, Black and Hispanic women are sometimes more likely to receive drugs with potential fetal effects, especially for conditions like gastrointestinal issues (Thunbo *et al.*, 2024). These patterns may arise from differences in disease prevalence, provider bias, systemic inequities or limited access to culturally appropriate prenatal care. However, there is a lack of equivalent data in non– Western populations, indicating an area in need of further research.

2.2. Maternal health and comorbid conditions

Underlying health status is one of the strongest drivers of potentially risky drug prescribing. Chronic illnesses– including obesity, hypertension, endocrine disorders and mental health conditions– often require continuous treatment throughout pregnancy. For example, individuals with a body mass index (BMI) ≥30 kg/m² may need medications to manage blood pressure or insulin levels, which occasionally fall into higher risk categories (Nagai *et al.*, 2022). Similarly, women with mood or anxiety disorders frequently receive antidepressants, benzodiazepines and mood stabilizers– some of which are flagged for use with caution during pregnancy. Comorbidity or the presence of multiple chronic diseases significantly increases the likelihood of polypharmacy. In these cases, the combined effect of several medications can raise the risk of fetal exposure to medication interactions or cumulative toxicity. Multimorbidity is becoming increasingly common among pregnant women in high income countries, especially in older age groups and those with socioeconomic disadvantages (Thunbo *et al.*, 2025). Pregnancies classified as high risk due to complications such as gestational diabetes, preeclampsia or a history of miscarriage may also involve more frequent use of medications. Common drugs in these cases include low dose aspirin, antihypertensives or anticoagulants like heparin. While these interventions are often necessary and supported by clinical guidelines, their timing and dosage must be carefully managed to avoid unintended effects on fetal development. Certain neurological and psychiatric conditions further complicate the prescribing landscape. Disorders such as epilepsy may require ongoing use of antiepileptic drugs like valproate or lamotrigine, both of which are associated with varying degrees of fetal risk. In these cases, physicians must weigh the danger of uncontrolled seizures against the potential impact of the medication on the developing fetus (Thunbo *et al.*, 2024).

2.3. Trimester specific concerns

The decision to prescribe or use medications during pregnancy is often influenced by the gestational period, as each trimester presents distinct physiological and developmental considerations for both the mother and fetus. During the first trimester, when organ systems are forming, there is heightened concern about congenital anomalies resulting from teratogenic exposure. Consequently, many healthcare providers prefer to withhold or delay pharmacotherapy during this stage unless absolutely necessary (Trønnes, Lupattelli and Nordeng, 2017). In the second trimester, as fetal growth accelerates and maternal conditions such as gestational diabetes or hypertension may emerge, pharmacological intervention is more frequently initiated. However, clinicians must still weigh out the potential for long term developmental effects, particularly with medications affecting hormonal or metabolic pathways (Lupattelli, Trinh and Nordeng, 2023). In the third trimester, attention shifts toward the risk of complications related to delivery or neonatal adaptation, including respiratory depression or symptoms similar to withdrawal sindrome, that is associated with certain psychotropic medicines. For example, nonsteroidal anti inflammatory drugs (NSAIDs) are generally avoided later in pregnancy due to their association with premature closure of the ductus arteriosus (Blotière *et al.*, 2021). These trimester specific factors underscore the complexity of safe prescribing in pregnancy and highlight the need for dynamic, individualized risk assessment throughout gestation.

2.4. Lifestyle and behavioral factors

Health behaviors such as tobacco and substance use have been correlated with higher prescription rates for certain medication types. Smokers, both current and former, are more frequently prescribed opioids, anxiolytics or respiratory medications, likely reflecting comorbidities, such as chronic bronchitis or anxiety disorders. Tobacco use during pregnancy is also linked to lower compliance with prenatal supplements, such as folic acid or multivitamins, which may increase the need for additional medical intervention. Although less studied, alcohol use has also been observed to correlate with higher rates of psychotropic drug prescriptions, potentially in relation to withdrawal management or the treatment of occurring mental illness. These behaviors may also interact with SES and mental health status, forming complex risk profiles for harmful drug exposure (Nagai *et al.*, 2022).

2.5. Polypharmacy and drug interactions

Taking multiple medications simultaneously– commonly referred to as polypharmacy– is one of the most significant predictors of exposure to medicines with higher fetal risk. Even in the absence of chronic illness, women prescribed five or more medications are substantially more likely to receive at least one Category D medication. This association is particularly strong in settings where combination treatments are common, such as for infections or pain management. Common polypharmacy patterns include the concurrent use of antimicrobials with hormonal agents or analgesics with gastrointestinal drugs. Such combinations can introduce complex pharmacokinetic interactions and may increase fetal exposure, particularly if medications are taken throughout the first trimester when organ development is most vulnerable (Verkerk *et al.*, 1993).

3. Methods

3.1. Setting

This study was conducted in Latvia, where the healthcare system is predominantly public, with the majority of healthcare services funded through a state run system. The Ministry of Health oversees the overall healthcare infrastructure and policy, while the National Health Service (NHS) manages the organization and financing of healthcare services. Latvia provides universal health coverage to all its residents, with the healthcare system primarily funded through taxes, with contributions from employers and employees. The public healthcare system in Latvia covers primary care, specialized care services, hospitalization and pharmaceuticals. The reimbursement system in Latvia allows patients to acquire medicines with state reimbursement of 100%, 75% or 50%, depending on the disease type and severity for treatment purposes. Pregnancy monitoring including consultations, lab tests and diagnostics is funded by the state and provided by specialists contracted with the National Health Service. A wide range of medications is available for pregnant women and prescriptions are managed by healthcare providers, including general practitioners, obstetricians and gynecologists. The state reimburses medicines for pregnant women up to 70 days postpartum and children up to 24 months of age. The Latvian National Health Service keeps detailed records of all medical prescriptions and dispensations, which was used in this study (Center for Disease Prevention and Control, no date).

3.2. Study design

A nationwide drug utilization study was performed to analyze prescribed and dispensed medications among pregnant women in Latvia who gave birth from 2020-2023 using national data sources. Information about maternal characteristics, prescribed and dispensed medicines, physician speciality, who prescribed the medication and diagnosis code (ICD-10) for medication use was requested from Health Care Quality and Efficiency Monitoring System. This drug utilization study included all pregnant women with deliveries between January 2020 and December 2023 regardless of the pregnancy outcome. Medication exposure is defined as prescribing of medications at least once during pregnancy period for women who gave birth 2020-2023.

The period for medication exposure was evaluated starting from pregnancy start date, which was retrospectively calculated based on the delivery date (day, month, year) and gestational age. The term "birth giver" or “women who gave birth 2020-2023" often is used instead of "pregnant women" because the study relies on data from the Medical Birth Register, which includes only pregnancies resulting in childbirth, meaning, no data was available on abortions– pregnancies less than 22 completed weeks of gestation (Veselības statistikas departaments, 2008). In this study "used medicines" refers to dispensed medicines. Prescribed medications do not necessarily indicate actual use if they were not dispensed from the pharmacy. Each prescribed medication within any trimester of pregnancy will be classified according to Swedish and Australian risk classification systems. Potentially harmful prescription medicines are defined as medications classified in category D. This drug utilization study included all birth givers between January 2020 and December 2023, irrespective of the delivery outcome. If a woman had more than one pregnancy during the study period, that resulted in a delivery, each was included independently. Both singleton and multiple births (e.g., twins, triplets) were included. All birth givers registered in the Medical Birth Register were eligible for the study, but only women with prescribed and/or dispensed at least one prescription medication within the study period was included in the comprehensive data evaluation. Study period spans from January 2020 to December 2023, however to capture data on prescribed and dispensed medications by all birth givers during this timeframe, a period of 9 months ± 2 months prior to the delivery date was considered. Consequently, medication consumption data from February 2019 and onward was requested from the Public Monitoring System of Health Care Quality and Efficiency.

A ±2 month period was applied to account for variations in gestational length, including the possibility of preterm delivery, which can occur between the 22^{nd} and 36^{th} week of

pregnancy and post term delivery, which occurs after the 42nd week. This adjustment ensures comprehensive capture of medication exposure data across the full range of pregnancy duration, accommodating for both early and late deliveries.

3.3. Data sources

In accordance with a 4-party (between the Center for Disease Prevention and Control, the National Health Service, the Emergency Medical Service and the Health Inspectorate) cooperation agreement on the creation of a health care quality and efficiency monitoring system, a database has been created where data characterizing health care information was collected from Center for Disease Prevention and Control and the National Health Service and connected at the individual level. Data is not collected from one institution, the linking of multiple data sets through the unique identifier for each person ensures the possibility of using data more widely. For the strict protection of personal data, the participating institutions apply a procedure for the anonymization of the direct identifier of persons, which excludes the possibility of one of the parties saving and reusing the encryption key. Thus, adding the current year's data essentially rebuilds the database. The database was created within the framework of the effective cooperation project of the Center for Disease Prevention and Control and the University of Latvia "Creation of a Public Monitoring System of Health Care Quality and Efficiency" (Center for Disease Prevention and Control, no date).

Center for Disease Prevention and Control is the custodian and keeper of the Medical Birth Register, that contain medical information about newborn children in the territory of Latvia, as well as information about the mother of the newborn, her previous pregnancies and deliveries, the last pregnancy, including the harmful habits of the mother and information about childbirth. Register has information about the pregnancy starting from 22 weeks gestational age (Ministru kabinets, 2018). Data of reimbursed medicines and the speciality of the prescriber were collected from the NHS database. View the variables section (3.4.) for data requested from the monitoring system.

The council evaluates the compliance of the data request with the certain criteria and then agrees on the opinion on providing or not providing information from the monitoring system. The data requester agrees with CDC on the process and terms of data preparation and provision.

Prior to initiating the study, approval was obtained from the Research Ethics Committee. The submitted application included all required documentation: the completed ethics application form containing the study title, objectives, data sources and processing plan. Additionally, a formal request for permission to use documented patient data for research

purposes was submitted. The research protocol provided to the committee outlined the study design, setting, data sources, analytical methods and data processing procedures. Ethical approval confirmed that the study met the necessary standards for the use of anonymized patient level data in compliance with data protection regulations, see Appendix 1.

