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

Sae Kyung Choi, PhD, Yeon Hee Kim, PhD, Su Mi Kim, MD, Jung Ha Wie, MD, Dong-Gun Lee, PhD, Ji Young Kwon, PhD, Jeong Hwa Song, MD, Su Jeong Lee, MD, In Yang Park, PhD

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, uterotonics, anti-infective, antidiabetic, analgesic, and antihypertensive drugs. Analgesics comprised 6 opioids (morphine, fentanyl, hydromorphone, oxycodone, tramadol, pethidine) and an anti-pyretic (acetaminophen). As an individual drug, ritodrine (24.4%) was the most frequently reported, followed by morphine, 5-HT3 serotonin antagonist, nefopam, fentanyl, magnesium sulfate, insulin lispro, cefazolin, sodium chloride, hydromorphone, oxycodone, cepotetan, 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.

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...
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. The incidence of ADRs has steadily increased, and fatal ADRs are the fourth and sixth leading causes of death in the United States. During a longitudinal study, the trend of serious ADRs increase over time. 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. 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. 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. 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, 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. 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.

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-O09.8, 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. Causality was assessed using the 6 categories outlined by the WHO-UMC criteria: certain, probable, possible, unlikely, conditional, and unassessable. 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. 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.
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, body-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 $P < 0.05$. 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 ($n = 7$); amiodipine ($n = 6$); 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.
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-HT3 serotonin antagonist, nefopam, fentanyl, magnesium sulfate, insulin lispro, cefazodone, sodium chloride, hydromorphone, oxycodone, cefotetan, sodium chloride, hydromorphone, oxycodone, cefotetan, nefopam, human insulin, tramadol, ketorolac, pethidine, 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), antiemetics (5-HT3 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, cefazodone), 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, and 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). The prevalence of the 20 medications was different among age groups (P = .004). 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-inflammatory, 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 mediation 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

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                      | 2906 ± 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.
prenatally, and to manage labor and delivery-related pain.\textsuperscript{[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\textsuperscript{[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.\textsuperscript{[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, 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[11]} Common drugs dispensed during pregnancy were similar among the studies,
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

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.
ritodrine) but with fewer side effects. 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 under-estimate 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 2
Medications commonly associated with adverse drug reactions according to age groups.

| Rank | Drugs               | Report (n,5642) | Person (n,3428) | Drugs (n, total) | Age groups |
|------|---------------------|-----------------|-----------------|-----------------|-------------|
| 1    | Ritodrine           | 844             | 839             | Ritodrine 30    | 15–24       |
| 2    | Morphine            | 663             | 560             | Morphine 29     | 25–34       |
| 3    | Serotonin (5HT3)    | 547             | 547             | Serotonin (5HT3) antagonist 22 | 35 - 49 |
| 4    | Nefopam             | 438             | 438             | Nefopam 16     |             |
| 5    | Fentanyl            | 216             | 208             | Fentanyl 9     |             |
| 6    | Magnesium sulfate   | 200             | 199             | Magnesium sulfate 8 |             |
| 7    | Insulin lispro      | 129             | 116             | Sodium chloride 8 |             |
| 8    | Cefazedone          | 116             | 116             | Hydromorphone 4 |             |
| 9    | Sodium chloride     | 114             | 114             | Tramadol 4     |             |
| 10   | Hydromorphone       | 103             | 103             | Cefazedone 3    |             |
| 11   | Oxycodone           | 103             | 103             | MISoprost 3     |             |
| 12   | Cefotetan           | 83              | 83              | Oxycodone 3    |             |
| 13   | Nifedipine          | 78              | 78              | Ceftriazone 2   |             |
| 14   | Insulin (human)     | 72              | 67              | Ceftriazone 2   |             |
| 15   | Tramadol            | 72              | 72              | Ceftriazone 2   |             |
| 16   | Ketorolac           | 64              | 64              | Ceftriazone 2   |             |
| 17   | Pethidine           | 64              | 63              | Ceftriazone 2   |             |
| 18   | Methylenepragmine   | 47              | 47              | Insulin (human) 2 |             |
| 19   | Metoclopramide      | 45              | 44              | Methylergometrine 2 |             |
| 20   | Misoprostol         | 45              | 45              | Methylergometrine 2 |             |

### 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    | Dyspnoea| 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.

Acknowledgments

The authors thank the Department of Medical Life Science, The Catholic University of Korea, and Mr. Jin-Hyung Jung for performing statistical analyses for this study.

Author contributions

Conceptualization: Dong-Gun Lee, Ji Young Kwon.
Data curation: Jung Ha Wie, Jeong Hwa Song, Su Jeong Lee.
Formal analysis: Su Mi Kim.
Methodology: Su Mi Kim, Ji Young Kwon.
Project administration: Dong-Gun Lee.
Resources: Jung Ha Wie, Dong-Gun Lee.
Supervision: Yeon Hee Kim, In Yang Park.
Validation: In Yang Park.
Visualization: In Yang Park.
Writing – original draft: Sae Kyung Choi.
Writing – review & editing: Yeon Hee Kim.

