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Exposure of Drugs for Hypertension, Diabetes, and Autoimmune Disease During Pregnancy and Perinatal Outcomes

An Investigation of the Regulator in Japan

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Abstract: Assessment of perinatal effects of drug exposure during pregnancy after approval is an important issue for regulatory agencies. The study aimed to explore associations between perinatal outcomes and maternal exposure to drugs for chronic diseases, including hypertension, diabetes, and autoimmune disease.

We reviewed 521 cases of adverse reactions due to drug exposure during pregnancy who were reported to the Pharmaceuticals and Medical Devices Agency, a regulatory authority in Japan. The primary outcomes were fetal and neonatal death and malformation of infants. Associations between perinatal outcomes and exposure to each drug category for hypertension, diabetes, and autoimmune disease were evaluated using logistic regression analysis.

Of the 521 cases (maternal age: 15–47 years; mean 32.3 ± 5.5), fetal and neonatal deaths were reported in 159 cases (130 miscarriage; 12 stillbirth; 4, neonatal death; and 13 abortion due to medical reasons), and malformations of infants were observed in 124 cases. In contrast to the trend of association between diabetes with or without medication and fetal and neonatal death (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.17–1.36), exposure to oral antidiabetics tended to be associated with fetal and neonatal death (OR, 4.86; 95% CI, 0.81–29.2). Malformation tended to be correlated with exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (OR, 2.98; 95% CI, 0.76–11.7). This association showed trends opposite to that of the association with hypertension itself (OR, 0.42; 95% CI, 0.18–1.02) or overall antihypertensives (OR, 0.42; 95% CI, 0.15–1.13). Occurrence of multiple malformations was associated with exposure to biologics (OR, 8.46; 95% CI, 1.40–51.1), whereas there was no significant association between multiple malformations and autoimmune disease with or without medication (OR 1.07; 95% CI, 0.37–3.06).

These findings suggest that drugs of different categories may have undesirable effects when used during pregnancy. However, the regulatory database was not originally designed to evaluate the causal associations between drug exposure and adverse drug reactions. The limitations of spontaneous reporting systems should be carefully taken into account. Further studies are needed to elucidate the effects of individual drugs in each category on perinatal outcomes.

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Abbreviations: ACE-I = angiotensin-converting enzyme inhibitors, ADR = adverse drug reaction, ARB = angiotensin receptor blockers, LBW = low birth weight, MHLW = Ministry of Health, Labor, and Welfare, PMDA = Pharmaceuticals and Medical Devices Agency, SGA = small for gestational age.

INTRODUCTION

Administering drugs to pregnant women is generally only allowed when it is determined that the benefits outweigh the potential harm, and some drugs are, in principle, prohibited during pregnancy because of risks to the maternal-infant safety. However, many drugs are often administered during pregnancy for various reasons,[1,2] especially for chronic diseases such as hypertension, diabetes, and autoimmune disease, as these diseases require long-term or, in some cases, lifetime medication. Moreover, medication for these diseases is often required during pregnancy because inadequate disease control may adversely affect the perinatal outcomes.[3,4] Therefore, the manner in which drug administration for chronic diseases during pregnancy affects perinatal outcomes, including fetal and neonatal death or malformation of infants, is a clinically important issue for both mothers and infants.

Data of various clinical trials are submitted to a regulatory agency as review materials at the time of application for drug approval. In these trials, the safety in pregnant women is never evaluated by actually administering the drugs to pregnant women. Moreover, reminders on package inserts for pregnant women are mainly based on the results of nonclinical studies. When a drug is approved and released to the market for the first time, there are still many unclear points regarding the safety of

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administering the drug to pregnant women. In monitoring highly specialized medications associated with significant financial costs, clinical patient registries established in some countries may be potentially useful components of postmarketing safety assessments.[5] However, it is difficult to establish clinical registry systems of pregnant women with common diseases, and in many countries including Japan, clinical patient registries have not been fully developed yet. For these reasons, it is vital to perform postmarketing safety assessments of the regulatory data to identify any signs of potential adverse drug reactions (ADRs) in pregnant women and infants. In that respect, national regulatory authorities such as the Food and Drug Administration and European Medicines Agency play important roles, as they can aggregate and analyze the latest nationwide information. In particular, the mutual exchange of information among the regulatory authorities will ensure an even higher level of safety. Furthermore, if risks associated with a certain drug are determined through international collaboration, this information may be useful in the future review of similar new drugs in the same category.[6]

