RESEARCH ARTICLE

Metin Deniz Karakoc[1]

[1] Pamukkale University, Faculty of Medicine, Department of Medical Pharmacology, Denizli, Türkiye

Corresponding Author:
Metin Deniz Karakoc
mail: mdkarakoc@pau.edu.tr

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konuralptipdergisi@gmail.com
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Retrospective Analysis of Pregnant Cases in Terms of Drug-Drug Interactions and Teratogenic Risks

ABSTRACT

Objective: While teratogenic risks in pregnant women are frequently discussed, polypharmacy and drug-drug interactions (DDI) are topics with little known information. The aim of this study is to determine the polypharmacy status, DDI, and teratogenic risk profile during pregnancy.

Method: A retrospective cohort study was conducted covering the year 2023 on pregnant women who were referred for pharmacology consultation due to a history of drug use. Investigation of DDI was performed through the Micromedex and Medscape online query modules.

Results: It was found that 113 pregnant women used a total of 71 different active ingredient drugs from 24 diverse pharmacological groups. The average number of drugs used per individual was 2.97. Analgesics, antibiotics, and gastric acid inhibitors were the most used medications, respectively. 11.6% of the women had a comorbidity, and cardiovascular diseases were the most common. It was determined that 28.3% of women had a serious or moderate DDI. The rate of drugs in categories D and X, which are particularly risky in terms of teratogenicity, was found to be 40.8%.

Conclusions: In addition to teratogenic effects, polypharmacy and DDI are also significant risk factors in pregnant women. There is still a crucial need for evidence on the medications prescribed in pregnancy, how it specifically affects women with comorbidities, and related benefits and harms.

Keywords: Polypharmacy, Teratogenicity, Drug Interactions, Comorbidities, Pregnancy.

Gebe Olguların İlaç-İlaç Etkileşimleri ve Teratojenik Riskler Açısından Retrospektif Analizi

ÖZET

Amaç: Gebelerde teratojenik riskler sıkça tartışılan bir konudur ancak polifarmasi ve ilaç-ilaç etkileşimleri (İİE) hakkında çok az bilgi mevcuttur. Çalışmanın amacı, gebelik sırasında meydana gelen polifarmasi durumunu, İİE ve teratojenik risk profillerini belirlemektir.

Yöntem: 2023 yılı süresince gebelikte ilaç kullanım öyküsü nedeniyle farmakoloji konsültasyonuna yönlendirilen kadınları kapsayan retrospektif bir kohort çalışması yapıldı. İİE araştırması Micromedex ve Medscape online sorgu modülleri kullanılarak gerçekleştirildi.

Bulgular: 113 gebenin toplamda 24 farklı farmakolojik gruptan 71 farklı etken madde içeren ilaç kullandığı bulundu. Birey başına kullanılan ilaçların ortalamasının 2,97 olduğu saptandı. Sırasıyla ağrı kesiciler, antibiyotikler ve mide asidi inhibitörlerinin en çok kullanılan ilaçlar olduğu belirlendi. Kadınların %11,6'sında bir komorbidite olduğu ve en sık kardiyovasküler hastalıklara sahip oldukları belirlendi. Gebelerin %28,3'ünde ciddi veya orta derecede İİE olduğu tespit edildi. Teratojenik açıdan özellikle riskli olan D ve X kategorisindeki ilaç oranının %40,8 olduğu saptandı.

Sonuç: Teratojenik etkilerin yanı sıra, polifarmasi ve İİE de gebelerde önemli risk faktörleridir. Gebelikte reçete edilen ilaçlar, özellikle komorbiditeleri olan kadınlar üzerindeki fayda ve zararları konusunda kanıtlara halen kritik derecede ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Polifarmasi, Teratojenite, İlaç Etkileşimleri, Komorbiditeler, Gebelik.

INTRODUCTION

Pregnancy is a lengthy physiological process that lasts approximately 40 weeks, ideally culminating in a healthy birth. Although women generally prefer to minimize medication use during this sensitive period, they often require drug treatment for various reasons related to chronic illnesses, infections, or pregnancy-related conditions (e.g., anemia, emesis). Additionally, it is common for women to use medications for acute or chronic diseases before recognizing their pregnancy. For pregnant women with various comorbidities, medication use becomes unavoidable, despite the potential adverse effects on both the expectant mother and the fetus (1). Avoiding treatment for certain conditions throughout pregnancy to mitigate the risks associated with medication use can negatively impact both maternal and fetal health (2). However, it is possible to reduce these risks by implementing rational precautions. The frequency of medication use during pregnancy can vary between countries due to differences in educational, cultural, and socioeconomic conditions, such as access to healthcare providers and medications. Various studies conducted in different populations indicate that between 60% and 84.7% of women use at least one medication during their pregnancies (3,4). The teratogenic risks and potential drug-drug interactions (DDIs) that may arise for individuals requiring multiple medications necessitate careful consideration, given their potential to create serious complications for maternal and fetal health.