References

[1] Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255–9.
[2] Miller RR. Hospital admissions due to adverse drug reactions. A report from the Boston Collaborative Drug Surveillance Program. Arch Intern Med 1974;134:219–23.
[3] Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200–5.
[4] Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998–2003. Arch Intern Med 2007;167:1752–9.
[5] Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA 1999;281:824–9.
[6] Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK ‘Yellow Card Scheme’: literature review, descriptive and qualitative analyses, and questionnaire surveys. Health Technol Assess 2011;15:1–234.
[7] Cleary BJ, Butt H, Strawbridge JD, et al. Medication use in early pregnancy: prevalence and determinants of use in a prospective cohort of women. Pharmacoeconomics Drug Saf 2010;19:408–17.
[8] Lacroix I, Damase-Michel C, Lapeyre-Mestre M, et al. Prescription of drugs during pregnancy in France. Lancet 2000;356:1735–6.
[9] Hardy JR, Leaderer BP, Helsford TR, et al. Safety of medications prescribed before and during early pregnancy in a cohort of 81,975 mothers from the UK General Practice Research Database. Pharmacoepidemiol Drug Saf 2006;15:535–64.
[10] Andrade SE, Gurwitz JH, Davis RL, et al. Prescription drug use in pregnancy. Am J Obstet Gynecol 2004;191:398–407.
[11] Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol 2011;205:e1–8.
[12] Palmsten K, Hernandez-Diaz S, Chambers CD, et al. The most commonly dispensed prescription medications among pregnant women enrolled in the US Medicaid Program. Obstet Gynecol 2015;126:465–73.
[13] Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. Fed Regist 2014;79:72063–103.
[14] Ye-Jee K, Joong-Yub L, Nam-Kyung C, et al. Pharmacovigilance system in general hospitals applied for the regional pharmacovigilance center in Korea. J Pharmacoepidemiol Risk Manag 2009;2:89–96.
[15] Olsson S. The role of the WHO Programme on International Drug Monitoring in coordinating worldwide drug safety efforts. Drug Saf 1998;19:1–0.
[16] World Health Organization. Adverse Reactions Terminology (WHO-ART), Geneva, Switzerland: WHO; 2005.
[17] World Health Organization. The Use of the WHO-UMC System for Standardized Case Causality Assessment. Uppsala, Sweden: The Uppsala Monitoring Centre; 2003.
[18] World Health Organization. Anatomical Therapeutic Chemicals (ATC) Classification System. 2013. Available at: https://www.whocc.no/atc_ddd_index/. [accessed January 8, 2018].
[19] Lim JW. The changing trends in live birth statistics in Korea, 1970–2010. Korean J Pediatr 2011;54:429–35.
[20] Callaway LK, Lust K, McIntyre HD. Pregnancy outcomes in women of very advanced maternal age. Aust N Z J Obstet Gynaecol 2005;45:12–6.
[21] Lammimipa R, Vehvilainen-Julkunen K, Gissler M, et al. Preeclampsia complicated by advanced maternal age: a registry-based study on primiparous women in Finland 1997–2008. BMC Pregnancy Childbirth 2012;12:47.
[22] Koo Y-J, Ryu H-M, Yang J-H, et al. Pregnancy outcomes according to increasing maternal age. Taiwan J Obstet Gynecol 2012;51:60–5.
[23] Kenny I, Lavender T, McNamee R, et al. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS One 2013;8:56583.
[24] Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician’s guide to terminology, documentation, and reporting. Ann Intern Med 2004;140:795–801.
[25] Bateman BT, Cole NM, Maeda A, et al. Patterns of opioid prescription and use after cesarean delivery. Obstet Gynecol 2017;130:29–33.
[26] Bateman BT, Hernandez-Diaz S, Rathmell JP, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. Anesthesiology 2014;120:1216–24.
[27] Engelstad A, Beaman JG, Daltveit AK, et al. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004–2006. Br J Clin Pharmacol 2008;65:653–60.
[28] Desai RJ, Hernandez-Diaz S, Bateman BT, et al. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol 2014;123:1097–1102.
[29] Klaman SL, IsaacS K, Leopold A, et al. Treating women who are pregnant and parenting for opioid use disorder and the concurrent care of their infants and children: Literature review to support national guidance. J Addict Med 2017;11:176–90.
[30] Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. Pediatrics 2015;135:842–50.
[31] Practice Bulletin, No. 171Managementof preterm labor. Obstet Gynecol 2016;128:e155–64.
[32] Barry G, Davies M, Godtahar M, et al. Preterm labour: summary of NICE guidance. BJM Clin Res Ed 2015;351:h6283.
[33] Andrade SE, Raela MA, Brown J, et al. Outpatient use of cardiovascular drugs during pregnancy. Pharmacoepidemiol Drug Saf 2008;17:240–7.
[34] Flennady V, Wojcieszek AM, Papatosim NS, et al. Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev 2014;4:CD002255.