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Opioid analgesics are the leading cause of adverse drug reactions in the obstetric population in South Korea

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Abstract

Medication use during pregnancy is gradually increasing; however, the safety of this practice remains largely unknown.

We investigated medications with the most adverse drug reactions (ADRs) among pregnant women and the clinical features of those medications.

Reports of ADRs among pregnant women were extracted from the Korea Adverse Events Reporting System (January 2012–December 2015). We analyzed the data of drugs frequently reported to cause ADRs and their clinical features among 3 age groups.

A total of 5642 ADRs among 3428 patients were analyzed. The number of ADR reports increased annually. The most common drug categories causing ADRs were analgesics, followed by gynecologic, uterotocolytic, anti-infective, antidiabetic, analgesic, and antihypertensive drugs. Analgesics comprised 6 opioids (morphine, fentanyl, hydromorphone, oxycodone, tramadol, pethidine) and an anti-pyretics (nefopam and ketorolac). As an individual drug, ritodrine (24.4%) was the most frequently reported, followed by morphine, 5-HT_3 serotonin antagonist, nefopam, fentanyl, magnesium sulfate, insulin lispro, cefazedone, sodium chloride, hydromorphone, oxycodone, cefotetan, nifedipine, human insulin, tramadol, ketorolac, pethidine, methylergometrine, metoclopramide, and misoprostol (in that order). ADRs most frequently occurred in women aged 25 to 34 years, and the trend of ADR with the 20 most commonly reported medications significantly differed among the age groups ($P = .011$). In addition, the kind of common causative drugs was different among the age groups.

Knowledge of medications and clinical conditions resulting in the highest ADR rates among pregnant women is necessary for medical practitioners to administer proper care.

Abbreviations: ADR = adverse drug reaction, ART = adverse reaction terminology, ATC = anatomical therapeutic chemical, FDA = Food and Drug Administration, ICH = International Conference on Harmonization, ICSR = individual case safety report, KAERS = Korea Adverse Event Reporting System, KCD-6 = Korean Classification of Diseases revision 6, KIDS = Korea Institute of Drug Safety and Risk Management, KIDS-KD = KIDS-KAERS database, PT = preferred term, RPVC = regional pharmacovigilance center, SOC = system-organ class, UMC = Uppsala Monitoring Centre, WHO = World Health Organization.

Keywords: adverse drug reaction, opioid analgesics, pharmacovigilance, pregnancy, ritodrine

1. Introduction

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is any noxious, unintended, and undesired effect of a drug that occurs at doses used by humans for prophylaxis, diagnosis, or therapy.[1] This definition excludes therapeutic failures, intentional and accidental poisoning, and

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drug abuse. Common ADRs are related to the dose of the drugs such as dry mouth, respiratory depression, bleeding, and orthostatic hypotension. These ADRs are predictable and have low mortality. On the other hand, there are unpredictable ADRs that are not related to the pharmacologic action of the drugs, such as hypersensitivity reactions. Anaphylaxis to penicillin and malignant hyperthermia with general anesthetic agents correspond to these ADRs.[1] The incidence of ADRs has steadily increased, and fatal ADRs are the fourth and sixth leading causes of death in the United States.[2,3] During a longitudinal study, the trend of serious ADRs increase over time.[4]

The safety of drug exposure during pregnancy is not well-understood because clinical trials typically exclude pregnant women for ethical reasons; therefore, knowledge is limited to postmarketing data generated from observational studies. In addition, premarketing pharmaceutical studies often fail to accurately identify adverse effects of drugs on humans.[5] A study performed in Great Britain found 47 new serious ADRs reported by both consumers and professional health providers that were not previously included in the summaries of product characteristics.[6] Therefore, because of the sparse premarketing research regarding the effects of medications during pregnancy, small studies or case reports are important for detecting their undesirable effects on pregnant women and the fetus or neonate. An investigation of ADRs in the obstetric population could provide critical information regarding public health.

Despite the lack of relevant information regarding the potential drug effects on pregnancy, a longitudinal investigation noted that medication use and the number of drugs used during pregnancy have continuously increased over time.[7–12] According to the estimates determined using a database of the Medicaid enrollees, approximately 80% of pregnant women were exposed to 1 or more medications during pregnancy, and the use of 4 or more drugs increased by more than 3-fold over decades. The United States Food and Drug Administration (FDA) announced a change in the labeling information of prescription drugs during pregnancy and lactation; instead of using A, B, C, D, and X to label drug categories during pregnancy,[13] a narrative describing the drug information is provided. However, during the transition period, this change might cause confusion for physicians who prescribe various medications to patients during pregnancy, thus compromising the safety of the mother, fetus, and/or neonate. Therefore, there is renewed interest in the need for information regarding drug safety and ADRs during pregnancy.