Developing a new drug requires years of meticulous research and substantial financial resources. However, due to social and ethical considerations, the opportunity to conduct clinical trials on pregnant women is highly restricted during this process. Consequently, teratogenicity data for the majority of drugs are primarily derived from experimental animal studies. Pregnant women gain access to medications only after the drug has been licensed. From that point onward, the teratogenic risk profile of the drug can be revealed over time through clinical observations, retrospective studies, and adverse event reports submitted by healthcare professionals. There remains insufficient information regarding the teratogenic effects of most drugs available on the market. Therefore, decisions about medication use during pregnancy must sometimes be made by physicians without adequate evidence regarding the effectiveness and safety of the treatment.

The development of standardized and comprehensible systems for assessing the teratogenic risk of drugs enables physicians, along with other healthcare professionals, patients, and their families, to make more informed decisions regarding potential risks. Various systematic approaches, differing in classification, are employed worldwide for evaluating drug-induced teratogenic risks. In our country, the Turkish Drug and Medical Devices Agency (TITCK), the authority responsible for medicines, uses a classification system that categorizes teratogenic risks into five groups: A, B, C, D, and X. Category A is deemed the safest, while category X is strictly contraindicated during pregnancy, providing essential therapeutic guidance to clinicians (5). The teratogenicity classification system used in our country aligns with the system established by the US Food and Drug Administration (FDA) in 1979. Although this organization proposed a novel method in 2015, the five-letter classification system remains widely preferred within the healthcare community due to its established and easily comprehensible language (6).

Given these considerations, our study aimed to contribute to the literature by analyzing the drug use profiles, potential drug-drug interactions (DDIs), and teratogenic risks in pregnant individuals referred for pharmacology consultation by gynecologists over a one-year period, based on the TITCK's five-letter classification system.

MATERIAL AND METHODS

Ethical Approval: The research is a retrospective cohort study covering the year 2023. Approval for the research was initially obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (permission number: E.462180), and it was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design and Subjects: The study population comprises pregnant individuals referred by gynecologists from our university hospital and four other private and public hospitals in the Denizli province for pharmacological evaluation. A report on drug use and teratogenic risk is prepared based on the anamnesis obtained from these individuals. Informed consent was obtained from all participants before the study commenced. The anamneses were collected by recording responses to standard questions found in the teratogenicity information form, which is available in printed format in our department.

In addition to identity and contact information, the form includes detailed questions regarding age, education status, number of pregnancies, gestational weeks, number of live births/stillbirths, number of normal births/cesarean sections, history of miscarriage, intentional abortion, or birth anomalies in previous pregnancies, presence of allergies or chronic diseases, and usage status of tobacco, alcohol, or other addictive substances. The form also captures details of medication use, including duration, dosage, and reasons for initiation (e.g., prescribed by a physician, heard from the media, or purchased over-the-counter from a pharmacy). All forms were

completed face-to-face under the supervision of the same pharmacologist, who also prepared the evaluation reports.

Data Processing Procedure: During the study period, counseling services were provided to a total of 113 pregnant women, all of whom had their forms completed in full, and a report was prepared for each individual. All participants were included in the study. The drugs were classified according to both the TITCK teratogenic risk classification and the degree of interaction. The TITCK pregnancy categories used in the risk classification of drugs are summarized in Table 1.

Table 1. TITCK* pregnancy categories used in risk classification of drugs

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester and there is no evidence of risk in later trimesters.
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

*TITCK: Turkish Drug and Medical Devices Agency

Potential DDI were analyzed using the IBM Micromedex DRUGDEX® online database (https://www.micromedexsolutions.com) and Medscape Drug Interaction Checker online query modules (https://reference.medscape.com/drug-interactionchecker). DDIs were classified into three categories: 'serious,' which should be avoided or for which an alternative treatment is preferred; 'moderate,' which should be used with caution and closely monitored; and 'minor,' where the clinical impact is insignificant or unknown, as described in the Medscape Drug Interaction Checker online query module.