3.4. Variables

Medication exposure was considered as prescribing of medicines, meaning when a medication is prescribed at least once between the estimated start and end date of pregnancy. All prescribed medications were included in data analysis and were coded into the corresponding Anatomical Therapeutic Chemical (ATC) codes at the fifth (substance) level in accordance with the World Health Organization ATC index (Norwegian Institute of Public Health, WHO Collaborating Centre for Drug Statistics Methodology, 2024).

To summarize medication use during pregnancy, prevalence of prescribing and dispensing medications was defined as the number of birth givers with prescribed and dispensed medication divided by the number of birth givers reported in the study population within 4-year period. Prevalence rate for prescribed and dispensed medicines also was analyzed in each year. The following maternal and medication data were requested and obtained from the Health Care Quality and Efficiency Monitoring System.

Medical Birth Register:

- Sociodemographic factors of the birth-giver:
    - Anonymous unique patient identifier;
    - Age (full years);
    - Education;
    - Marital status;
    - Nationality;
- Factors associated with the overall health status and current pregnancy of the birth-giver:
    - Total number of previous pregnancies, births, abortions;
    - Harmful habits of the mother (smoking at the time of first antenatal visit and at the time of admission for delivery, alcohol and psychoactive substance use);
    - Pregnancy and childbirth complications for the mother related to the fetus (ICD-10 code);
    - Mode of delivery, analgesia until childbirth;
- Factors of the newborn:
    - Gender;

- Gestational age (weeks and days);
- Pathology of newborns (IDC-10 code);

National Health Service:

- Anonymous unique patient identifier;
- Factors of reimbursed medicines:
  - Anatomical Therapeutic Chemical (ATC) code;
  - Brand name and International Non-proprietary Name (INN) of prescribed and subsequently dispensed medicines;
  - Main diagnosis code and co-diagnosis code (IDC-10 code) for which the medicine was prescribed;
  - Date of the prescription;
  - Date when medication was dispensed;
  - Amount of dispensed medication in packages;

3.5. Data cleaning

The dataset initially contained medication names prescribed and dispensed during pregnancy but lacked critical identifiers such as Anatomical Therapeutic Chemical (ATC) codes and international risk classifications (Swedish FASS and Australian). To address this, a systematic data cleaning and integration workflow was implemented in *Power BI*, leveraging its *Power Query Editor* and *merge* functionalities.

3.5.1. Data import and standardization

To enable accurate analysis, all relevant datasets were imported, reviewed and standardized prior statistical processing. The data preprocessing phase involved the integration of primary medication records with external risk classification sources, followed by harmonization of variable formats and content. The primary dataset included medication records containing brand and generic names, prescription and dispensing dates and maternal identifiers. A secondary reference dataset was compiled to provide ATC codes and corresponding risk classifications from Swedish FASS and Australian TGA systems. To ensure consistency across sources, medication names were standardized to International Nonproprietary Names (INN). Duplicate records were identified and removed to prevent data redundancy and ensure clean input for subsequent analysis.

Source datasets:

- Primary dataset: Medication records (brand/generic names, prescription/dispensing dates, maternal IDs);

- Reference dataset: ATC codes and corresponding risk classifications from Swedish FASS and Australian systems;

Standardization:

- Medication names were harmonized to align with International Nonproprietary Names (INN) to resolve discrepancies (e.g., "Paracetamol" vs. "Acetaminophen");
- Duplicate entries in both datasets were removed using the Remove Duplicates function;

3.5.2. Merging datasets to assign ATC codes and risk classifications

A *Left Outer Join* was performed to retain all records from the primary dataset while appending ATC codes and risk classifications from the reference dataset. Medication names were matched exactly between datasets. For partial matches (e.g., combination drugs), fuzzy matching (with a similarity threshold of 85%) was applied to minimize manual intervention. Medications without ATC codes (e.g., compounded formulations) were flagged for manual review. Discrepancies in risk classifications across systems (e.g., a drug categorized as "B3" in Australia but "C" in Sweden) were retained as separate columns for comparative analysis.

3.5.3. Post merge data validation

Regarding data completeness, it was validated that 98.7% of medications received ATC codes. The remaining 1.3% (e.g., herbal supplements, unlicensed drugs) were excluded from safety profile analyses but retained in dispensing and prescribing prevalence calculations. Regarding consistency, approximately 500 random entrie samples were cross-referenced against authoritative sources (FASS and FDA databases) to ensure accurate classification. Regarding temporal alignment, prescription and dispensing dates were compared against gestational timelines to exclude medications used outside pregnancy (e.g., preconception or postpartum periods). Key variables were collected and dated across several cleaned datasets, refer to table 3.1 for a detailed overview.

3.1. Table

Key variables from primary and reference datasets

Maternal_ID	Unique identifier for birth-givers	Primary dataset
Medication_Name	Standardized INN name	Merged dataset
ATC_Code	5th-level ATC code (e.g., N02BE01)	Reference dataset
FASS_Category	Swedish risk classification (A, B1-B3, C, D)	Reference dataset
Australian_Category	Australian classification (A, B1-B3, C, D, X)	Reference dataset
Prescription_Date	Date of prescription	Primary dataset
Dispensing_Date	Date of dispensing	Primary dataset

3.5.4. Handling missing or ambiguous data

Medicines without risk classifications (e.g., newer biologics) were analyzed separately to avoid misclassification bias. Cases where prescriptions were not dispensed were identified by comparing Prescription_Date and Dispensing_Date fields. These were quantified to assess adherence and medication access issues.

3.5.5. Output for analysis

The final merged dataset was loaded into *Power BI* for visualization and statistical modeling, enabling calculations of prescribing and dispensing prevalence rates and stratification by risk category. This rigorous cleaning process ensured data integrity and facilitated robust, reproducible analysis of medication safety patterns in the Latvian cohort.

To identify maternal factors associated with high risk medication use, the final dataset prepared for analysis included all relevant variables obtained from the Health Care Quality and Efficiency Monitoring System. In R Studio, this output was analyzed using statistical methods such as binomial logistic regression.

3.6. Data analysis

Continuous variables were described using mean and standard deviation (in case data follow a normal distribution), minimal and maximal values. For categorical variables, percentages were used of patients in each category. An exploratory, descriptive analysis was conducted and baseline characteristics as observed on the cohort entry date was summarised.

Statistical analysis results were reported separately for the Swedish and Australian risk classification systems. The prevalence of prescribing and dispensing medicines during pregnancy for birth givers was calculated as the number of birth givers with prescribed and dispensed prescription medication divided by the number of women reported in the study population within four-year period. Prevalence rates of prescribing and dispensing medicines during pregnancy were further stratified by year.

To evaluate the consistency of the two internationally recognized pregnancy risk classification systems, the Swedish Farmaceutiska Specialiteter i Sverige (FASS) and the Australian categorization system– *Cohen's Kappa* coefficient was calculated. This statistical method assesses the level of agreement between two raters– risk classification systems in this context, and is suitable for categorical data. The analysis focused on medications prescribed to pregnant women in Latvia who gave birth between 2020 and 2023 and categorized according to both risk classification systems. The data included categorical risk assessments assigned to each prescribed drug using both the FASS (*Läkemedelsindustriföreningen. FASS for vårdpersonal*, no date) and Australian (*Australian Government Department of*

Health. Australian categorisation system for prescribing medicines in pregnancy, no date) systems. However, Australian and Swedish risk classification systems include subcategories within category B, namely B1, B2, and B3, that differ slightly in risk interpretation compared to categories "A", "C", "D" and "X" but can be preserved for analysis to obtain full classification details and more precise insight into agreement and disagreement, a thorough description of the different risk categories used in the two classification systems is reported in Appendix 2. Several studies have employed similar methodology when comparing different pregnancy risk classification systems (Addis, Sharabi and Bonati, 2000; ZHANG Chuan, 2016). However some cons to this method is that in occasion of sparse data, it can lower *Kappa* reliability and make it harder to interpret the coefficient in small samples. The dataset was then filtered to include only those medications with a non missing classification in both systems. This step was essential because *Cohen's Kappa* requires complete paired observations. Rows with missing values in either the FASS or Australian classification fields were excluded solely from this specific analysis, while retained for other data analysis. The missingness was not random, but instead reflected the unavailability of official classification data for certain less commonly used or newer substances. Data were processed and analyzed using R (*version RStudio 2025.05.0+496 "Mariposa Orchid"*) with the *psych* package. Classifications were converted to factors and the agreement analysis was performed using the *cohen.kappa()* function from the package. The output of this analysis includes the *Kappa* coefficient, which ranges from -1 to 1, with values closer to 1– indicating stronger agreement. According to the interpretation scale by (Landis JR, 1973), *Kappa* values between 0.61 and 0.80 represent substantial agreement, while values above 0.81 indicate almost perfect agreement. The result also provides a *p-value* to test the null hypothesis that the agreement might have occured only by chance. By performing the comparison, the consistency of both RCS will be understood. Identifying mismatches between systems can help in assessing the robustness of risk categorization approaches and may inform future efforts to allign prescribing guidelines across systems used in European and other countries.

To identify subgroups of women at higher risk of receiving potentially harmful prescriptions during pregnancy, maternal characteristics associated with such prescriptions will be examined. These characteristics include sociodemographic, chronic conditions and healthcare utilization patterns. Adjusted odds ratios (ORs) with 95% confidence intervals were calculated using multivariate logistic regression, accounting for within-subject correlation in women with more than one delivered newborn during the 2020 – 2023 study period through generalized estimating equations (GEE) with a binomial distribution.

No data imputation method was performed. The absence of relevant information on prescriptions was interpreted as no medication being prescribed. The proportion of patients with missing values were reported. Not all information about a mother's diagnosis is included in the system. Also, not all pregnancies are reported in this study, as data on abortions is limited.

4. Results

In total 58 844 birth givers and 64 506 deliveries were identified in Latvia during the 2020 – 2023 period. Between 2020 and 2023, the proportion of newborns born to mothers under the age of 25 increased from 4.2% to 7.2%, indicating an upward trend in younger maternal age, refer to table 4.1 for a detailed overview.