In South Korea, the Korea Institute of Drug Safety and Risk Management (KIDS) was established to expand national pharmacovigilance by monitoring ADRs observed in the Korean population and to suggest regulatory interventions.[14] In 2012, KIDS developed the Korea Adverse Event Reporting System (KAERS) based on cumulative reports to facilitate the reporting and management of adverse events. It has become the management center for all regional pharmacovigilance centers (RPVCs). In 2016, there were 27 RPVCs, including 25 local teaching hospitals and 2 nationwide RPVCs, including the National Medical Center and Korea Pharmaceutical Association, which are linked with nationwide health centers and pharmacies, respectively.

The present study aimed to determine the medications with the highest ADR rates (referred to hereafter as "most commonly reported") among pregnant women and their clinical features using the KAERS database.

2. Methods

2.1. Data collection

This study used the KIDS-KAERS database (KIDS-KD) from January 2012 to December 2015. Data were collected from spontaneously reported individual case safety reports (ICSRs) from RPVCs, health care professionals, consumers, and pharmaceutical companies, from studies (re-examination, post-marketing studies, individual case studies), and from the literature. KIDS evaluated cumulative reports to generate the database and perform signal detection to provide drug safety information. This database is compatible with the international standards of the WHO-UMC (Uppsala Monitoring Centre) international drug monitoring program.[15]

The study proposal was submitted to the institutional review board at Uijeongbu St. Mary's Hospital, and ethical approval was waived as the research included analysis of the existing data that are publicly available and did not include any personal information.

Data were selected to include cases with disease codes related to pregnancy and its associated conditions or diseases, including childbirth and puerperium (O00-O99.8, Z32–34.99, 35, 35.9, 64, and 87) according to the Korean Classification of Diseases revision 6 (KCD-6) (supplementary data 1, http://links.lww.com/MD/C996). We excluded cases with disease codes pertaining to neoplastic or malignant diseases that possibly involved chemotherapy; patients younger than 15 years or older than 50 years, and patients who were male or who had an unclear gender (Fig. 1). This study only included ADRs associated with a dose normally used by humans and reports associated with drugs administered for ordinary prophylactic or therapeutic purposes. To reduce duplication of data, each report was individually compared based on patients' initials and age and the source of the report. If these factors were identical, then the reports were further examined for other information, including the reaction term; suspected duplicated reports were omitted. Patient records were anonymized before analysis.

The reports were inspected for patient age, year of the report, drug indication, the diagnosis or description of the adverse reaction according the WHO adverse reaction terminology (WHO-ART), the reporter's profession, progress of the adverse reaction, and causality assessment.[16] Causality was assessed using the 6 categories outlined by the WHO-UMC criteria: certain, probable, possible, unlikely, conditional, and unassessable.[17] This assessment was primarily performed by the ADR monitoring team at each regional pharmacovigilance center and confirmed by KIDS healthcare professionals. Cases classified as certain, probable and possible were analyzed for this study. Medications that caused ADRs were grouped using the second degree of the anatomical therapeutic chemical (ATC) classification system.[18] Medications may have multiple classes according to various indications, drug mechanisms, routes of administration, and ingredients. Therefore, medications with multiple ATC codes were assigned a category according to the clinical indication of the drug prescription. We identified the 20 medications that were most commonly reported to cause ADRs in this study population. We reported the overall prevalence, the prevalence according to maternal age groups, and the prevalence according to the ATC classification system category. Additionally, the common indicative disease codes and symptoms of ADRs associated with the medications were examined.