Statistical Analysis: Statistical analysis of the data was conducted using the IBM Statistical Package for the Social Sciences (SPSS) version 29.0. Descriptive statistics, including frequency, mean ($\bar{x}$) ± standard error, and percentage (%), were employed to present the data. The chi-square (χ^2) test was utilized to assess the relationship between categorical variables, such as smoking and alcohol history, as well as abortion and stillbirth history. For the analysis of relationships between continuous variables, such as age, number of pregnancies, and time of physician consultation, the suitability of parameters for normal distribution was assessed using the Shapiro-Wilk test, and the homogeneity of variances was checked with Levene's test. Since the parameters met the criteria for normal distribution, the variables were analyzed using the independent sample t-test. One-way analysis of variance (ANOVA) was applied for multiple groups, including education level, number of medications used, and reasons for medication use, as parametric conditions were satisfied. Post-hoc pairwise comparisons were conducted using the Bonferroni-corrected Mann-Whitney U test, with $p < 0.05$ considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of the Participants: It was determined that 7% of the study group (n = 8) continued to use substances with addictive and teratogenic effects until they learned about their pregnancy (2 smokers, 2 alcohol users, and 4 individuals who used both tobacco and alcohol). No significant relationship was found between the individuals' educational status and their smoking or alcohol use ($p = 0.757$). Additionally, those who used addictive substances sought pharmacology consultation later than those who did not (9.5 ± 1.77 vs. 7.8 ± 2.62, respectively; $p = 0.032$).

It was determined that the mean age of the study group was 26.4 ± 4.7 (minimum: 19, maximum: 37). It was detected that all individuals had at least basic literacy levels, with the majority being high school graduates (50.4%, n= 57) and university graduates (38.9%, n= 44). It was determined that pregnant women referred for risk assessment sought consultation at an average gestational age of 8 weeks (7.92 ± 2.60 weeks), with a minimum of 4 weeks and a maximum of 16 weeks. It was found that there is no significant difference between educational level and the duration of seeking medical consultation for teratogenic risk assessment (p= 0.830). The distribution of the pregnant women in the study according to some obstetric characteristics is presented in Table 2.

Table 2. Distribution of pregnant women according to some obstetric characteristics at the time of application

Parameters	n	%
Pregnancy period		
1st Trimester	107	94.7
2nd Trimester	6	5.3
3rd Trimester	0	0
Miscarriage or stillbirth		
No	99	87.6
Yes	14	12.4
Number of previous live births		
Primigravida	69	61.1
1	38	33.6
2	4	3.5
3	2	1.8
Anomalies in previous births*		
No	39	88.6
Yes	5	11.4

*Evaluated among 44 individuals who had one or more pregnancies before their current pregnancy.

The Results of Subgroup Analysis: It was found that 11.6% of the individuals (n = 13) had a chronic disease diagnosed at least one year prior to pregnancy, requiring continuous medication. Additionally, 7% of the participants (n = 8) reported allergies to various substances. The average number of active substances used by pregnant women with chronic diseases (2.77 ± 1.48) was slightly lower than that of those without chronic diseases (3.00 ± 1.23); however, this difference was not statistically significant (p = 0.599). The distribution of the study group according to comorbidities and drug use status is presented in Table 3.

It was found that there is no significant relationship between individuals who use addictive substances and those who do not regarding a history of stillbirth or abortion (p = 0.665). Furthermore, no significant differences were observed between individuals who have experienced stillbirth or abortion in previous pregnancies and those with a chronic illness, compared to other pregnant women, in terms of the timing of seeking medical consultation for teratogenic risk assessment (p = 0.539 and p = 0.457, respectively).

Table 3. Distribution of pregnant women according to comorbidities and drug usage status

Parameters	n	%
Distribution of chronic diseases		
Cardiovascular system	4	3.5
Respiratory system	3	2.7
Endocrine system	3	2.7
Musculoskeletal system	1	0.9
Gastrointestinal system	1	0.9
Dermatological	1	0.9
Number of active substance used*		
1	13	11.5
2	30	26.5
3	34	30.1
4	22	19.5
5	7	6.2
6	4	3.5
7	3	2.7
Reason for starting the drug therapy		
Prescription drugs	103	91.2
Self medication	4	3.5
Advice of a friend/relative	4	3.5
Over-the-counter from a pharmacy	2	1.8

* Except for prenatal vitamins, minerals and antiemetic drugs routinely used during pregnancy

In our study, it was found that pregnant women used an average of 2.97 ± 1.26 active substances, with the majority of these drugs prescribed by other physicians (91.2%). The participants utilized a total of 71 different active ingredient drugs from 24 diverse pharmacological groups. The distribution of active substances used by pregnant women according to pharmacological groups is presented in Table 4.