4.1. Table

Number of newborns by maternal age and year of delivery (2020–2023)

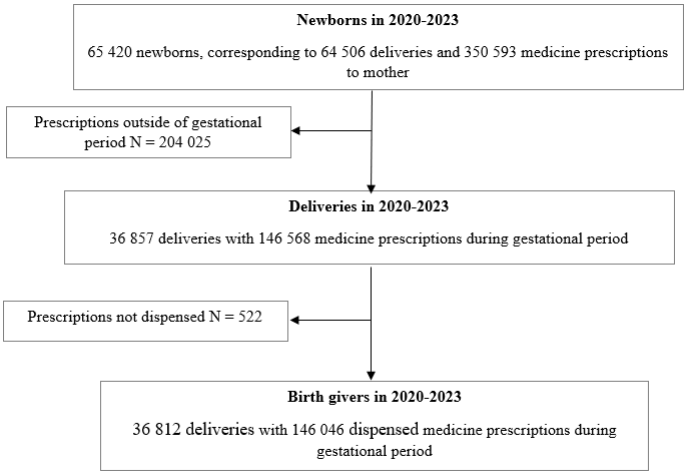
Characteristics	Overall* (N=65 420)	Year of birth			
		2020* (N=17 589)	2021* (N=17 442)	2022* (N=15 893)	2023* (N=14 496)
Maternal age at conception					
<25 years	2 735 (4,18%)	350 (1,99%)	570 (3,27%)	776 (4,88%)	1036 (7,15%)
25-29 years	8 970 (13,71%)	1972 (11,21%)	2066 (11,84%)	2403 (15,12%)	2529 (17,45%)
30-34 years	19 198 (29,35%)	4 621 (26,27%)	5 303 (30,40%)	4 779 (30,07%)	4 495 (31,01%)
>35 years	34 517 (52,76%)	10 646 (60,53%)	9 503 (54,48%)	7 935 (49,93%)	6 436 (44,40%)

*N(%) Count of newborns

4.1. Prevalence of prescribing and dispensing medicines

Among all birth givers during 2020-2023, 57% dispensed at least one prescription medication during pregnancy.

4.2. Figure



4.2. Figure. Data filtering steps for prescription records during gestational period (2020–2023)

Birth givers in 2023 had the highest prevalence of medication prescribing and dispensing medications through community pharmacies, 64.1% and 64% respectively, and birth givers in 2020 had the lowest prevalence of medication prescribing and dispensing 50.9% and 50.9% respectively, refer to table 4.3. for a detailed overview. These findings show that medication prescribing during pregnancy is highly prevalent in Latvia, affecting more than half of all women that gave birth in 2020-2023.

4.3. Table

Prevalence of prescribing and dispensing medications to women who gave birth during 2020-2023

Birth givers in 2020: prescribed medicines (%)	Birth givers in 2020: dispenced medicines (%)	Birth givers in 2021: prescribed medicines (%)	Birth givers in 2021: dispenced medicines (%)	Birth givers in 2022: prescribed medicines	Birth givers in 2022: dispenced medicines (%)	Birth givers in 2023: prescribed medicines	Birth givers in 2023: dispenced medicines (%)
50,92%	50,91%	54,90%	54,88%	60,12%	59,89%	64,09%	64,04%

4.2. Yearly trend 2020–2023

Over the four year observation period, the proportion of pregnant women in Latvia who received prescription and subsequently had medications dispensed showed a year after year increase. Both prescribing and dispensing rates were calculated annually for women who gave birth between 2020 and 2023.

In 2020, just over half (50.9%) of all women who gave birth had been prescribed at least one medication during pregnancy. Almost the same proportion had these medications dispensed. This minimal absolute difference between prescribing and dispensing was 0.01 percentage points and implies that nearly all women who received a prescription also dispensed it.

In 2021, the proportion of women receiving prescriptions and dispensing them remained stable at 54.9%. The difference between the two values remained minimal with 0.02 percentage points.

In 2022, the prescription rate increased to 60.1%, while the dispensing rate reached 59.9%, resulting in a difference of 0.23 percentage points.

In 2023, the highest rates during the study period were observed: 64.1% of pregnant women were prescribed at least one medication, and 64% had at least one medication dispensed. The difference between these values was 0.05 percentage points.

To statistically evaluate the observed increase in prescription prevalence between 2020 and 2023, a comparison of proportions was performed. In 2020, 50.9% of women (N = 17 344)

were prescribed medication, compared to 64.1% (N = 14,270) in 2023. The absolute difference was 13.17 percentage points (95% CI: 12.1% - 14.3%), indicating a statistically significant increase in prescription prevalence (*p-value* < 0.0001).

A corresponding test was also performed for dispensing prevalence. In 2020, 50.9% of women (N = 17 344) had at least one medication dispensed, compared to 64 % (N = 14 270) in 2023. The absolute difference was 13.13 percentage points (95% CI: 12% - 14.2%), indicating a statistically significant increase in dispending prevalence (*p-value* < 0.0001).

Overall, both prescribing and dispensing rates increased significantly during the 2020–2023 period with minimal yearly differences between the two measures the overall prevalence of medication prescribing among pregnant women who gave birth in Latvia was calculated at 57.1% (95% CI: 56.75% - 57.51%). This estimate is based on 36 812 women who dispensed medications during gestational period out of a total of 64 506 birth givers. In comparison, the overall dispensing prevalence, defined as the proportion of women who had at least one prescribed medication dispensed during pregnancy was 57.06% (95% CI: 56.68% - 57.44%).

4.3. Breakdown by ATC codes, risk classification categories (A, B, C, D, X)

The analysis presents a detailed breakdown of the most frequently prescribed medications during pregnancy, categorized by ATC codes and total prescription counts, as well as percentage of the total number of prescriptions (146 046), refer to 4.4. table for a detailed overview. The data reflects prescribing practices within the studied population and provide insight into both the types of medications most commonly utilized and the therapeutic areas prioritized in maternal care.

4.4. Table

Top 10 frequently prescribed medications (ATC 5th level) by number of prescriptions among women who gave birth in Latvia 2020-2023

ATC code	ATC name	Count of prescriptions	% of Total Prescriptions
G03DA04	progesterone	34250	23.45%
A11CC05	colecalciferol	11744	8.04%
B03AB05	ferric oxide polymaltose complexes	7937	5.43%
C02AB01	methyldopa (levorotatory)	6914	4.73%
G03DB01	dydrogesterone	6860	4.70%
J01CA04	amoxicillin	4758	3.26%
G01AF15	butoconazole	3395	2.32%
G01AF05	econazole	3245	2.22%
J01XE03	furazidin	1150	0.79%
J01CA01	ampicillin	1041	0.71%

Hormonal therapies and supplements, specifically progesterone (G03DA04) was the leading medication with 34 250 prescriptions. This high volume underscores the central role of progestogens in pregnancy management, likely reflecting use for luteal phase support, prevention of miscarriage or other gynecological indications. Dydrogesterone (G03DB01), another progestogen was also prescribed frequently (6 860 prescriptions), indicating a substantial reliance on hormonal therapies for pregnancy support.

Colecalciferol (A11CC05), a form of vitamin D, ranked second overall with 11 744 prescriptions. The prominence of this supplement highlights the emphasis on nutritional support and the prevention of vitamin D deficiency during gestation.

Hematological agents, specifically ferric oxide polymaltose complexes (B03AB05) that are used to address iron deficiency, accounted for 7 937 prescriptions. Iron supplementation is a cornerstone of prenatal care, reflecting both routine prophylaxis and treatment of diagnosed anemia.

Cardiovascular and antihypertensive agents, like methyldopa (C02AB01), an antihypertensive agent, was prescribed 6 914 times. Its established safety profile in pregnancy makes it a preferred option for managing elevated blood pressure, particularly in the second and third trimesters.

Antimicrobial medications like amoxicillin (J01CA04) was the most prescribed antibiotic with 4 758 prescriptions, indicating its role as a first line agent for bacterial infections during pregnancy. Ampicillin (J01CA01), another penicillin class antibiotic, was prescribed 1 041 times, supporting its continued use for specific infections where sensitivity is assured. Furazidin (J01XE03) with 1 150 prescriptions, suggests a notable preference for this agent in the treatment of urinary tract infections, a common concern in pregnant populations.

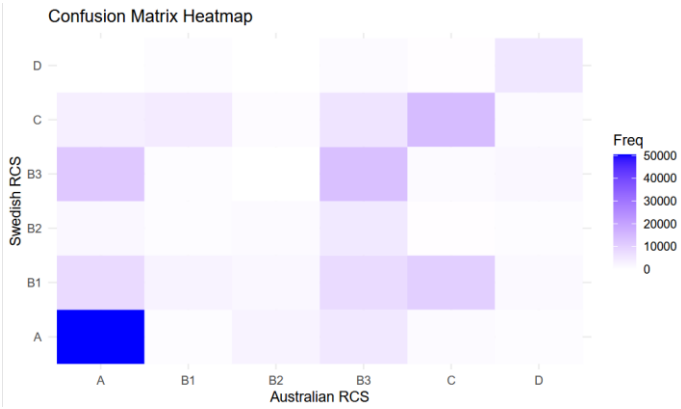
Antifungal agents, like butoconazole (G01AF15) and econazole (G01AF05) with 3 395 and 3 245 prescriptions respectively, were the most commonly used antifungals. Their use likely reflects the management of vulvovaginal candidiasis, which is frequent in pregnancy due to hormonal and immunological changes.

In summary, the most commonly prescribed medications during pregnancy in this population are dominated by hormonal therapies at 28.2% (progesterone, dydrogesterone), nutritional supplements at 13.5% (colecalciferol, ferric oxide polymaltose), antihypertensives at 4.7% (methyldopa), antibiotics at 4.8% (amoxicillin, ampicillin, furazidin) and antifungals at 4.5% (butoconazole, econazole). These findings reflect clinical priorities in pregnancy care, including reproductive support, nutritional adequacy and infection control. The results underscore the importance of ongoing monitoring of prescribing patterns to ensure both maternal and fetal safety, as well as alignment with evolving clinical guidelines.