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) was established as a regulatory agency in 2004. The Japanese pharmaceutical affairs law requires companies to report ADRs that occur during postmarketing, and the PMDA collectively manages and evaluates this information. These reports are recorded in the PMDA safety information database. In this study, using this regulatory database, we reviewed the reports of perinatal ADRs associated with drug administration during pregnancy. Furthermore, as an exploratory analysis, we evaluated the associations between perinatal outcomes and exposure to the following different drug categories for chronic diseases whose maternal use during pregnancy is clinically problematic: antihypertensives (in particular, angiotensin-converting enzyme inhibitor [ACE-I] and angiotensin receptor blocker [ARB]),[7] oral antidiabetics,[8] and drugs for autoimmune diseases (in particular, biologics).[9,10] It has been reported that perinatal outcomes, including fetal and neonatal death[11–13] and malformation,[13,14] are also affected by maternal age. Therefore, we moreover explored the associations between maternal age and perinatal outcomes.

METHODS

ADR Reporting System of the PMDA

Information regarding ADRs is electronically reported in a format specified in the E2B guideline agreed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and recorded in a database of the PMDA. The reported drugs include commercialized prescription drugs; biological products, such as vaccines; and over-the-counter drugs. Adverse reactions reported from preapproval or postapproval clinical trials are not included, as these belong to another database category. ADRs are reported by the drug manufacturers or medical institutions after personal identifiers are removed. The PMDA evaluates the potential causal relationships of the suspected drugs and those reports, and then orders the companies to respond accordingly. Of the reported ADRs, those in which maternal drug exposure is confirmed are registered in the perinatal category. The reported ADRs in this category are overall adverse reactions, which also include reactions other than obstetric events. The available data include maternal age, height, weight, underlying diseases, and all drugs that were confirmed to have been administered to the mother during pregnancy, including suspected drugs. The type of ADRs observed in the mother and infant, progress of reaction, and the opinions/further responses of the attending physician and company are also recorded. ADRs are classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Progress reports include data on perinatal outcomes such as miscarriage, stillbirth, neonatal death, malformation, cesarean section, multiple pregnancy, sex of infants, birth weight, gestational age at birth, and Apgar score at birth. In some cases, time courses of laboratory data are also attached.

Study Population

Of the regulatory data reported to the PMDA from January 2012 to October 2013, cases of adverse reactions due to perinatal drug exposure were identified. Individuals who experienced any kind of ADRs due to drug exposure during pregnancy were extracted and reviewed by the PMDA medical officers. Multiple reports of the same ADR were considered as one case, and the latest report was used for the analysis. Reports involving implausible clinical data, reports from overseas, or reports of abortion performed due to nonmedical reasons were excluded. The analyzed variables included maternal age, height, body weight, body mass index (BMI), and underlying disease. In the present study, common underlying diseases in the case reports were classified according to International Classification of Disease (ICD)-10 codes (Table 1). Information regarding not only suspected drugs, but also all drugs that were reportedly administered to the mothers during pregnancy were extracted. The drugs most frequently reported to the PMDA were categorized according to the World Health Organization Anatomical Therapeutic Chemical classification (Table 1). The present study was reviewed and approved by the institutional review board.

Outcomes and Statistical Analysis

Perinatal outcomes were descriptively analyzed using the database of perinatal ADR reports. The primary outcomes were fetal and neonatal death (miscarriage, stillbirth, neonatal death, and abortion due to medical reasons) and malformation of infants. As the secondary outcomes, the components of fetal and neonatal deaths (miscarriage/ stillbirth + neonatal death), cesarean section, low birth weight (LBW; birth weight <2500 g), preterm birth (<37 weeks), small for gestational age (SGA), multiple pregnancy, sex of infants (female), multiple malformations, and Apgar scores <7 at 5 minutes were also evaluated. In accordance with the definition of the Japan Society of Obstetrics and Gynecology, pregnancy discontinuations before and after 22 weeks of gestation were defined as miscarriage and stillbirth, respectively. Diseases belonging to Q00-Q99 in the ICD-10 codes were defined as malformation of infants. When different kinds of malformations were observed in an infant, it was defined as multiple malformations. The SGA status was determined according to standards developed by a study group of the Ministry of Health, Labor, and Welfare (MHLW) in Japan to be a birth weight below the 10th percentile for the gestational age.[15]

As exploratory analyses, associations between each outcome and drug exposure were analyzed. The associations between drug exposure and perinatal outcomes were evaluated using the case/non-case methodology.[16–18] This approach is widely used for disproportionality analysis of certain ADRs in