Table 4. Distribution of active substances used by pregnant women according to pharmacological groups

Pharmacological group	Number of active substances	Number of pregnant women using*	Percentage of pregnant women using (%) *
Analgesics (NSAIDs)	6	49	43.4
Antibiotics	4	37	32.7
Proton pump inhibitors & H_2 receptor antagonists	6	36	31.9
Antidepressants	5	33	29.2
Cold remedies (combined)	3	29	25.7
Muscle relaxants	3	26	23.0
Hormone derivatives & corticosteroids	6	25	22.1
Ionic and non-ionic contrast agents	5	22	19.5
Antipsychotics	2	12	10.6
Laxatives & Purgatives	3	11	9.7
Antihistaminics	2	8	7.1
Vitamins & Minerals**	3	7	6.2
Antianemics	2	5	4.4
Antiepileptics	2	5	4.4
Antihypertensives	3	4	3.5
Antivirals	2	4	3.5
Respiratory system drugs	2	4	3.5
Antiarrhythmics	2	3	2.7
Antidiarrheals	2	3	2.7
Antifungals	2	3	2.7
Others	6	10	9.0
Total	**71**	**336**	

*The majority of women use more than one **active substances**. **Prenatal vitamin & minerals were excluded; NSAIDs: Non-steroidal anti-inflammatory drugs; H_2 receptor antagonists: Histamine 2 receptor antagonists

DDI in Pregnant Women: In the study, it was found that there were 14 "serious" DDIs among 18 active substances, which required treatment discontinuation or modification. Additionally, 23 "moderate" DDIs were identified among 33 different drugs that necessitated close monitoring. No pregnant woman was observed with the simultaneous presence of two or more serious DDIs. However, it was determined that five pregnant women had one serious and one moderate DDI simultaneously. Consequently, the rate of pregnant women with identified DDIs that should be considered was calculated to be 28.3% (n= 32). Furthermore, 89 "minor" DDIs with no clinical significance and requiring no special precautions were also identified. Among the detected DDIs, the types categorized as "serious" are presented in Table 5, while "moderate" interactions are detailed in Table 6.

Table 5. Serious drug-drug interactions and interaction mechanisms detected in pregnant women

Mechanism of interaction	Interacting drug pairs
Accelerating the metabolism of the other by inducing the CYP450 enzyme*	carbamazepine - esomeprazole carbamazepine - tetracycline
Increasing serum levels of each other or potentiating their effects by affecting the p-gp and CYP450 systems	clarithromycin - colchicine diltiazem - colchicine
Potentializing each other's effects by increasing the QTc interval	clarithromycin - escitalopram clarithromycin - formoterol clarithromycin - sertraline
Reducing the absorption of the other by reducing gastrointestinal absorption*	ferric maltol - tetracycline magnesium sulfate - tetracycline
Increasing the level of the other by decreasing renal clearance*	flurbiprofen - methotrexate
Increasing the level and effects of the other through CYP450 enzyme inhibition*	isoniazid - omeprazole
Physiological antagonism	perindopril - flurbiprofen perindopril - ibuprofen
Potentializing each other's toxic effects	perindopril - pregabalin

*The first drug causes changes in the metabolism of the second drug.

Table 6. Moderate drug - drug interactions and interaction mechanisms detected in pregnant women

Mechanism of interaction	Interacting drug pairs
Increasing the serum level and effects of the other by CYP450 enzyme inhibition	bupropion - metoprolol clarithromycin - dexamethasone clarithromycin - prednisolone esomeprazole - escitalopram methylprednisolone - alprazolam metronidazole - alprazolam miconazole vaginal - dexamethasone omeprazole - escitalopram sertraline - metoprolol
Effect on increasing serum potassium level	drospirenone -diclofenac propranolol - ibuprofen
Increased toxic effects due to functional synergism	chlorpheniramine - quetiapine escitalopram - ibuprofen pregabalin - chlorpheniramine tizanidine - escitalopram
Increase the serum level and effects of the other drug by causing an increase in gastric pH	famotidine - methylphenidate
Increased toxic effect with functional synergism	gabapentin - alprazolam
Reducing the expected therapeutic effect by physiological antagonism	metoprolol - albuterol
Potentializing each other's toxic effects	perindopril - flurbiprofen valsartan - diclofenac
Increase in expected therapeutic effect with physiological synergism	perindopril - insulin aspart tizanidine - valsartan
Additive interaction on increasing the QTc interval	albuterol - loperamide

Teratogenic Drug Use in Pregnant Women: In our study, it was determined that 43.7% of the drugs used by pregnant women are in category 'C', 26.7% in category 'D', 14.1% in category 'X', 12.7% in category 'B', and 2.8% in category 'A'. The rate of drugs in categories D and X, which are particularly risky in terms of teratogenicity, was found to be 40.8% and listed in Table 7. The distribution of the number of drugs used according to TITCK classification is presented in Figure 1.