During the data preparation process, it was observed that a substantial proportion of prescribed medications lacked classification information in one or both of the risk categorization systems under study. Specifically, the Australian risk classification system did not provide data for 6 895 substances (4%), while the Swedish FASS system had missing classifications for 7 207 substances (4.2%). These missing values represent drugs that could not be assessed for risk using the respective system due to the absence of an official classification. The discrepancies are likely due to several factors, including differences in national drug formularies, availability of certain medications in only one country or the lack of published fetal risk data for newer or less commonly prescribed drugs. Since *Cohen's Kappa* requires complete paired classifications, only medications with available data in both systems were included in the agreement analysis. As a result, a subset of the total dataset was used for this part of the evaluation. While this filtering step was methodologically necessary, it also highlights an important limitation that the data incompleteness of internationally recognized risk classification systems when applied to a national prescribing context. These findings emphasize the ongoing need for harmonized and comprehensive risk categorization efforts.

The results of the classification model are presented in the form of a confusion matrix, heatmap and associated performance statistics. The heatmap provides a visual color coded overview of classification performance across classes where agreement and disagreement occur the most, refer to 4.5. Figure.

4.5. Figure



4.5. Figure. Heatmap of agreement between Swedish and Australian RCS

The confusion matrix displays the relationship between the predicted and actual classes for each observation. The rows represent the true classes (reference), while the columns correspond to the predicted classes (prediction). The entries in the matrix indicate the number of instances where a particular prediction was made for each true class. The confusion matrix shows significant misclassification across all classes, with particularly high misclassification

rates for classes B1, B2 and C. These discrepancies indicate that the model has difficulty correctly predicting these classes, which may be due to class imbalances or the inherent complexity of distinguishing between these categories, refer to 4.6. Table.

4.6. Table

Confusion matrix and agreement statistics between Australian and Swedish RCS

Prediction \ Reference	A	B1	B2	B3	C	D
A	50406	748	167	1286	324	86
B1	2454	2163	204	800	65	37
B2	448	277	53	73	4	0
B3	2294	1699	434	12608	666	301
C	1006	742	138	753	5389	684
D	369	303	108	715	839	3199

The model achieved an overall accuracy of 0.535, which reflects that the model correctly predicted the class of approximately 53.5% of the instances. The 95% confidence interval (CI) for the accuracy is between 0.5325 and 0.5374, indicating that the result is statistically reliable. The No Information Rate (NIR) is 0.3662, which represents the accuracy a model would achieve if it predicted the most frequent class for every observation. The p-value for the comparison of accuracy against the NIR is less than 2.2e-16, indicating that the model's accuracy is significantly better than random guessing. The *Kappa* statistic is 0.3784, which indicates a fair level of agreement between the predicted and actual classifications. *Kappa* values range from 0 (no agreement) to 1 (perfect agreement), with values below 0.4 generally considered to reflect moderate agreement. The McNemar's test p-value is less than 2.2e-16, indicating that there is a significant difference between the two classification methods being compared, meaning, the observed disagreements are not due to random chance, refer to 4.7. Table.

4.7. Table

Overall model performance statistics for Cohen’s Kappa analysis

Metric	Value
Accuracy	0.535
95% CI	(0.5325, 0.5374)
No Information Rate	0.3662
P-Value [Acc > NIR]	< 2.2e-16
Kappa	0.3784
McNemar's Test P-Value	< 2.2e-16

The following statistics are calculated for each class in the confusion matrix, providing deeper insights into the model's performance for each category, refer to 4.8. Table.

In class A the model correctly identified 84.7% of all instances with sensitivity– true positive rate– of 0.8473. However the specificity– true negative rate– was 0.7617, meaning the model correctly classified 76.2% of non-A instances. The positive predictive value (PPV) was 0.6726, showing that when the model predicted class A, it was correct 67.3% of the time. The negative predictive value (NPV) was 0.8962, indicating that when the model predicted non-A, it was correct 89.6% of the time. The balanced accuracy was 0.8045, which is the average of sensitivity and specificity providing a more balanced measure of performance across classes.

In class B1 the model correctly identified only 8% of all instances with sensitivity of 0.0798, suggesting a poor ability to identify this class. Specificity was 0.9562, meaning the model did well in identifying non-B1 instances. The positive predictive value (PPV) was 0.3005, indicating that when B1 was predicted, it was correct 30.1% of the time. The negative predictive value (NPV) was 0.8149, showing that non-B1 predictions were correct 81.5% of the time. The balanced accuracy was 0.518, which reflects a poor balance between the model's ability to predict B1 correctly and its ability to reject non-B1 cases.

In class B2 the model correctly identified 10.6% of all instances with sensitivity of 0.1062, revealing a low rate of correctly predicting class B2. Specificity was 0.9679, indicating high accuracy in predicting non-B2 instances. The positive predictive value (PPV) was 0.1516, showing that predictions of class B2 were correct only 15.2% of the time. The negative predictive value (NPV) was 0.9526, indicating a very high rate of correct non-B2 predictions. Balanced accuracy was 0.5371, suggesting moderate performance for class B2.

In class B3 the model correctly identified 48.2% of all instances with sensitivity of 0.4821, showing that the model predicted class B3 correctly about 48.2% of the time. Specificity was 0.8223, indicating that the model successfully identified non-B3 instances 82.2% of the time. The positive predictive value (PPV) was 0.3647, meaning that 36.5% of the predicted B3 cases were correct. The negative predictive value (NPV) was 0.8824, showing a good rate of correct non-B3 predictions. Balanced accuracy was 0.6522, which suggests moderate accuracy in distinguishing class B3 from other classes.

In class C the model correctly identified 49.8% of all instances with sensitivity of 0.4983, indicating a relatively moderate sensitivity for class C. Specificity was 0.9100, reflecting high specificity in identifying non-C instances. Positive predictive value (PPV) was 0.5435, meaning the model was correct 54.4% of the time when predicting class C. Negative predictive value (NPV) was 0.8940, showing that predictions of non-C were accurate 89.4% of

the time. Balanced accuracy was 0.7041, reflecting decent performance across both sensitivity and specificity for class C.

In class D the model correctly identified 79.1% of all instances with sensitivity of 0.7908, showing that the model correctly identified 79.1% of class D instances. Specificity was 0.9716, indicating that the model was highly accurate in predicting non-D cases. Positive predictive value (PPV) was 0.5364, reflecting that the model was correct 53.6% of the time when predicting class D. Negative predictive value (NPV) was 0.9911, showing excellent accuracy for non-D predictions. Balanced accuracy was 0.8812, indicating very strong performance for class D.

4.8. Table

Statistics by risk category class for Cohen's Kappa analysis

Statistic	A	B1	B2	B3	C	D
Sensitivity	0.8473	0.4716	0.0869	0.8223	0.422	0.5914
Specificity	0.9602	0.9684	0.9951	0.8916	0.9651	0.9682
Pos Pred Value	0.8934	0.3984	0.0566	0.6303	0.6572	0.6003
Neg Pred Value	0.9326	0.9771	0.9966	0.9618	0.9163	0.9663
Prevalence	0.3602	0.1494	0.0553	0.1826	0.0873	0.1652
Detection Rate	0.3052	0.0705	0.0048	0.1503	0.0368	0.0977
Detection Prevalence	0.3416	0.177	0.0852	0.2381	0.056	0.162
Balanced Accuracy	0.9037	0.72	0.541	0.872	0.6936	0.7798

The model shows moderate overall accuracy, with the highest performance observed for class A and class D and much poorer performance for classes B1 and B2. The substantial differences in sensitivity and specificity across classes suggest that the model may benefit from class specific optimization or addressing class imbalances to improve its predictive performance.

4.4. Maternal factors associated with prescribing potentially harmful medicines

There were 64 506 deliveries analyzed between 2020 and 2023, the number of women giving birth declined each year from 17 344 in 2020 to 14 270 in 2023. Despite this reduction in total births, the proportion of pregnant women receiving at least one prescription for a Category D drug increased steadily according to both classification systems.

According to Australian classification, in 2020, 691 women were prescribed category D medications, corresponding to a prevalence of 4%. This proportion nearly doubled by 2021, with 1 279 women (7.4%) exposed to at least one Category D drug. The upward trend continued in 2022 and 2023, reaching 1 404 (9%) and 1 500 (10.5%) women, respectively. Over the four years, the prevalence of Category D drug prescribing more than doubled, indicating a notable

increase in the use of medications with known fetal risk as defined by the Australian system, refer to 4.9. Table for a detailed overview. To statistically evaluate the observed increase in prevalence of prescribing category D medications between 2020 and 2023, a comparison of proportions was performed. The absolute difference was 6.5 percentage points (95% CI: 5.95% - 7.12%), indicating a statistically significant increase in prevalence of prescribing category D medications (*p-value* < 0.0001).

When applying the Swedish classification, the prevalence figures were consistently lower in each year. In 2020, 348 women (2%) were exposed to Category D medications. This number rose to 890 (5.2%) in 2021, 896 (5.7%) in 2022, and 916 (6.4%) in 2023. While the overall trend mirrored the Australian system, the absolute prevalence remained substantially lower, highlighting differences in how drugs are categorized between the two systems. A corresponding test was also performed for prevalence of prescribing category D medications between 2020 and 2023 according to Swedish RCS. The absolute difference was 4.4 percentage points (95% CI: 3.97% - 4.88%), indicating a statistically significant increase in prescribing category D medications (*p-value* < 0.0001).

The data reveal that regardless of the classification system, the proportion of pregnant women prescribed Category D drugs has increased annually. However, the Australian system consistently identifies a higher prevalence of exposure than the Swedish system. For instance, in 2023, the prevalence under the Australian system was 10.5%, compared to 6.4% using the Swedish criteria. This discrepancy reflects differences in the scope and interpretation of fetal risk within each system.

The increase in Category D drug prescribing is notable given the established association between these medications and elevated risk of fetal malformations or irreversible effects. The findings underscore the importance of ongoing monitoring and review of prescribing practices, as well as the need for clear clinical guidance to ensure that the use of higher risk medications in pregnancy is justified by maternal health needs and available alternatives.

In summary, from 2020 to 2023, the prevalence of Category D drug prescriptions among pregnant women rose significantly, with higher rates consistently observed using the Australian risk classification system. This trend emphasizes the necessity for careful evaluation of medication safety and risk communication in prenatal care, as well as the impact of classification criteria on reported exposure rates.