TABLE 1. Disease Categories According to the ICD-10 Codes and Drug Categories According to the ATC classification

Category	ICD-10 Codes / ATC Classification
Disease	
Hypertension	I10-I15
Heart disease	I05-I09, I20-I25, I30-I52
Diabetes	E10-E14
Endocrine disease	C73-C75; D34, D35, D44; E00-E07, E20-E35
Autoimmune disease	D59.0, D59.1, D69.3; E05.0, E06.3, E10, E27.1, E27.2, E31.0; G61, G63.5, G70; J99; K50, K51, K74.3, K75.4; L93, L94; M05-M09, M30-M36; N01, N08.5, N16.4
Asthma	J45, J46
Epilepsy	G40, G41
Mental disorder	F20-F48, F50-F99; G47
Hematological disease	C81-C96; D45-D47, D50-D77
Gynecological disease	C51-C58; D25-D28; E28; N70-N77, N80-N98
Renal disease	N00-N08, N10-N23, N25-N29
Neoplastic disease	C00-C26, C30-C41, C43-C58, C60-C97; D00-48
Drug	
Antihypertensives	C02
ACE-I and ARB	C09A, C09B, C09C, C09D
Oral antidiabetics	A10B
Corticosteroids	H02A, H02B
Biologics*	L04AA24, L04AB, L04AC07
Other immunosuppressants†	L01AA01, L04AA06, L04AA13, L04AD01, L04AD02, L04AX01, L04AX03
Psychotropic drugs‡	N05, N06
Antiepileptic drugs	N03
NSAIDs	M01A, M02A, N02BA
Antithyroid drugs	H03B
Female hormone-related drugs	G03C, G03D, G03E, G03F, G03G
Antiallergic drugs	R03DC, R06
Warfarin	B01AA03
Vaccines	J07

ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, ATC = Anatomical Therapeutic Chemical, ICD = International Classification of Disease, NSAIDs = non-steroidal anti-inflammatory drugs.

* Human monoclonal antibodies and Fc fusion proteins for the treatment of autoimmune diseases, such as infliximab, etanercept, tocilizumab, adalimumab, abatacept, golimumab, and certolizumab pegol, which have all been approved in Japan as of October 2013.

† Immunosuppressants other than corticosteroids/biologics, such as cyclophosphamide, mycophenolic acid, leflunomide, cyclosporine, tacrolimus, azathioprine, and methotrexate.

‡ Antipsychotic, antianxiety, and hypnotic drugs.

the pharmacovigilance database. Cases were defined as reports of a certain perinatal outcome, whereas non-cases were defined as reports of all other ADRs in the perinatal period. With regard to fetal and neonatal deaths and miscarriages, the groups with and without the events among all the reported cases were compared. With regard to the other outcomes, the group with a certain outcome and all cases with outcomes other than that particular outcome were compared in the reported cases in which the pregnancy continued after 22 weeks (i.e., the groups without miscarriage or abortion due to medical reasons) (Figure 1). Logistic regression analyses, adjusted for maternal age and BMI, were performed to evaluate the associations between drug exposure and perinatal outcomes. The same model, including maternal age and BMI as adjustment factors, was also used to evaluate the associations between maternal underlying diseases and perinatal outcomes. Associations between maternal age ($\leq$29 vs 30–34 years and $\geq$35 years) and perinatal outcomes were evaluated using logistic regression analyses adjusted for BMI. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC, USA), and the level of significance was set as $P < 0.05$.

RESULTS

Descriptive Data

During the study period, a total of 710 reports were identified as reports of ADRs due to perinatal drug exposure. Of these, 521 reports were included in the analysis of the present study (Figure 1). Table 2 shows the descriptive data concerning the maternal clinical characteristics. The maternal age ranged from 15 to 47 years, and the mean age was 32.3 ± 5.5 years. With regard to maternal underlying diseases, the most common disease category was autoimmune disease (123 cases in total; 80, 11, 11, and 4 cases of autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, respectively), followed by 96 cases of endocrine disease, 96 cases of gynecological disease, and 90 cases of mental disorder.