Table 7. Distribution of fetotoxic D and X category drugs

Category D active substances	Number and percentage (%) of individuals	Category X active substances	Number and percentage (%) of individuals
Amitriptyline	3 (2.65)	Ethinyl estradiol	3 (2.65)
Paroxetine	3 (2.65)	Drospirenone	3 (2.65)
Tetracycline	3 (2.65)	Isotreonine	2 (1.77)
Alprazolam	2 (1.77)	Levonorgestrel	2 (1.77)
Carbamazepine	2(1.77)*	Atorvastatin	1 (0.88)
Imipramine	2 (1.77)	Methotrexate	1 (0.88)
Topiramate	2 (1.77)	Misoprostol	1 (0.88)
Valproic Acid	2(1.77)*	Norgestrel	1 (0.88)
Candesartan	1 (0.88)	Simvastatin	1 (0.88)
Clonazepam	1 (0.88)	Warfarin	1 (0.88)
Irbesartan	1 (0.88)		
Lisinopril	1 (0.88)		
Lithium	1 (0.88)		
Losartan	1 (0.88)		
Perindopril	1 (0.88)		
Phenobarbital	1 (0.88)		
Phenytoin	1 (0.88)		
Ramipril	1 (0.88)		
Valsartan	1 (0.88)		
	30 (%26.6)		**16 (%14.2)**

The classification system is based on the pregnancy categories established by the United States Food and Drug Administration in 1979 for the risk classification of drugs in pregnancy. *****1 individual use valproic acid and carbamazepine simultaneously. **Abbreviations:** DDI, drug-drug interactions; e.g, for example; FDA, United States Food and Drug Administration; NSAIDs, non-steroidal anti-inflammatory drugs; TITCK: Turkish Drug and Medical Devices Agency.

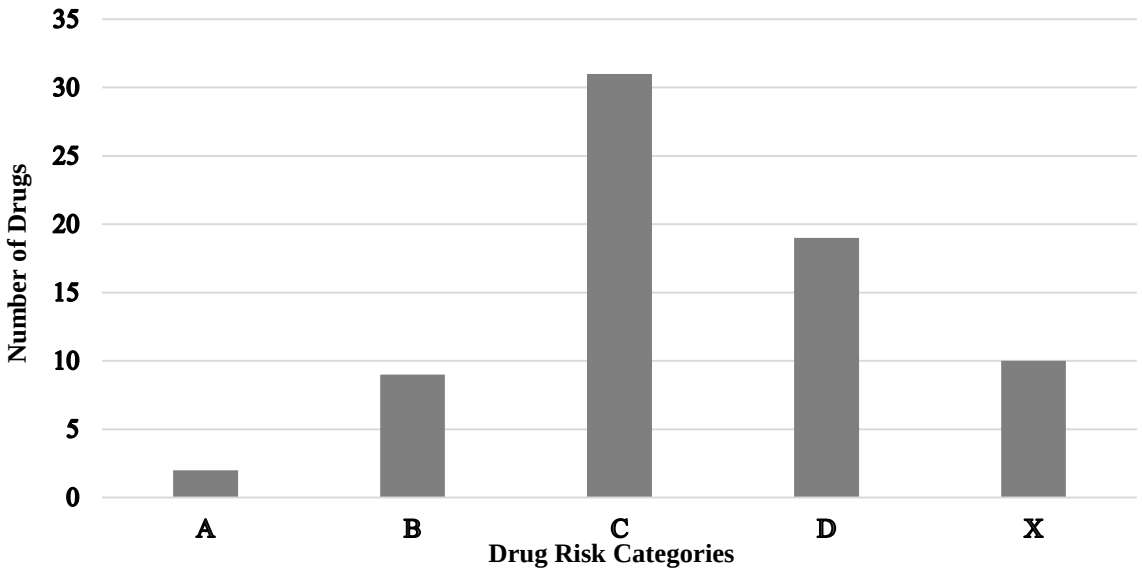

Figure 1. The distribution of the number of drugs used according to TITCK classification

DISCUSSION

A healthy pregnancy encompasses various factors that directly influence both maternal and fetal health. Many women may resort to drug therapy to address various health issues that arise during pregnancy and in the period before they become aware of their pregnancies. However, the teratogenic risks associated with drug use, along with potential DDIs, raise serious concerns for maternal and fetal health. The use of addictive

substances such as tobacco and alcohol increases the risk of miscarriage, causes premature births, and results in teratogenic effects (7). In our study, it was found that individuals using addictive substances did not differ from other pregnant women in terms of education level. However, these individuals tended to seek consultation later than their counterparts. This delay is likely associated with lifestyle choices and a lack of awareness. The data obtained highlight the importance of raising awareness about the risks of addictive substances during pregnancy for all individuals in society, regardless of gender, starting from adolescence.