4.9. Table

Comparison of Class D prescription prevalence in pregnancy by Australian and Swedish RCS, 2020–2023

		Australian RCS		Swedish RCS	
Year	Birth givers (N)	Birth givers with Class D Prescriptions (N)	Prevalence (%)	Birth givers with Class D Prescriptions (N)	Prevalence (%)
2020	17 344	691	3,98	348	2,00
2021	17 216	1279	7,43	890	5,17
2022	15 676	1404	8,96	896	5,71
2023	14 270	1500	10,51	916	6,42

An analysis of the most commonly prescribed drugs classified under Category D– typically associated with potential fetal risk revealed several noteworthy findings in the study population. The data include medications identified as having evidence of risk to the human fetus, but which may still be clinically indicated when safer alternatives are not effective or available.

The antifungal agent fluconazole (ATC code J02AC01) was the most frequently prescribed Category D drug, with 726 prescriptions, making it the leading potentially harmful agent in terms of use during pregnancy, refer to 4.10. Table for a detailed overview. This is particularly significant given that fluconazole is often associated with teratogenic concerns when administered in high or repeated doses, although it may still be used in specific clinical scenarios requiring systemic antifungal treatment.

Next, doxycycline (J01AA02), a broad spectrum antibiotic, appeared in the dataset with counts of 705. Despite its usefulness in treating various infections, its association with dental staining and possible effects on bone development often limits its use during pregnancy to exceptional cases.

The anticonvulsant lamotrigine (N03AX09) accounted for 133 prescriptions and carbamazepine (N03AF01) appeared 55 times. Both are frequently used in the management of epilepsy, a condition in which ongoing pharmacological treatment is often essential to protect both maternal and fetal health. The necessity of such medications in pregnancy, despite their known risks, reflects the complexity of balancing teratogenic concerns with the dangers of uncontrolled maternal illness. Paroxetine (N06AB05), a selective serotonin reuptake inhibitor (SSRI) used to manage depressive and anxiety disorders, appeared in 110 prescriptions. Although it has been associated with certain congenital outcomes, its use in women requiring psychiatric support may reflect a careful risk-benefit evaluation.

Enalapril (C09AA02), an antihypertensive agent was recorded in 87 prescriptions. While generally avoided in pregnancy due to fetal renal toxicity, it may have been prescribed before pregnancy recognition or in transitional periods of care. Other Category D medications observed include sulfamethoxazole and trimethoprim (J01EE01) with 153 prescriptions, commonly used for urinary tract and other bacterial infections and propylthiouracil (H03BA02), an antithyroid drug, with 22 prescriptions. Though less frequently prescribed, their presence underlines the variety of conditions requiring drug therapy even amid potential fetal risk.

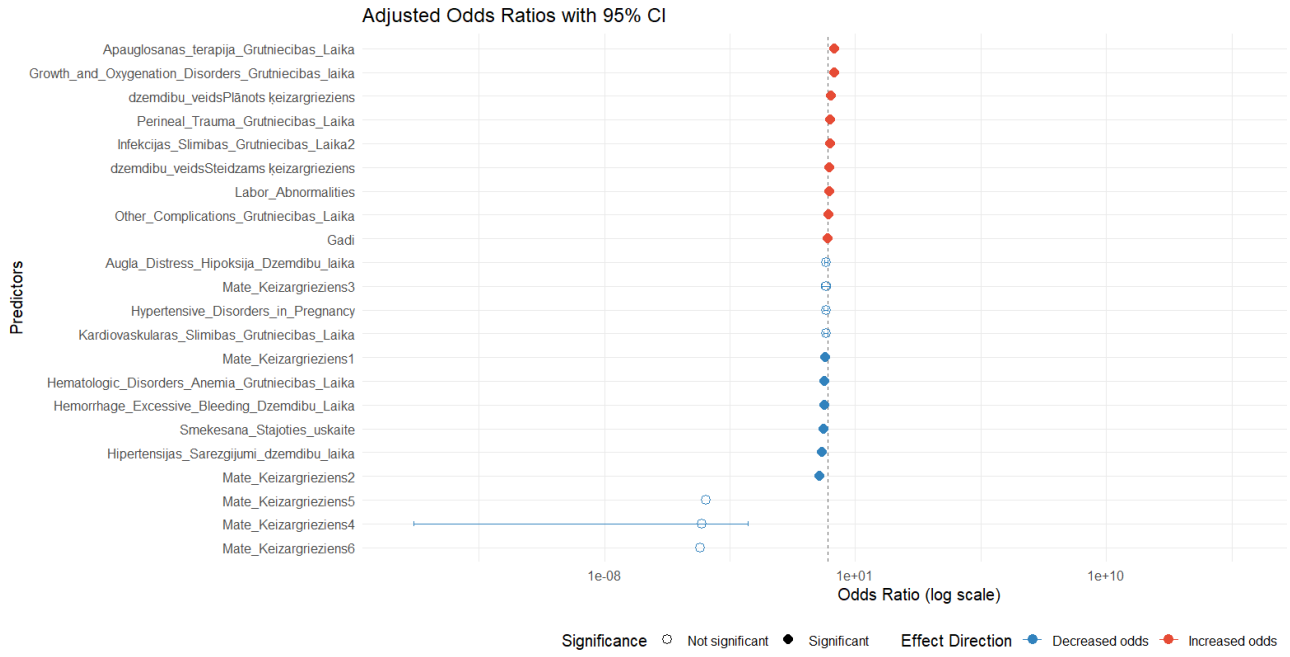
4.10. Table

Top 10 frequently prescribed Category D medications (ATC 5th level) by number of prescriptions among women who gave birth in Latvia 2020-2023

ATC code	ATC name	Count of prescriptions	% of Total Prescriptions
J02AC01	fluconazole	726	0.50
A12CC04	magnesium sulfate	205	0.14
N03AX09	lamotrigine	133	0.09
J01AA02	doxycycline	705	0.48
N06AB05	paroxetine	110	0.08
N03AF01	carbamazepine	55	0.04
J01EE01	sulfamethoxazole and trimethoprim	153	0.1
C09AA02	enalapril	87	0.06
H03BA02	propylthiouracil	22	0.02

To examine which maternal characteristics are associated with the use of potentially harmful (Category D) medications during pregnancy, a binomial logistic regression model was constructed, refer to 4.11. Figure for a visual summary of associations and to 4.12. Table for a detailed review.

4.11. Figure



4.11. Figure. Forest plot of adjusted odds ratios and 95% CI for maternal factors associated with Class D medication prescribing

The dependent variable was D_Class, a binary indicator of whether a woman received a Category D drug during pregnancy or not. The model included various independent variables related to maternal age, comorbidities, obstetric complications, smoking status and delivery related outcomes. The full model was fitted using the *glm()* function with a binomial family in R and included all available predictors. A stepwise model selection process using the *step()* function was applied to improve model simplicity based on Akaike's Information Criterion (AIC). The final selected model retained 23 predictors. The final model had a residual deviance of 38 930 on 123 603 degrees of freedom and an AIC of 38 976, indicating improved fit compared to the null model (null deviance = 39 488). Due to data quality constraints 49 022 observations were excluded from the analysis because of missing values in one or more predictors. The model converged after 12 Fisher scoring iterations.

Significant predictors of potentially harmful medication use were "age", which was significantly and positively associated with Category D drug exposure ($\beta = 0.0237$, $p < 0.001$). This means that for each additional year of maternal age, the odds of receiving a potentially harmful medication increase by approximately 2.4% ($OR = \exp(0.0237) \approx 1.024$). This finding aligns with existing evidence that older pregnant women are more likely to require pharmacological management due to chronic comorbidities.

Smoking at the time of initial prenatal registration “Smoking at pregnancy registration” was associated with significantly lower odds of Category D drug exposure (β = -0.293, p = 0.008). This inverse relationship may reflect clinician hesitancy to prescribe additional pharmacologic agents to smokers or may suggest differences in health seeking behavior. Several maternal chronic and gestational conditions showed strong associations with Category D prescribing– assisted reproductive therapy “Fertility treatment during pregnancy” was a particularly strong positive predictor (β = 0.597, $p < 0.001$), possibly reflecting the higher medical complexity of these pregnancies and increased monitoring. Growth and oxygenation disorders during pregnancy were also positively associated (β = 0.581, $p < 0.001$), potentially indicating a clinical preference to intervene in higher risk fetal conditions, even when doing so involves higher risk medicines. Hematologic disorders and anemia were negatively associated with Category D prescribing (β = -0.257, $p < 0.001$), suggesting more conservative pharmacologic approaches may be taken with this patient group. Hypertensive disorders in pregnancy had a negative but marginally nonsignificant association (β = -0.130, p = 0.083), indicating a trend that may warrant further investigation.

Regarding obstetric outcomes and delivery characteristics– the type of delivery also emerged as a significant determinant, specifically, women undergoing a planned cesarean had a 30% increased odds of receiving a Category D medication (β = 0.295, $p < 0.001$), while emergency cesareans also showed elevated odds (β = 0.144, p = 0.002). Several intrapartum complications such as perineal trauma (β = 0.241, $p < 0.001$), labor abnormalities (β = 0.135, p = 0.033) and other pregnancy complications (β = 0.085, p = 0.031) were significantly associated with increased risk of harmful drug exposure. In contrast, conditions like hemorrhage during delivery (β = -0.259, $p < 0.001$) and hypertensive complications during labor (β = -0.464, $p <$ 0.001) were associated with reduced odds of exposure. These findings may reflect clinical caution during acute obstetric emergencies.

When evaluating the model and its goodness of fit, the logistic model showed reasonable fit as indicated by residual deviance drop from the null model– from 39 488 to 38 930. There was improvement in AIC, supporting model refinement via stepwise selection. Majority of coefficients had small standard errors, suggesting model stability.