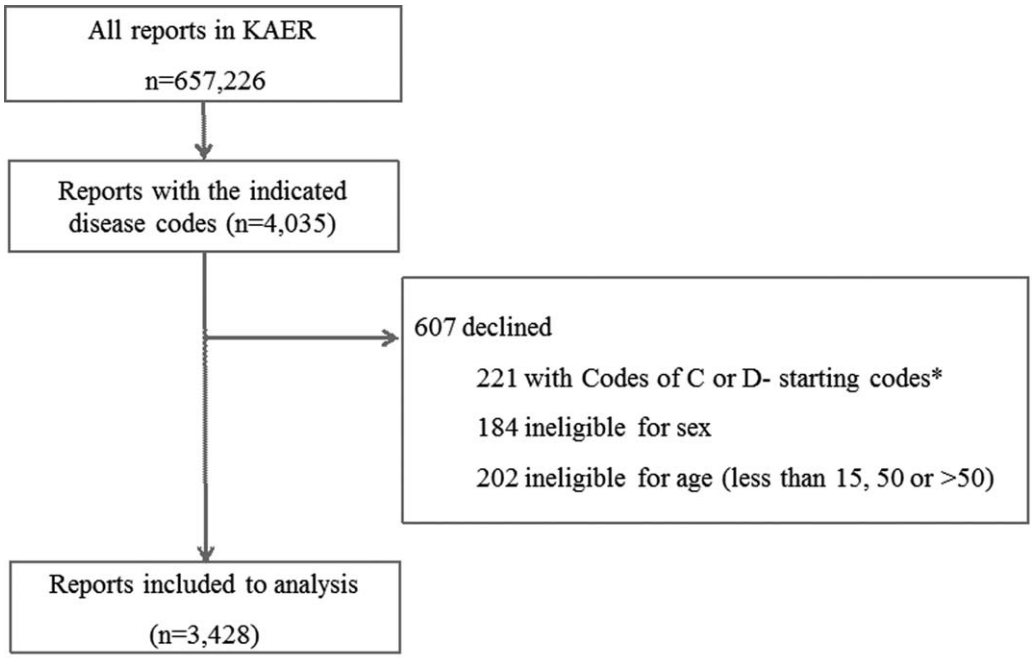

Figure 1. Selection of study cases from the KAER database. *Codes of malignant or neoplastic disease, KCD-6: C00 - C97, malignant neoplasm; D00-D099, in situ neoplasm; D37-D48, neoplasms of uncertain or unknown behavior. KAER = Korea Adverse Events Reports.

Patients were divided into 3 age groups (15–24, 25–34, and 35–50 years) to examine age differences. In a recent report of the birth registry in Korea, those in the younger than 25 years and 25- to 35-year age groups had the lowest and highest live birth rates, respectively.[19] We assumed that the features of ADRs were differently observed. In addition, maternal age older than 35 years was regarded as one of the risk factors that increased adverse pregnancy outcomes and obstetric complications; therefore, these women were likely exposed to therapeutic or prophylactic medications during pregnancy.[20–23]

According to the International Conference on Harmonization (ICH) E2D Guidelines, all ADRs were categorized as either serious or not serious.[24] Adverse events that caused death, were life-threatening, caused prolonged hospitalization, induced a congenital anomaly, or caused any other outcome considered medically important were classified as serious. Outcomes were evaluated according to 6 different categories: recovered, not recovered, recovering, recovered with sequelae, recovered with fatal damage, and unknown result.

Clinical symptoms were categorized using the WHO-ART system. Among the 4-level hierarchical system structure, system-organ classes (SOCs) and preferred terms (PTs) were used during the analysis.[16] ICSRs describing 2 or more PTs in 1 patient who was receiving 1 drug were treated as different adverse reactions. For patients using 2 or more medications at the same time, it was assumed that each medication was responsible for any reported adverse reactions. The frequency of clinical symptoms was assessed according to the age group and compared to the clinical symptom frequency of all cases reported to KIDS in 2015.

2.2. Statistical analyses

Demographic and clinical characteristics were analyzed using means and standard deviation (for continuous variables) and frequencies and percentages (for categorical variables). Causative medications with the highest ADRs and overall symptoms of ADRs were compared among age groups using the Chi-squared test or Fisher exact test. The significance level was set at $P < .05$. All statistical calculations were performed using SAS statistical software package version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

A total of 657,226 patients experienced ADRs during the study period; 4035 patients were selected using KCD-6 disease codes related to obstetric conditions. During the initial inspection, we excluded 607 patients with malignant diseases, ineligible sex, or ineligible age (Fig. 1). No duplicates were identified. A total of 5642 cases for 3428 patients were analyzed in the current study, which comprised 4907 cases involving suspicious drugs and 735 cases involving combined drugs (Table 1). The number of reported cases increased annually, reaching 2875 cases in 2015. Management included stopping the medication (n = 2306), maintaining the dosage (n = 1260), decreasing the dosage (n = 232), not applicable (n = 535), and unknown (n = 826). The mean patient age was 32.8 years, and most (63.5%) were in the 25- to 34-year age group. An average of 1.5 ADR cases per patient (range, 1–6; median, 1) was observed.