The individuals in our study were primarily young women, with an average age of approximately 27 years, the majority of whom were in the first trimester of their first pregnancy (around 8 weeks). Despite this young average age, a notable 11.6% of participants had comorbidities requiring continuous drug use, which poses various risks for a healthy pregnancy. Cardiovascular, respiratory, and endocrine system diseases were the most frequently encountered comorbidities. Cardiovascular diseases, in particular, warrant attention due to their association with an increased risk of stroke, myocardial infarction, and cardiomyopathy during the peripartum period (8). The severity of these conditions necessitates the ongoing use of one or more medications, despite potential fetal risks.

In our study, the average number of drugs used by patients with comorbidities was 2.77, while the overall average for the entire study group was 2.97 (with a range from 1 to 7), suggesting that medication use may not always be rational. Analysis of the most commonly used medications revealed that Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), antibiotics, and gastric acid inhibitors were among the most frequently prescribed. Such irrational drug use during pregnancy is likely to result in permanent health problems for both the expectant mother and the fetus.

Polypharmacy, defined as the concurrent use of multiple drugs, is a critical concern for pregnant individuals due to the associated risks, such as DDIs, increased side effects, and treatment failures (9). Our study found that 88.5% (n= 100) of participants were using two or more active substances (excluding prenatal vitamins, minerals, and antiemetic medications used during pregnancy). A recently published study on polypharmacy among pregnant women in Indonesia reported that 39.1% of participants used two or more active substances, with NSAIDs and gastric acid inhibitors being the most commonly used, primarily prescribed by physicians (10). In Türkiye, it was reported that 65% of pregnant women used two or more active substances, with an average of 2.6 active substances per participant; the most frequently used drugs were antibiotics and pain relievers (6). A meta-analysis encompassing studies conducted between 2013 and 2019 found that pregnant women in Ethiopia used an average of 1.7 medications per pregnancy, with 86.9% of these being prescription drugs. This study highlighted the widespread use of medications with high teratogenic risks, identifying antianemic agents, antibiotics, NSAIDs, and gastric acid inhibitors as the most commonly used drugs (11). A recently published study covering a 20-year period in England, which examined approximately 1.5 million pregnant women, found a polypharmacy prevalence of 58.7%. This study also reported that pregnant women with multimorbidity, obesity, a history of smoking, and those outside the 25-34 age range were at a higher risk of polypharmacy than their peers. It noted that the most commonly used medications included antibiotics, gastric acid inhibitors, antifungals, and analgesics (12). As evidenced by the studies described above, the commonly used drug groups among pregnant women may vary from country to country, influenced by socio-economic conditions and lifestyle. Nevertheless, it is generally observed that pregnant women commonly use medications such as NSAIDs, antibiotics, and gastric acid inhibitors. All these studies conducted in diverse regions underscore that polypharmacy is prevalent among pregnant women (excluding prenatal vitamins, minerals, and antiemetic drugs), with most medications being prescription drugs. In this context, our research aligns with the findings of these studies.

DDI is defined as the alteration of expected therapeutic and toxic effects that occurs when two or more drugs interact with each other. These interactions can occur at pharmacokinetic levels (such as absorption, distribution, metabolism, and elimination) and/or pharmacodynamic levels (involving receptor agonism or antagonism) (5). DDI is commonly encountered, particularly among the elderly, due to the prevalence of various chronic diseases and organ failures (14). Conversely, pregnant women are not typically considered a population where DDIs are prevalent, largely due to their younger average age and the tendency to minimize medication use during this sensitive period. However, our study found that pregnant women used an average of three active substances, influenced by comorbidities and irrational drug use, leading to exposure to significant DDIs. Notably, 28.3% of pregnant participants were affected by severe or moderate DDIs, which poses substantial risks to both maternal and fetal health. In a study involving pregnant and breastfeeding women, it was reported that 91% of prescriptions contained DDIs, with 1.4% involving drugs that were contraindicated for concurrent use (15). Another study assessing DDIs in pregnant women receiving inpatient treatment in a maternal intensive care unit revealed that 95.1% were exposed to at least one

moderate or severe DDI. The primary drugs associated with serious interactions in that study included magnesium sulfate, metoclopramide, propranolol, and diazepam (16). In contrast, our research identified carbamazepine, clarithromycin, and perindopril as the main drugs responsible for serious interactions. It is important to note that our study did not account for clinically insignificant or unknown minor drug interactions, which may contribute to discrepancies in total DDI rates across different studies. While variations exist regarding the most common interacting drugs and the rates of serious interactions, a consistent theme across all studies is the highlighted risk of polypharmacy and DDIs in medication use during pregnancy, alongside the inherent teratogenic risks.