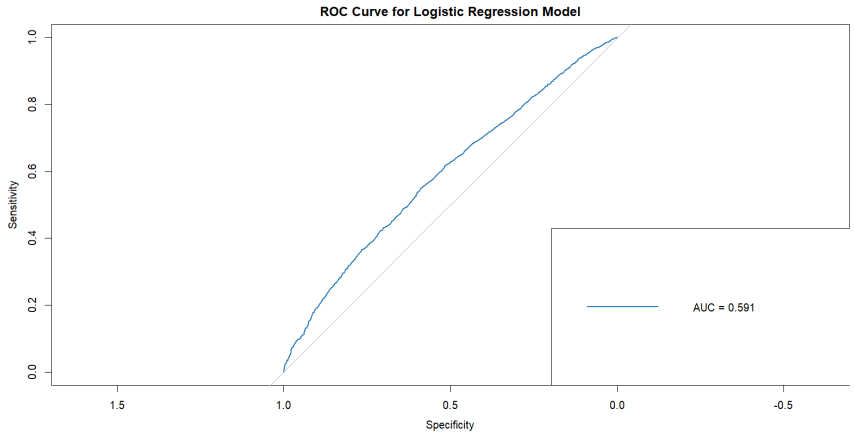
4.11. Table

Logistic regression results for maternal factors associated with class D medication prescriptions during pregnancy

	OR	OR_CI_Lower	OR_CI_Upper	p_value	Log_odds
Age	1.02E+00	1.02E+00	1.03E+00	<2e-16	2.37E-02
Smoking at pregnancy registration	7.46E-01	0.596	0.934	8.24E-03	-0.293
Infectious diseases during pregnancy	1.27E+00	1.13	1.42	1.57E-04	0.237
Fertility treatment during pregnancy	1.82E+00	1.68	1.97	<2e-16	0.597
Mode of delivery: planned caesarean section	1.34E+00	1.22	1.47	1.46E-09	0.295
Mode of delivery: emergency caesarean section	1.15E+00	1.05	1.26	2.38E-03	0.144
Growth and oxygenation disorders during pregnancy	1.79E+00	1.47	2.18	2.03E-09	0.581
Hematologic disorders/anemia during pregnancy	7.30E-01	0.65	0.82	1.22E-07	-0.257
Other complications during pregnancy	1.09E+00	1.01	1.17	3.06E-02	0.085
Hypertensive complications during delivery	6.29E-01	0.484	0.816	7.09E-04	-0.464
Labor abnormalities	1.14E+00	1.01	1.28	3.28E-02	0.135
Perineal trauma during pregnancy	1.27E+00	1.11	1.45	2.50E-04	0.241

The Area Under the ROC Curve (AUC) reflects model's ability to distinguish between pregnant women who were prescribed potentially harmful (Category D) medications and those who were not. An AUC of 0.5 means the model performs no better than random chance, while an AUC of 1.0 means perfect classification. With AUC of 0.591, as seen in the model, refer to 4.13. Figure for a detailed overview.

4.13. Figure



4.13. Figure. ROC curve for the logistic regression model

It can be concluded that the model has a very weak discrimination ability– only slightly better than random. The area under the receiver operating characteristic (ROC) curve (AUC) for the final logistic regression model was 0.591, suggesting limited discriminatory ability to distinguish between women who were and were not prescribed Category D medications during pregnancy. While the model includes several statistically significant predictors, the overall predictive performance is relatively low. This may reflect the complexity of prescribing decisions, which are influenced by both measurable and unmeasured clinical and contextual factors. Further refinement of the model or inclusion of additional relevant predictors may be necessary to improve its classification performance. I acknowledge the limited discrimination ability in the model and conclude that other interaction terms (e.g., age × comorbidity) or non-linear effects (splines, quadratic terms) could be explored, as well as other classification models (e.g., random forest or gradient boosting) could be populated for comparison.

5. Discussion

This national level study found that 50.9% of pregnant women in Latvia were prescribed and dispenced at least one medication during pregnancy in 2020. By 2023 the prescribing and dispensing converged around 64%, suggesting an upward trend in pharmacological management during pregnancy. Over the four year study period, a statistically significant increase of 13.2% in prescribing prevalence was observed, which is consistant with patterns seen in other European countries (Stephansson *et al.*, 2011; Trønnes, Lupattelli and Nordeng, 2017). Prescribing rates in Latvia exceeded those reported in Sweden (57,6%) and Norway (60–70%) but remained below those in France, where up to 91% of pregnant women receive prescriptions (Blotière *et al.*, 2021). Similar trends have been observed in other European countries, although the exact figures vary depending on study design and data sources. For instance, a Swedish study (Stephansson *et al.*, 2011) reported that 57.6% of pregnant women received at least one dispensed prescription, while in the Netherlands researchers (van Gelder, Bos, *et al.*, 2014) observed rates exceeding 80%, especially when broader definitions of medication use were applied. In a Norwegian study (Engeland *et al.*, 2018), the overall rate of medication use in pregnancy ranged from 60% to 70% across different years, which aligns closely with the findings from Latvia. Similarly, a multinational European study (Trønnes, Lupattelli and Nordeng, 2017) highlighted that although many medications are prescribed during pregnancy, actual use varies depending on perceived risk, maternal characteristics and trimester specific concerns. The year by year increasing trend in prescribing may also reflect shifting maternal demographics, for example, the proportion of mothers aged ≥35 years rose from 28.4% in 2020 to 31.5% in 2023, which may contribute to higher medication needs due to age related comorbidities. The moderate to high prescribing rate in Latvia may reflect good access to healthcare and regular antenatal monitoring, where medication is often prescribed to treat common pregnancy symptoms, manage chronic conditions or prevent complications. However, it also highlights the need for careful assessment of the types of medications being prescribed, particularly in light of potential fetal risks. These results suggest that over three in five pregnant women are exposed to prescription drugs during gestation period, with the vast majority of those prescriptions women also dispensed their medicines. These results support the need for continuous monitoring of both prescribing and dispensing trends, particularly when assessing the safety and appropriateness of pharmacotherapy in pregnant populations. In 2020 prescribing and dispensing rates likely reflect more cautious prescribing patterns in the early stages of the COVID-19 pandemic, combined with restricted access to in person

consultations. In 2021 the stable rate of prescribing and dispensing may be linked to the restoration of health services and a return to routine prenatal care following initial pandemic disruptions (Butler *et al.*, 2023). This trend may reflect enhanced antenatal surveillance, broadened use of prophylactic medications or increasing clinical comfort with prescribing certain therapies in pregnancy. Compared to prior European studies, the overall prescribing prevalence in Latvia lies within the upper range of reported values, indicating alignment with broader European patterns.

The minimal gap between prescribing and dispensing (often <0,1%) reflects strong pharmaceutical access and low administrative barriers to drug acquisition. However, this alignment may not necessarily reflect medication use, as dispensing is only a proxy for consumption (Bandoli *et al.*, 2020). Importantly, the gap between prescribed and dispensed medications remained negligible, indicating that women continued to have good access to the medications they were prescribed. These figures point to a continued normalization of antenatal healthcare and perhaps a more proactive approach to managing conditions that require pharmacotherapy during pregnancy. The very small difference between the two rates suggests that most prescribed medications were actually taken home by patients. These results may reflect several factors– improved integration of pharmaceutical care into pregnancy management, higher comfort levels among healthcare providers when prescribing during gestation and strong support systems that enable women to access the medications they need. The nearly parallel movement in prescribing and dispensing trends across all years also suggests that barriers to access, such as cost or availability were minimal during this period. The small difference between prescribed and dispensed rates (<1%) underscores strong patient compliance and efficient healthcare delivery. Although it also emphasizes the importance of not relying on prescribing data alone when evaluating drug exposure during pregnancy. Dispensing data, especially when combined with prescription records, offers a clearer picture of real world medication use, allowing for more accurate assessments of exposure and potential risk.

Previous studies have raised concerns about the safety of some commonly prescribed drugs during pregnancy, especially those falling into higher risk categories (Andrade *et al.*, 2006; Blotière *et al.*, 2021). Therefore, identifying which drugs are being used and how they align with international safety classifications is a crucial next step in this study. Overall, the data reveal a strong emphasis on hormonal support, nutritional supplementation and infection management. Hormonal and gynecological medications– progesterone and dydrogesterone together account for over 40 000 prescriptions, indicating that nearly half of the most common medications are dedicated to reproductive health. The predominance of progesterone and

dydrogesterone suggests a clinical strategy focused on supporting early pregnancy and preventing complications such as threatened miscarriage. Nutritional supplements– colecalciferol and ferric oxide polymaltose complexes together represent nearly 20 000 prescriptions, highlighting the prioritization of micronutrient sufficiency. The high use of colecalciferol and iron complexes reflects adherence to guidelines recommending supplementation to prevent deficiency states that could impact maternal and fetal outcomes. Antimicrobials– the combined total for amoxicillin, ampicillin and furazidin exceeds 6 900 prescriptions, demonstrating the routine management of bacterial infections, particularly urinary and respiratory tract infections. Antifungals– butoconazole and econazole, with a combined total of over 6 600 prescriptions, indicate a significant burden of fungal infections managed in this cohort. The notable use of antibiotics and antifungals underscores the importance of infection control in prenatal care, as untreated infections can have serious consequences for both mother and child. Methyldopa's position among the top medications confirms its status as a preferred antihypertensive in pregnancy, likely due to its favorable safety profile and long standing clinical experience. While the data do not include direct demographic breakdowns, the medication profile suggests a population with a considerable burden of anemia, a need for hormonal support and frequent infectious complications. The choice of specific agents, such as methyldopa for hypertension and furazidin for urinary infections, aligns with established safety considerations in pregnancy. Compared to international studies, this cohort shows similar trends in the prioritization of progestogens, iron and vitamin D supplementation, as well as the use of penicillin class antimicrobials for infection management (Daw *et al.*, 2011; Trønnes, Lupattelli and Nordeng, 2017; Raichand *et al.*, 2020; Blotière *et al.*, 2021). The relatively high prescription counts for antifungals may reflect either a higher incidence of fungal infections or a proactive approach to symptomatic management.