A total of 280 cases were classified as serious ADRs, and the most commonly reported medications were (from most frequent to least frequent): ritodrine (n = 32); insulin lispro (n = 26); insulin (human) (n = 14); fentanyl (n = 9); everolimus (n = 8); insulin detemir (n = 8); serotonin (5HT3) antagonists (n = 7); tramadol (n = 7); amlodipine (n = 6); and morphine (n = 6). Among the serious cases, the following were observed: death (n = 1) with propofol; disability (n = 3) with levonorgestrel and ritodrine; life threatening (n = 5) with fentanyl, gentamicin, methylergometrine,

Table 1

General patient characteristics and clinical outcomes.

	By person (N = 3428)		By case report (N = 5642)	
	n or mean	% or SD	n or mean	% or SD
Age, years (Mean ± SD)	32.83	4.47	32.96	4.45
15–24	128	3.73	189	3.35
25–34	2176	63.48	3543	62.8
35–49	1124	32.79	1910	33.85
Form reported				
ICSR	3358	97.96	5119	90.73
investigation	52	1.52	446	7.9
literature	17	0.5	60	1.06
other	1	0.03	17	0.3
Initial or follow-up				
initial report	3337	97.35	5428	96.21
follow-up	91	2.65	214	3.79
Date reported				
2012	12	0.35	45	0.8
2013	408	11.9	698	12.37
2014	1171	34.16	2024	35.87
2015	1837	53.59	2875	50.96
Serious				
No	2996	95.93	4679	94.35
Yes	127	4.07	280	5.65
Suspicious or combined				
suspicious drug	3227	94.14	4907	86.97
combined drug	–	–	735	13.03
both suspicious and combined drugs	201	5.86		

ICSR = individual case safety report.

and midazolam; hospitalization (n = 244); and other medical concern (n = 151).

Figure 2 shows the 20 medications with the highest rates of ADRs; 3935 out of a total of 4907 cases were classified. Ritodrine (24.4%) was the most commonly reported individual drug, followed by morphine, 5-HT_3 serotonin antagonist, nefopam, fentanyl, magnesium sulfate, insulin lispro, cefazedone, sodium chloride, hydromorphone, oxycodone, cefotetan, nifedipine, human insulin, tramadol, ketorolac, pethidine, methylergometrine, metoclopramide, and misoprostol (in that order). Ritodrine is a potent beta-2 stimulant that produces direct relaxation of uterine smooth muscle and is clinically used to manage preterm labor. According to the category classified by the second degree of the ATC code, analgesics were the most common category, followed by gynecologic drugs (ritodrine, methylergometrine, misoprostol), antiemetic drugs (serotonin antagonist), drugs for constipation (magnesium sulfate), anti-diabetes drugs (insulin lispro, insulin human), blood substitutes and perfusion solutions (sodium chloride, magnesium sulfate), antibacterial agents for systemic use (cefotetan, cefazedone), calcium channel blockers (nifedipine), anti-inflammatory and anti-rheumatic products (ketorolac), and drugs for functional gastrointestinal disorder (metoclopramide). Notably, analgesics comprised 5 opioids (morphine, fentanyl, hydromorphone, oxycodone, tramadol, pethidine) and other kind of analgesics (antipyretics for nefopam).

In the comparison of age groups, Figure 3 shows that the trend of the 20 medications differed among age groups ($P = .011$, Fig. 3). The prevalence of the 20 medications was different among age groups ($P = .004$, supplementary data 2, http://links.lww.com/MD/C996). Pain was the most common clinical indication, followed by preterm labor and delivery (supplementary data 3, http://links.lww.com/MD/C996). The type of commonly reported medications was different among age groups; morphine and misoprostol were more prevalent for women 15 to 24 years, and anti-diabetes agents were associated with the highest rates of ADRs for women older than 35 years (Table 2).

Regarding clinical manifestations of ADR in the study population, the most commonly affected SOCs were the central and peripheral nervous systems, followed by the gastrointestinal system and the skin and appendage system. In all Korean adverse effect reports in 2015, trends of palpitations, tremors, chest discomfort, and tachycardia were more frequent in the study population (Table 3).

4. Discussion

Analgesics comprised the most commonly reported ATC category causing ADRs in the population with obstetric conditions, followed by gynecologists, antiemetics, drugs for constipation, anti-diabetes drugs, blood substitutes, calcium channel blockers, anti-inflammatories, and antirheumatics for functional gastrointestinal disorder. Most analgesics were classified as prescription opioids. Ritodrine was the most common individual medication that caused ADRs. ADRs were most commonly reported in the 25- to 34-year age group, and the type of causative medication significantly differed according to age groups. The most common manifestation was nausea for the involved organ system; the central and peripheral nervous systems were most frequently involved in SOC in the study population.