In our study, the majority of pregnant women (94.7%) were in their first trimester, while the remainder were in the second trimester. During this early stage of pregnancy, which is particularly vulnerable to teratogenic effects, the participants used a total of 71 different active substances. Among these, 19 drugs were classified in category "D", indicating potential risks, while 10 were in category "X", which contains definitive evidence of teratogenic risk. Notably, many participants began their medication regimens before becoming aware of their pregnancies, and some were required to continue using medications due to chronic health conditions. The high percentage (40.8%) of individuals using fetotoxic drugs in our study may be attributed to the specific nature of our study group, which consisted of pregnant women referred for pharmacologist consultation by gynecologists due to their history of medication use, rather than representing a general pregnant population. As detailed in Table 7, the most commonly identified drugs included oral contraceptives, anti-acne preparations, antidepressants, antibiotics, and antiepileptics. In a study examining 18,575 prescriptions over a 3-year period in Canada, it was reported that 9.1% of pregnant women were exposed to category D or group X drugs (17). In another study conducted in Taiwan, it was reported that 1.1% of the 217,226 prescriptions written for 14,125 pregnant women over a period of three years were identified as category D or X drugs. It was noted that hormonal preparations used for birth control were the most commonly encountered medications in the first trimester (18). A study conducted in Italy, which examined 33,343 prescriptions written within one year, was reported that approximately 1% of pregnant women were exposed to category X drugs (19). While the ranking of the most commonly exposed drugs in these studies shows slight variations, the findings are generally consistent with those of our study. However, the higher rate observed in our research can be attributed to the focus on a specialized population referred by gynecologists for risky drug use, rather than a general pregnant population. In our study, it was determined that not only category D drugs, but also category X drugs such as warfarin, isotretinoin, misoprostol, atorvastatin, simvastatin, methotrexate, and various hormone preparations were administered to women who were not yet aware of their pregnancy. The most common teratogenic effects resulting from the use of these drugs are stillbirth, low birth weight babies, developmental disorders, and organ failure (20). Warfarin has teratogenic effects, leading to embryopathy, Angiotensin-Converting Enzyme (ACE) inhibitors cause cranial malformations, statins lead to skeletal system anomalies, and tetracyclines cause bone and dental abnormalities as well as neural tube defects (21, 22). Antiepileptic drugs such as valproic acid, carbamazepine, phenytoin, phenobarbital and topiramate have specific teratogenic effects such as craniofacial anomalies, orofacial clefts, mental retardation and neurodevelopmental disorders (23). In our study, we also found that a significant number of women used various ionic and non-ionic contrast agents for radiological imaging before recognizing their pregnancy. Although radiological contrast agents are not directly teratogenic, exposure to ionizing radiation during the first trimester can have direct teratogenic and carcinogenic effects on the fetus (24). Therefore, physicians should thoroughly question women about their pregnancy status and only perform such radiological imaging once pregnancy is confirmed.

Furthermore, our study determined that a vast majority of the drugs used by these women (91.2%) were initiated through a physician's prescription. This underscores the necessity for physicians to inquire about potential pregnancy status or plans for pregnancy when prescribing medications to women of childbearing age. In a study conducted in Canada, which examined the prescriptions of approximately 110,000 pregnant women, it was reported that 6.3% of women used at least one medication posing a risk to the fetus (25). Similarly, a study in the Netherlands indicated that 95.5% of women used at least one drug during pregnancy (excluding prenatal vitamins, minerals, and anti-emetics), with 6.5% of these substances classified as teratogenic, and roughly one-third having suspected pharmacological effects on the fetus (26). A study in Brazil found that 26% of the prescribed drugs were classified as category C, 1.5% as category D, and 1.5% as category X (27). Additionally, a retrospective study evaluating a five-year period in Canada determined that drugs in category D were prescribed to 5.5% of pregnant women, while drugs in category X were prescribed to 2.5%. During the first trimester, benzodiazepines and antidepressants were the most commonly prescribed drugs in category D, whereas oral contraceptives and ovulation stimulants were the most frequently prescribed in category X (28). Our research focused on a participant group referred for

pharmacological consultation due to the use of risky drugs, rather than on a general pregnant population. Consequently, the rates of risky drug usage in our study were higher compared to the studies mentioned above. However, the findings from our study, along with those from others, highlight that the use of risky drugs classified in categories D and X is a common issue on a global scale.