While most prescriptions were in line with established pregnancy guidelines, a subset involved drugs with known or suspected fetal risks. This study found that 9.2% of pregnancies involved Category D medications according to the Australian Therapeutic Goods Administration (TGA), whereas only 6.3% were classified as high risk by Swedish FASS guidelines. These results replicate findings from French registry data, where risk estimates fluctuated by up to 7% depending on classification source (Blotière *et al.*, 2021). (Lupattelli, Trinh and Nordeng, 2023a)The rising trend may be influenced by several factors, including changes in clinical practice, increased recognition or diagnosis of conditions requiring Category D medications or evolving guidelines regarding risk-benefit assessment in pregnancy. The consistently higher prevalence reported by the Australian system suggests it encompasses a broader range of medications or applies more inclusive criteria for Category D assignment

compared to the Swedish system. Despite most prescribed drugs falling into safe categories, the proportion of women exposed to Category D medications (drugs with known fetal risk) increased steadily across the study period. According to the Australian classification, the prevalence rose from 3.9% in 2020 to 10.4% in 2023. The Swedish risk classification system reported lower values with 2% in 2020 and 6.3% in 2023, but the upward trend was consistent. Importantly, the rising trend in Category D prescribing occurred despite declining birth rates, suggesting an absolute increase in clinical scenarios where higher risk drugs are considered necessary. The most frequently prescribed potentially harmful drugs included fluconazole (726 prescriptions) and doxycycline (705 prescriptions), both of which are commonly flagged in pregnancy due to possible teratogenic effects. Although low dose fluconazole is sometimes considered safe, repeated or high doses are associated with congenital malformations (Lupattelli, Trinh and Nordeng, 2023). Doxycycline's continued use likely reflects its efficacy against resistant bacterial infections, despite known risks to fetal skeletal development. Also prominent were lamotrigine (133 prescriptions), paroxetine (110 prescriptions) and enalapril (87 prescriptions), medicines typically used to manage chronic or psychiatric conditions. These findings reflect real world clinical decision making where clinicians often face complicated tradeoffs in balancing maternal treatment needs with fetal safety concerns. Certain medications with known risks may still be used due to the severity of maternal conditions, lack of safer alternatives or timing of prescription relative to gestational age. The data highlight the importance of individualized risk assessment and continued efforts to provide safer therapeutic options for pregnant women.

Disagreement between risk classification systems was a key finding. *Cohen's Kappa* analysis demonstrated moderate agreement (κ = 0.61–0.81), aligning with prior studies in France and Sweden, where only 26% of drugs shared identical categories between the FDA, TGA, and FASS (Blotière *et al.*, 2021). For instance, lamotrigine is classified as Category C by the TGA, but Category D under FASS, underscoring the clinical uncertainty and complexity in interpreting teratogenic risk. This inconsistency is not merely academic, it affects clinical decision making, documentation and patient counseling. The European Medicines Agency has recently emphasized the importance of harmonizing pregnancy risk communication across the EU to avoid fragmented clinical practices (European Medicines Agency, 2019). Studies evaluating drug use during pregnancy reveal significant variability in agreement metrics depending on risk classification systems and data sources. For risk categorization, a French study comparing Swedish (FASS) and Australian (TGA) systems reported strong agreement (*Cohen's Kappa* = 0,81) for harmful drug classifications, yet only 26% of drugs shared identical risk categories across FDA, TGA and FASS systems (Addis, Sharabi and Bonati, 2000). This

inconsistency underscores challenges in standardizing teratogenicity assessments, as classification discrepancies arise from divergent evidence interpretations and regional guidelines (Harris, Wood and Nordeng, 2020). For data reliability, Norwegian research on triptan exposure demonstrated fair agreement (*Cohen's Kappa* = 0,36) between prescription records and self reports, with sensitivity as low as 39% for capturing episodic use. Similarly, rheumatoid arthritis medication analyses showed κ values ranging from 0,32 (ibuprofen) to 0,90 (etanercept), highlighting poorer concordance for intermittent versus chronic therapies (Harris, Wood and Nordeng, 2020). Critiques of *Cohen's Kappa* in attitude studies have pointed out that using weighted *Kappa* can improve agreement between groups. For example, when medical students' views on substance use during pregnancy were analyzed, the agreement improved from "good" (*Cohen's Kappa* = 0,78) to "very good" (*Cohen's Kappa* = 0,83) by applying weighted *Kappa*. This suggests that more sophisticated statistical methods are needed for analyzing data with mixed categories (Yu *et al.*, 2023). Overall, these findings highlight the need for having consistant risk classification systems, multimodal data collection– like combining prescription data with patient reports– and choosing appropriate methods for measuring agreement to improve the reliability of studies in pregnancy pharmacoepidemiology. *Cohen's Kappa* analysis revealed only moderate agreement between the Australian and Swedish risk classification systems. Thousands of medications lacked classifications in one or both systems (6 895 missing in Australian and 7 207 in Swedish RCS), reducing the size of the comparative dataset and underscoring a major challenge in harmonizing safety assessments. The modest *Kappa* statistic suggests that international inconsistency in medicine risk communication remains a barrier to unified policy and patient counseling. Model performance was statistically significant, but predictive ability was modest. Although the logistic regression model included statistically significant predictors, its area under the curve (AUC) was 0.591, indicating only marginally better than random ability to discriminate between those who were and were not prescribed harmful medications.

The binomial logistic regression model identified several maternal factors associated with higher odds of being prescribed Category D drugs. Notably, maternal age was a significant predictor (OR = 1.024 per year, $p < 0.001$), aligning with earlier studies reporting a 1.5–2.0 times increase in medication use among women aged 35 or older (Lupattelli, Trinh and Nordeng, 2023). Certain complications during pregnancy, such as growth and oxygenation disorders, increased the odds by nearly 79% (OR ~ 1,79, $p < 0,001$). Women who underwent assisted reproduction were over 80% more likely to receive Category D medications ($\beta = 0.597$, $p < 0.001$). This reflects both the increased medical oversight of such pregnancies and the pharmacological protocols involved in hormonal support. Planned cesarean deliveries were

associated with a 30% increase in odds of harmful prescribing (β = 0.295, *p < 0.001*). Similar patterns have been reported in France, where medication intensity often correlates with delivery complexity (Blotière *et al.*, 2021). Interestingly, smoking at antenatal registration was unexpectedly associated with a reduced risk of Category D drug exposure (OR ≈ 0.75, *p = 0.008*) possibly reflecting clinical caution or behavioral confounding. One hypothesis is that Latvian physicians may avoid prescribing potentially teratogenic medications to smokers out of caution or that smoking is underreported in clinical records. Obstetric complications such as labor abnormalities, perineal trauma and planned cesarean section were also positively associated with increased risk, likely due to the need for pre and intrapartum pharmacological interventions. Although the regression model contained several significant predictors, its AUC of 0.591 indicates only marginal discriminatory ability. Similar limitations have been observed in prior pharmacoepidemiological studies (van Gelder, van Rooij, *et al.*, 2014). This suggests that factors not captured in the registry data– such as physician specialty, gestational age at prescriptionbor the patient's own beliefs and preferences may significantly influence prescribing decisions. Collectively, these findings indicate that risk of exposure is not randomly distributed across the pregnant population, but instead clustered among women with complex medical or obstetric profiles. This suggests that while maternal characteristics do provide some predictive insight, clinical decisions are likely influenced by unmeasured factors such as provider judgment, medication availability and trimester specific risk assessments. To improve predictive accuracy, future modeling efforts should explore non linear terms, interaction effects or machine learning approaches like random forests or gradient boosting.

As with all observational research, the validity of findings depends on both the quality of the source data and the analytical strategy employed. This study relied on registry based datasets that, while comprehensive, are not immune to bias. For example, 49 022 observations were excluded due to missing values, which may have introduced selection bias. The lack of medication timing data (e.g., trimester of exposure) limits the ability to assess critical windows of teratogenicity. The Medical Birth Register does not include pregnancies ending before 22 weeks gestation, precluding early loss analysis, which is crucial since teratogenic damage often occurs in the first trimester (Andrade *et al.*, 2006). Moreover, dispensing data was used as a proxy for drug exposure, but real world adherence remains uncertain. According to international surveys, up to 30% of pregnant women modify or discontinue medications without professional advice (van Gelder, Bos, *et al.*, 2014). Without patient reported adherence, true exposure remains difficult to quantify. Another limitation is the non inclusion of over the counter (OTC) medications. In Germany, for example, 28% of pregnant women report using OTC medications, which likely contributed to underestimation in the present study (Blotière *et al.*, 2021). Lastly,

risk classification inconsistencies– where 6 895 medications lacked a TGA label and 7 207 were unclassified in FASS, which complicate the analysis. This underlines the importance of data harmonization efforts, particularly in cross national studies.

With over 1 in 10 Latvian pregnancies in 2023 involving Category D drugs, there is a clear mandate for targeted action. Preconception counseling must be expanded to reduce unintentional first trimester exposures. From a policy standpoint, some risk alert systems have been integrated into prescribing platforms in the United Kingdom's OpenPrescribing system. These alerts would prompt healthcare providers when high-risk medications are selected and suggest safer alternatives. In Europe, prescribers are alerted to the risks of medication use during pregnancy through a combination of regulatory documents, classification systems and digital prescribing safeguards. The primary source of information is the Summary of Product Characteristics (SmPC), which includes a section on use during pregnancy and lactation, outlining whether a medicine is contraindicated or should be used with caution. Additionally, EMA issues safety communications, such as Direct Healthcare Professional Communications (DHPCs), when new evidence emerges about teratogenic risks. For high risk medicines like valproate or isotretinoin, prescribers must follow specific Risk Minimisation Measures (RMMs), which may include educational materials and pregnancy prevention programs. Mandatory training modules, based on the Dutch Lareb model, which led to a 40% reduction in valproate use, could help standardize safe prescribing behavior (Netherlands Pharmacovigilance Centre Lareb, no date). Educational campaigns are also needed to help patients understand the balance between treatment and risk. However, informed choice must be based on accessible, comprehensible safety data something currently lacking in the Latvian healthcare system.

For future research directions, as seen in other studies, qualitative interviews with prescribers could illuminate the clinical reasoning behind selecting certain medications in pregnancy– especially those flagged as risky. Development of artificial inteligence based algorithms for risk prediction could improve real time clinical support. These tools would ideally integrate multiple classification systems to provide harmonized, patient specific risk scores. Inclusion of sociodemographic variables like education, income or urban or rural status could help assess equity in maternal pharmacotherapy access and safety.

(Harris, Wood and Nordeng, 2020) nationwide drug utilization study provides the first comprehensive, longitudinal assessment of medication prescribing and dispensing patterns among pregnant women in Latvia from 2020 to 2023. The analysis included 64 506 deliveries, representing virtually the entire national population of birth givers during the study period. The

results clearly demonstrate that medication use in pregnancy is both prevalent and increasing.