Pregnant women can be prescribed opioids for various conditions during pregnancy and the postpartum period, to manage pain in the abdomen, low back, and pelvis, migraines

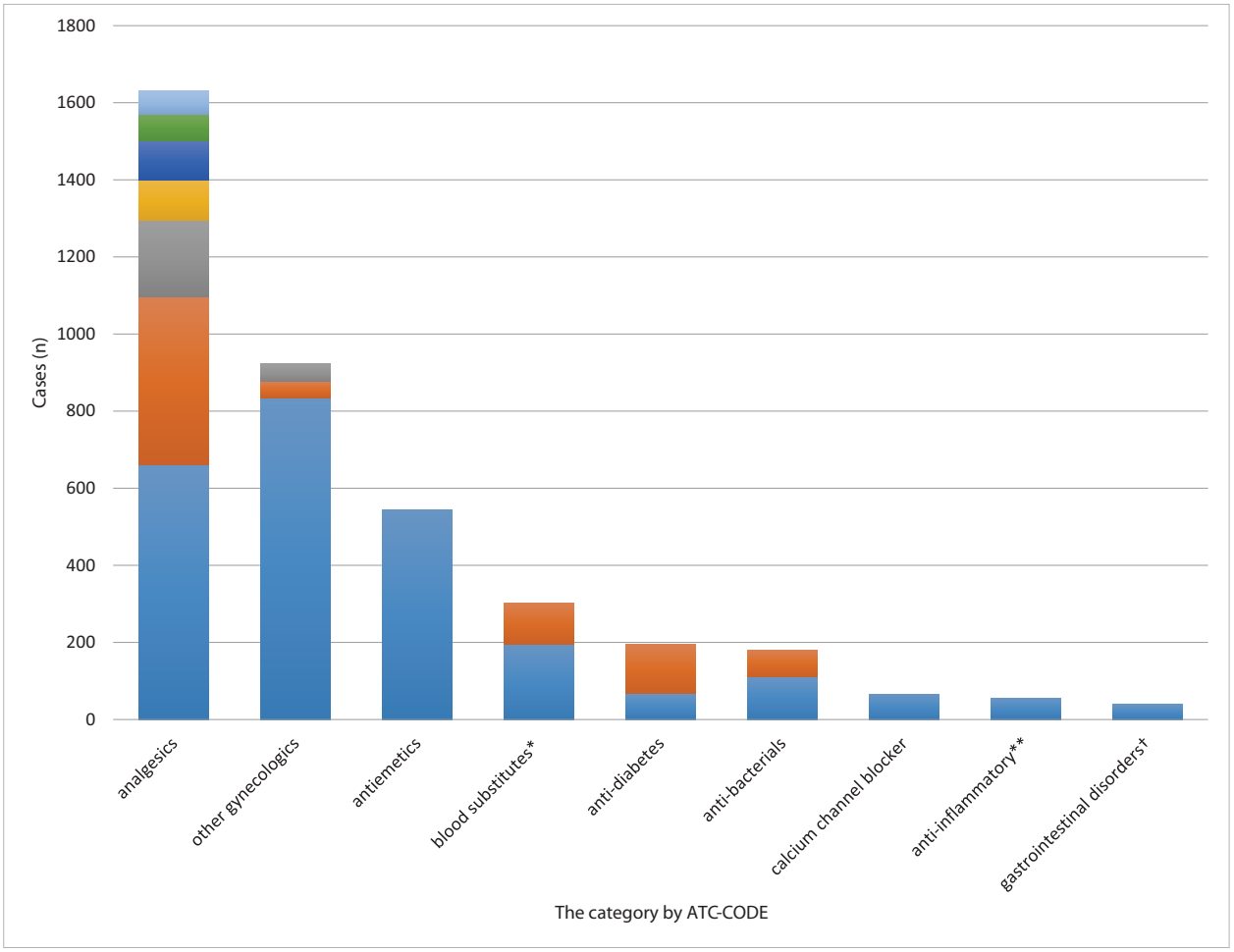

Figure 2. The prevalence of 20 causative medications with highest ADRs by the category classified according to the second degree of Anatomical Therapeutic Chemical (ATC) classification system. ATC-code = the second degree codes of Anatomical Therapeutic Chemical classification system; *, blood substitutes and perfusion solution; **, anti-inflammatory and anti-rheumatic products; †, drug for functional gastrointestinal disorders. Analgesics are morphine, nefopam, fentanyl, hydrormophone, oxycodone, tramadol, and pethidine, in order of frequency. Among the drugs of gynecologicals (ritodrine, methylergometrine, misoprostol), ritodrine is the most frequently reported drug in the population with obstetric condition. Anti-emetics and antinauseants (serotonin (5HT3) antagonist), blood substitutes and perfusion solution (magnesium sulfate, sodium chloride), anti-diabetes (insulin lispro, insulin (human)), antibacterial for systemic use (cefazedone, cefotetan), calcium channel blocker (nifedipine), anti-inflammatory and anti-rheumatic products (ketorolac), and drug for functional gastrointestinal disorder (metoclopramide).

prenatally, and to manage labor and delivery-related pain.[25,26] In particular, the use of opioid analgesics during pregnancy has steadily increased approximately 6% in European countries and up to 22.8% in the United States in 2014[27,28]; however, fetal safety after exposure to these medications is not well understood. Subsequently, the increasing opioid exposure experienced by the fetus in the intrauterine environment has led to an increased rate of neonate abstinence syndrome in the United States.