In our study, it was determined that the most commonly used active substances (43.7%) were classified as category C drugs. Compounds in this category have demonstrated fetotoxic effects in pregnant experimental animals; however, due to insufficient studies in humans, their use should be carefully considered based on the benefit-to-harm ratio. This indicates that the use of category C drugs during pregnancy is not entirely safe (5). Notably, many frequently used medications in our study, including pain relievers, antidepressants, proton pump inhibitors, cold remedies, and muscle relaxants, fall into this category. In a separate study, it was reported that two out of every three pregnant women in Israel were prescribed an antimicrobial drug during pregnancy (29). Another study indicated that antibiotic treatment during pregnancy is also prevalent in Western countries, accounting for 80% of the drugs prescribed to pregnant women (30). Furthermore, a review noted that one in four women received antibiotics during their pregnancy. The review stated that antibiotics such as beta-lactams, vancomycin, nitrofurantoin, metronidazole, clindamycin, and fosfomycin are relatively safe and effective during pregnancy, while fluoroquinolones and tetracyclines should be avoided. Additionally, antibiotic exposure during pregnancy has been associated with adverse effects in newborns, including congenital anomalies, asthma, and atopic dermatitis (31). Consistent with these findings, antibiotics emerged as one of the most frequently prescribed drug groups in our research. However, our study identified that, in addition to other antibiotics, clarithromycin, tetracycline, and levofloxacin were also prescribed to pregnant women, which contradicts the recommendations from the aforementioned studies. Furthermore, serious DDIs were detected, particularly among pregnant women using clarithromycin, due to the concurrent use of various antidepressants and asthma medications.

The use of NSAIDs and antidepressants during pregnancy, much like antibiotic use, poses significant risks. NSAIDs can lead to various complications, including miscarriage, premature birth, low birth weight, and organ failure in newborns, primarily due to the inhibition of prostaglandin synthesis as these drugs cross the placenta. A recently published study evaluating six years of data corroborates our findings, reporting that NSAIDs are the most commonly used drug class among pregnant women (32). Therefore, during pregnancy, even if pregnancy is suspected, painkillers should be avoided as much as possible, or they should be used in the lowest possible effective dose and for the shortest possible time. In our study, among the frequently used antidepressants, the most commonly prescribed were selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, and escitalopram. A meta-analysis reported that the prevalence of antidepressant use during pregnancy was approximately 1.5% in Europe and Australia, while in North America, this rate was 5.5%, with SSRIs being the most commonly utilized class (33). The use of antidepressants during pregnancy has been linked to an increased risk of gestational diabetes mellitus, spontaneous abortion, and premature birth (34, 35). Additionally, children exposed to antidepressants in utero may experience delays in psychomotor, cognitive, and language development, as well as an increased incidence of attention deficit hyperactivity and autism spectrum disorders (36, 37). In cases where patients are on antipsychotic medications or when individuals with major depression cannot postpone treatment, it is crucial to emphasize the importance of contraception to both patients and their partners. In instances of an unintended pregnancy, considering the risks of discontinuing treatment, the option of abortion may need to be discussed. Conversely, due to the toxic effects and significant risk of drug interactions associated with antidepressants, redirecting pregnant individuals using these medications for indications like social anxiety toward psychological consultation instead of pharmacological therapy may be a prudent approach. Our study found a high prevalence of antidepressant use among pregnant women, aligning with the previously discussed studies. Additionally, the identification of various DDIs associated with these medications underscores the seriousness of the situation.

In the study, significant data were obtained regarding polypharmacy and DDIs, topics for which there is limited information concerning pregnant women. However, because the study was conducted at a single center with a limited number of patients from a specific population, the results cannot be generalized. These were the limitation of the study.

CONCLUSION

Our study revealed that approximately 84% of the medications used by pregnant women pose uncertain safety profiles or potential teratogenic risks. Additionally, we found a high prevalence of polypharmacy and significant drug-drug interactions (DDIs) among this population. Therefore, it is essential for physicians to conduct thorough inquiries with patients who are planning or suspecting pregnancy and to clearly explain the associated risks before prescribing medications. Active substances should be selected from low-risk

categories whenever possible. Furthermore, educating pregnant women about rational drug use and highlighting the risks linked to polypharmacy is crucial for safeguarding both maternal and fetal health. In cases of potentially harmful drug use during pregnancy, it is crucial to seek immediate guidance from a pharmacologist or a teratogenicity service. The pregnant woman and her physician should be thoroughly informed about the potential consequences of medication use during pregnancy, including options for discontinuation, modification, postponement of treatment, or even considering pregnancy termination. Our study highlights that drug use during pregnancy represents a significant public health concern, necessitating a multidisciplinary approach to address it effectively. Nevertheless, further multicenter and large-scale studies are required to gain a more comprehensive understanding of this issue.

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