The findings of this research can affirm that medication use during pregnancy in Latvia is widespread and increasing with over 64% of women receiving prescriptions and nearly as many obtaining them from pharmacies by 2023. While most medications fall within safe categories, exposure to potentially harmful drugs, especially Category D, remains a concern and has increased over time. Maternal age, obstetric history and comorbidities are significant drivers of such prescribing and risk classification inconsistencies across international risk classification systems create added complexity for clinicians. This study underscores the need for continued national monitoring of prescribing and dispensing trends. As well as targeted interventions for high risk groups– older mothers and women with chronic illness. A stronger alignment of international risk classification systems for medicine safety is needed to provide safer alternatives and clearer clinical guidance for high risk pregnancies.

As a biostatistics based pharmacoepidemiological investigation, this research offers an evidence based foundation for optimizing maternal pharmacotherapy and shaping future public health policy in Latvia. The study successfully fulfilled its aim of evaluating medication prescribing and dispensing patterns and their safety profile, as well as what maternal factors are associated with the prescribing of potentially harmful medicines during pregnancy. Thereby providing valuable insights for clinical and policy decision making.

Conclusions

1. Medication prescribing and dispensing during pregnancy in Latvia between 2020 and 2023 was found to be widespread, with overall prevalences of 57.13% [95% CI: 56.75%–57.51%] and 57.06% [95% CI: 56.68%–57.44%], respectively. These findings underscore the need for ongoing monitoring and systematic evaluation to reduce unnecessary fetal exposure to medications.
2. The use of multiple risk classification systems revealed inconsistencies in fetal safety assessments, highlighting the need for a harmonized international approach to evaluating medication risks during pregnancy.
3. A substantial proportion of pregnant women between 2020 and 2023 were exposed to potentially harmful medications, with a statistically significant ($p<0.0001$) increase in prescribing prevalence of 6.5% [95% CI: 5.95%–7.12%] and 4.4% [95% CI: 3.97%–4.88%] based on the Australian and Swedish risk classification systems. These findings reflect the complexity of clinical decision making and underscore the need for thorough risk benefit assessments prior to prescribing.
4. Analysis of maternal characteristics indicated that certain factors are associated with the prescribing of potentially harmful medicines– maternal age, use of assisted reproductive therapy, planned cesarean section and specific pregnancy or delivery complications, suggesting that prescribing decisions are often based on complex patient profiles rather than simple clinical algorithms.
5. The comparison of classification systems demonstrated only moderate agreement, confirming that existing systems are not interchangeable without careful contextual interpretation.
6. Throughout the 2020-2023 study period, the proportion of women who had medications dispensed closely matched to the proportion who were prescribed them, with a maximum difference of only 0.2 percentage points in 2022, this consistency suggests that, in most cases, prescribed medications were also collected, reflecting reliable access and adherence within the healthcare system.

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Appendix

Veidlapa Nr. E-9(3)
APSTIPRINĀTA
ar Rīgas Stradiņa universitātes rektora
2018. gada 26. septembra rīkojumu Nr. 5-1/238/2018

Rīgas Stradiņa universitātes
Pētījumu ētikas komitejas
LĒMUMS
Rīgā

14.02.2025 2-PĒK-4/366/2025

	Komitejas sastāvs	Kvalifikācija	Nodarbošanās
1.	Profesors Jānis Vētra	Dr.habil. med.	Morfoloģijas katedra, profesors
2.	Profesore Ingrīda Čēma	Dr.habil. med.	Mutes, sejas un žokļu un mutes medicīnas katedra, profesore
3.	Asoc. Prof. Anita Vētra	Dr.med.	Rehabilitācijas katedra, asociētā profesore
4.	Docente Anna Junga	Dr.med.	Morfoloģijas laboratorijas vadītāja
5.	Docente Agnese Zariņa	Dr.med.	Bioloģijas un mikrobioloģijas katedra
6.	Marina Siņkovska		Datu drošības un pārvaldības nodaļas datu aizsardzības speciālists

Pieteikuma iesniedzējs/i: **Tīna Nulle, Medicīnas fakultāte**

Pētījuma / pētnieciskā darba nosaukums: Pētījums par recepšu zāļu lietošanu grūtniecēm Latvijā 2020-2023

Pētījumu ētikas komitejas sēdes datums: 19.12.2024.

Pētījuma protokols:
Izskatot augstāk minētā pētījuma pieteikuma materiālus, t.sk., protokolu, secinām, ka pētījuma mērķi - noteikt recepšu medikamentu izrakstīšanas un izsniegšanas prevalences rādītājus grūtniecēm ar fiksētām dzemdībām Latvijas Jaundzimušo reģistrā laika periodā no 2020. gada 1. janvāra līdz 2023. gada 31. decembra, kā arī raksturot medikamentu drošības profilu un noskaidrot, kādi mātes raksturojošie faktori ir saistīti ar potenciāli kaitīgu medikamentu izrakstīšanu grūtniecības laikā. Pētījuma protokols angļu valodā pieejams pielikumā ("*Drug Utilization Study: Prescription Medication Use in Pregnant Women in Latvia 2020–2023 Protocol v1.0 11Nov2024*"), ir paredzēts sasniegt, veicot datubāzes izpēti, iegūto datu apstrādi un analīzi, kā arī publiskojot iegūtos rezultātus. Iegūto personu (dalībnieku) datu apstrāde un aizsardzība, to pielietošana, glabāšana, anonimitāte un konfidencialitāte ir nodrošināta. Pētījumā izvirzītais mērķis, pielietotās metodes un pētījuma sabiedrības veselības ieguvums ir samērojams, personas datu aizsardzība ir nodrošināta, pētījums atbilst pētījuma ētikas prasībām. Pētījuma protokols sastādīts atbilstoši Pacientu tiesību likuma 10. panta 8.[4] daļas prasībām. Medicīniskajā dokumentācijā fiksētos pacienta datus atļauts izmantot pēc atbilstošo ārstniecības iestāžu piekrišanas.

Komitejas lēmums:
Piekrist pētījumam.

Komitejas priekšsēdētājs Jānis Vētra Tituls: Dr.habil. med., profesors.

ŠIS DOKUMENTS IR ELEKTRONISKI PARAKSTĪTS AR DROŠU ELEKTRONISKO PARAKSTU UN SATUR LAIKA ZĪMOGU

Logistic regression results for maternal factors associated with class D medication prescriptions during pregnancy

	OR	OR_CI_Lower	OR_CI_Upper	p_value	Log_odds	Std_Error	z_value
(Intercept)	1.55E-02	1.26E-02	1.91E-02	<2e-16	-4.17	0.107	-39.1
Age	1.02E+00	1.02E+00	1.03E+00	<2e-16	2.37E-02	0.0029	8.19
Smoking at pregnancy registration	7.46E-01	0.596	0.934	8.24E-03	-0.293	0.111	-2.64
Cardiovascular disorders during pregnancy	8.71E-01	0.759	1	5.56E-02	-0.137	0.0718	-1.91
Infectious diseases during pregnancy	1.27E+00	1.13	1.42	1.57E-04	0.237	0.0628	3.78
Fertility treatment during pregnancy	1.82E+00	1.68	1.97	<2e-16	0.597	0.0443	13.47
Mode of delivery: planned caesarean section	1.34E+00	1.22	1.47	1.46E-09	0.295	0.0488	6.05
Mode of delivery: emergency caesarean section	1.15E+00	1.05	1.26	2.38E-03	0.144	0.0473	3.04
Hypertensive disorders in pregnancy	8.78E-01	0.765	1.01	8.28E-02	-0.13	0.075	-1.74
Growth and oxygenation disorders during pregnancy	1.79E+00	1.47	2.18	2.03E-09	0.581	0.0969	6
Hematologic disorders/anemia during pregnancy	7.30E-01	0.65	0.82	1.22E-07	-0.257	0.0485	-5.29
Other complications during pregnancy	1.09E+00	1.01	1.17	3.06E-02	0.085	0.0394	2.16
Hypertensive complications during delivery	6.29E-01	0.484	0.816	7.09E-04	-0.464	0.137	-3.39
Labor abnormalities	1.14E+00	1.01	1.28	3.28E-02	0.135	0.0633	2.14
Fetal distress or hypoxia during delivery	9.03E-01	0.813	1	6.23E-02	-0.102	0.0545	-1.86
Hemorrhage / excessive bleeding during labor	7.71E-01	0.676	0.879	9.77E-05	-0.259	0.0665	-3.9
Perineal trauma during pregnancy	1.27E+00	1.11	1.45	2.50E-04	0.241	0.0657	3.66
Caesarean section	8.13E-01	0.728	0.907	8.20E-05	-0.207	0.0525	-3.94

Definitions of risk categories in Australian and Swedish RCS (Addis, Sharabi and Bonati, 2000)

Risk category	Australian classification (*Australian Government Department of Health. Australian categorisation system for prescribing medicines in pregnancy*, no date)	Swedish classification (*Läkemedelsindustriföreningen. FASS for vårdpersonal*, no date)
A	Drugs which have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the fetus having been observed.	Medicinal products which may be assumed to have been used by a large number of pregnant women and women of childbearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect effects on the fetus. This category comprises: drugs that have been available for many years; those that have been used by many pregnant women and women of child-bearing age and; drugs for which satisfactory retrospective studies in pregnant women are considered to have been carried out.
B	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in frequency of malformation or other direct or indirect harmful effects on the fetus having been observed. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups: **B1**: Studies in animals have not shown evidence of an increased occurrence of fetal damage. **B2**: Studies in animals are inadequate and may be lacking, but available data show no evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans. **B3**: Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	Medicinal products which may be assumed to have been used only by a limited number of pregnant women and women of childbearing age without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the fetus. As experience of effects of medicinal products in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of 3 subgroups B1, B2 or B3 according to the following definitions: **B1**: Reproduction toxicity studies have not given evidence of an increased incidence of fetal damage or other deleterious effects on the reproductive process. **B2**: Reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other deleterious effects on the reproductive process. **B3**: Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans.
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or	Medicinal products, which by their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproductive process that

	neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.	may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.
D	Drugs which have caused an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.	Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in humans, or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects that may directly or indirectly have a harmful effect on the fetus.
X	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.	