[29,30] In this study, analgesics were the most common drug category related to ADRs and included several prescription opioids (morphine, fentanyl, hydromorphone, oxycodone, tramadol, and pethidine). There have been reports of other substance abuse, such as alcohol or smoking, during pregnancy; however, but there has been no report of the use of prescription opioids during pregnancy in Korea. Most opioid analgesic usage during pregnancy might be occurred during the process of vaginal or cesarean delivery. Results concerning the frequency of ADRs related to opioid analgesics, however, address the need to evaluate prescribing and dispensing opioids to pregnant women.

Ritodrine was the most commonly reported individual drug causing ADRs in the study population. It is a beta-adrenergic agonist that is used as a tocolytic agent to treat preterm labor or delivery. However, it frequently causes maternal side effects such as tachycardia, palpitations, tremors, chest discomfort and dyspnea, and hyperglycemia. There are no clear guidelines regarding the first-line therapy for preterm labor; currently, it is different among nations. The practice guidelines of the American Committee of Obstetrics and Gynecology recommend that the first-line tocolytics should be beta-mimetics, calcium channel blockers, and oxytocin receptor antagonists.[31] However, in 2015, the National Institute for Health and Care Excellence and Royal Committee of Obstetrics and Gynecology stated that nifedipine should be the first-line treatment for acute preterm labor, and that beta-agonists should not be used.[32]

A longitudinal investigation performed over decades noted that the rate of using medications during pregnancy and the number of drugs used are steadily increasing.[11] Common drugs dispensed during pregnancy were similar among the studies,

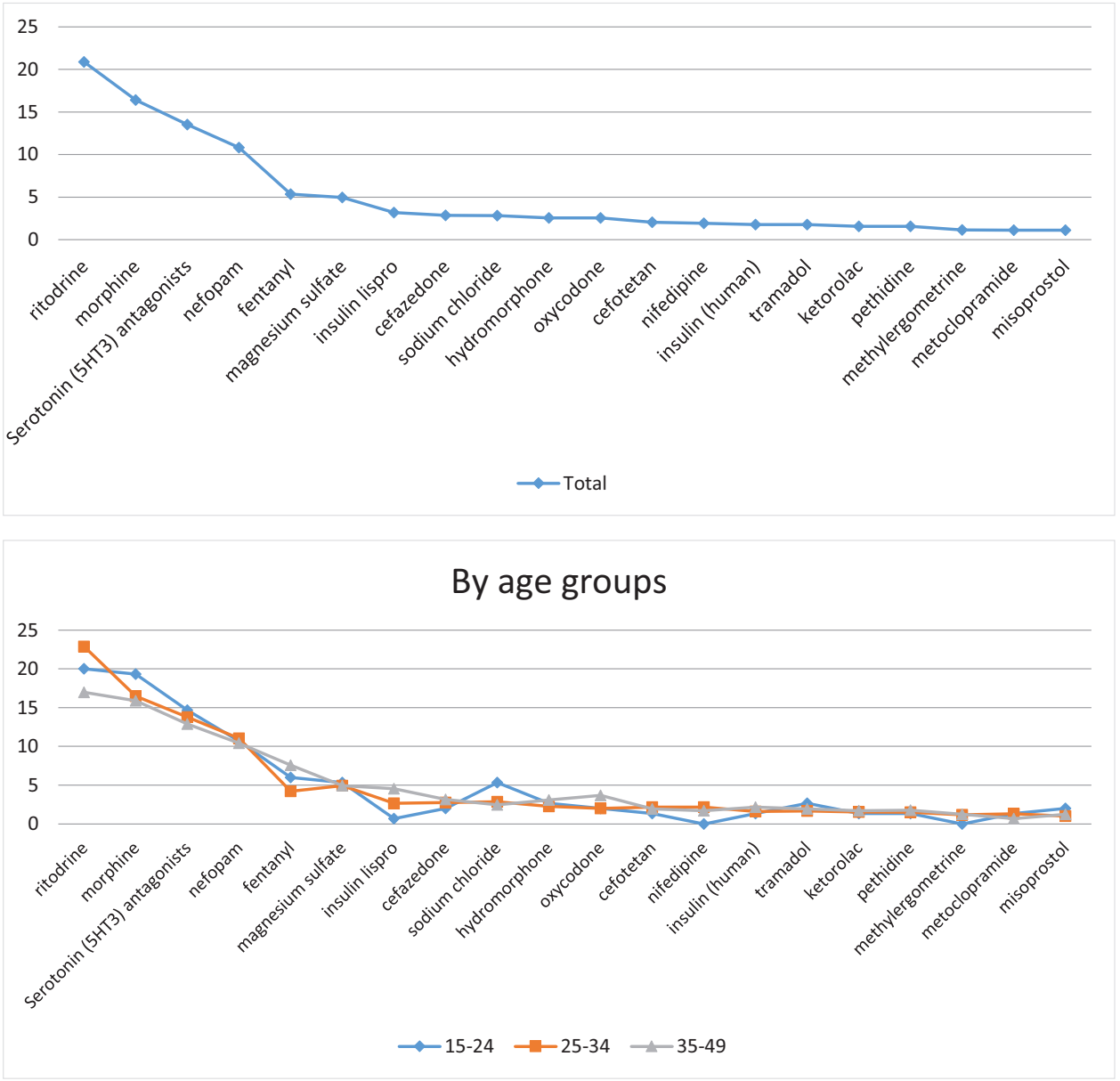

Figure 3. The 20 causative medications with highest ADR according to age group. *P* value, .011 for comparison of the trend of medications among age groups.

including anti-infectives, analgesics, respiratory and gastrointestinal drugs, and dermatological steroids, with difference found for maternal age and ethnicity.[8–12] This study evaluated ADRs of patients with obstetric conditions; therefore, it cannot be directly compared with previous studies regarding common medications used during pregnancy. However, it is assumed that both studies were affected by maternal age and the risk of pregnancy complications. ADRs were most frequently reported in the 25- to 34-year age group, followed by the older than 35-year age group and 15- to 24-year age group. This finding might reflect comorbidity, basic physical strength, and the degree of adaptation to the physiologic changes during pregnancy. Mothers of advanced age are likely to have coexisting chronic diseases such as hypertension or pregestational diabetes, in addition to being at increased risk for obstetric morbidities such as miscarriage, preterm labor, hypertension, gestational diabetes, and cesarean delivery,[20–23] which might reflect the more frequent reports of drugs classes such as analgesics (fentanyl and oxycodone) and antidiabetic drugs (Fig. 3).

After observing disease codes for prescriptions of drugs related to ADRs, it can be presumed that the frequency of ADRs is dependent on the clinical indications for the drug used. Disease codes related to preterm labor and delivery were the most common among prescription drugs that caused ADR, regardless of the approved labels. Nifedipine, a calcium channel blocker that is the primary drug indicated for angina and hypertension, was reportedly most commonly dispensed in the United States for cardiovascular reasons during pregnancy regardless of its clinical indications.[33] In this study, the disease code O60 (preterm labor and delivery) was a leading reason for nifedipine- related ADR cases. A Cochrane review reported that as a tocolytic, nifedipine is comparable to magnesium sulfate and beta-agonists (including

Table 2

Medications commonly associated with adverse drug reactions according to age groups.

	Total			Age groups					
				15–24		25–34		35 - 49	
Rank	Drugs	Report (n,5642)	Person (n,3428)	Drugs	n (total, 189)	Drugs	n (total, 3543)	Drugs	n (total, 1910)
1	Ritodrine	844	839	Ritodrine	30	Ritodrine	594	Ritodrine	220
2	Morphine	663	560	Morphine	29	Morphine	428	Morphine	206
3	Serotonin (5HT3) antagonists	547	547	Serotonin (5HT3) antagonists	22	Serotonin (5HT3) antagonists	358	Serotonin (5HT3) antagonists	167
4	Nefopam	438	438	Nefopam	16	Nefopam	287	Nefopam	135
5	Fentanyl	216	208	Fentanyl	9	Magnesium sulfate	128	Fentanyl	98
6	Magnesium sulfate	200	199	Magnesium sulfate	8	Fentanyl	109	Magnesium sulfate	64
7	Insulin lispro	129	116	Sodium chloride	8	Sodium chloride	74	Insulin lispro	59
8	Cefazedone	116	116	Hydromorphone	4	Cefazedone	72	Oxycodone	48
9	Sodium chloride	114	114	Tramadol	4	Insulin lispro	69	Cefazedone	41
10	Hydromorphone	103	103	Cefazedone	3	Hydromorphone	59	Hydromorphone	40
11	Oxycodone	103	103	Misoprostol	3	Cefotetan	56	Sodium chloride	32
12	Cefotetan	83	83	Oxycodone	3	Nifedipine	56	Insulin (human)	28
13	Nifedipine	78	78	Cefbuperazone	2	Oxycodone	52	Cefotetan	25
14	Insulin (human)	72	67	Cefmetazole	2	Tramadol	43	Tramadol	25
15	Tramadol	72	72	Cefminox	2	Insulin (human)	42	Pethidine	23
16	Ketorolac	64	64	Cefotetan	2	Ketorolac	40	Ketorolac	22
17	Pethidine	64	63	Ibuprofen	2	Pethidine	39	Nifedipine	22
18	Methylergometrine	47	47	Insulin (human)	2	Metoclopramide	34	Methylergometrine	16
19	Metoclopramide	45	44	Ispaghula (psylla seeds)	2	Methylergometrine	31	Misoprostol	16
20	Misoprostol	45	45	Ketorolac	2	Ceftriaxone	30	Ampicillin and Enzyme inhibitor	14
				Pethidine	2				
				Metoclopramide	2				
				Paracetamol, combinations	2				

ritodrine) but with fewer side effects.[34] Nevertheless, it causes more ADRs when used as a tocolytic than when used as an antihypertensive. Magnesium sulfate for parenteral injection was categorized as a drug for blood substitute and perfusion solution, and mineral supplements in the ATC code index. Among the ADRs associated with magnesium sulfate, ADRs caused by magnesium sulfate were most frequently associated with the disease code for preterm labor and delivery (O60); they were second most frequently associated the disease code for eclampsia.

This study had several limitations. First, data were obtained from spontaneous reporting, which has a tendency to underestimate the true rate of ADRs and may include heterogeneous reports with a range of sources and a lack of information. Therefore, we could not perform statistical analyses that controlled for confounding factors during group comparisons. Second, we could not produce a reliable estimate of the overall incidence of adverse reactions experienced by patients who received specific drugs because of the lack of information regarding total drug usage. Third, the ADR occurrence when a specific drug was "off-label" could not be analyzed. Further research is needed to evaluate medication used during pregnancy in Korea because the management of pregnant women of advanced age is an important issue for the public health service because these patients have more opportunities to receive medications during pregnancy.

Table 3

Comparison of commonly reported clinical manifestations of adverse drug reactions between the study population and the entire KAER report in 2015.

	Study population	%	Entire reports	%
1	Nausea	24.5	Nausea	16.3
2	Itching	13.1	Pruritus	9.5
3	Dizziness	12.6	Dizziness	8.5
4	Palpitations	11.1	Urticaria	8.2
5	Vomiting	9.9	Vomiting	7.8
6	Pruritus	6.4	Rash	6.6
7	Tremor	5.6	Headache	3.5
8	Giddiness	5.4	Diarrhea	3.4
9	Chest discomfort	5.1	Dyspepsia	3.1
10	Tachycardia	4.9	Somnolence	2.6

KAER = Korea Adverse Events Reporting.

In conclusion, ADRs experienced by the obstetric population were frequently associated with opioid analgesics and treatment agents for preterm labor and delivery. Ritodrine caused the highest ADR rates across all age groups and the highest rates of serious cases. The findings regarding medications frequently resulting in ADRs contribute to the informed and safe prescribing of relevant drugs as health care providers manage obstetric conditions.

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Writing – review & editing: Yeon Hee Kim.

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