Table 3 shows the descriptive data of drug exposure and perinatal outcomes. The drug category with the most commonly reported exposure was female hormone-related drugs (99 cases). Other drug categories with perinatal exposure reports of 50 cases or more included psychotropic drugs (90 cases), antithyroid drugs (75 cases), corticosteroids (66 cases), and

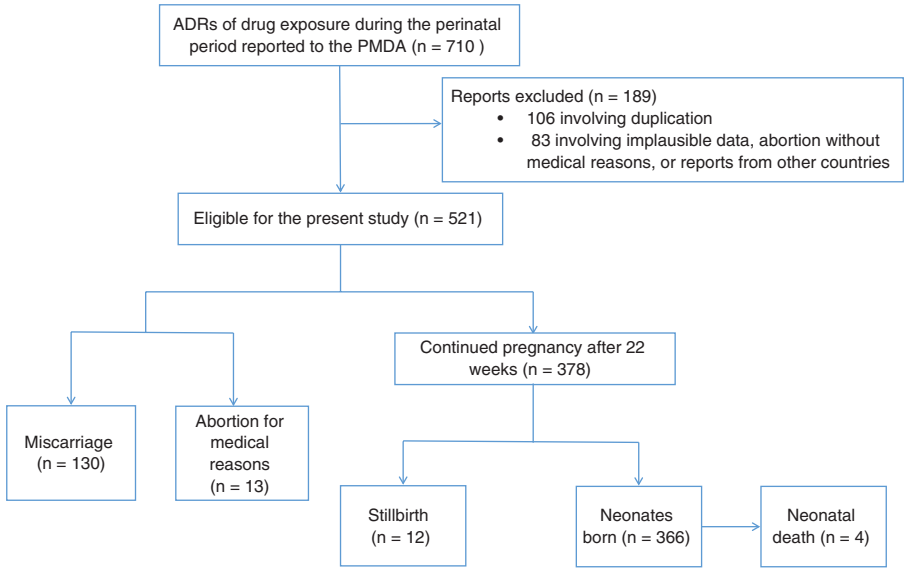

FIGURE 1. Study flow.

antiepileptic drugs (55 cases). The outcome that was most frequently reported was cesarean section (31%), followed by fetal and neonatal death (30.5%), miscarriage (25.0%), malformation (23.4%), preterm birth (22.5%), and LBW (20.3%). The mean birth weight of the infants fell below the LBW threshold (2500 g), and the mean gestational age also fell below the preterm birth threshold (<37 weeks). Of the primary outcomes, the drug categories wherein fetal and neonatal deaths accounted for 30% or more of all ADR reports were female hormone-related drugs (79/99 cases; 79.8%), oral antidiabetics (4/6 cases; 66.7%), antiallergic drugs (10/16 cases; 62.5%), warfarin (4/7 cases; 57.1%), non-steroidal anti-inflammatory drugs (NSAIDs) (10/21 cases; 47.6%), biologics (7/15 cases; 46.7%), vaccines (4/9 cases; 44.4%), ACE-I/ARB (5/14 cases; 35.7%), and corticosteroids (20/66 cases; 30.3%). Drug categories wherein malformation (as the other primary outcome) accounted for 15% or more of all ADR reports were antithyroid drugs (64/75 cases; 85.3%), antiepileptic drugs (20/55 cases; 36.4%), ACE-I/ARB (5/14 cases; 35.7%), oral antidiabetics (2/6 cases; 33.3%), and psychotropic drugs (16/90 cases; 17.8%). The organ-based reporting frequency of malformation was the highest for the cardiovascular system (42/122 cases, 34.4% of all malformations), followed by the central nervous system (31/122 cases, 25.4%) and digestive system (30/

TABLE 2. Maternal Clinical Characteristics

	Maternal Age			
Variables	**≤29 Years (n = 129)**	**30–34 Years (n = 138)**	**≥35 Years (n = 135)**	**Total* (n = 521)**
Height, cm	157.4 ± 4.9	158.9 ± 7.7	158.1 ± 5.2	158.2 ± 6.1
Body weight, kg	55.4 ± 10.8	56.5 ± 9.9	57.4 ± 12.4	56.6 ± 11.1
Body mass index	22.4 ± 4.3	22.5 ± 3.7	22.7 ± 4.0	22.5 ± 4.0
Preexisting disease				
Hypertension	15 (11.6)	11 (8.0)	22 (16.3)	54 (10.4)
Diabetes	5 (3.9)	7 (5.1)	9 (6.7)	25 (4.8)
Autoimmune disease	30 (23.3)	25 (18.1)	30 (22.2)	123 (23.6)
Others				
Gynecological disease	11 (8.5)	38 (27.5)	41 (30.4)	96 (18.4)
Endocrine disease	18 (14.0)	24 (17.4)	19 (14.1)	96 (18.4)
Mental disorder	32 (24.8)	19 (13.8)	16 (11.9)	90 (17.3)
Epilepsy	19 (14.7)	8 (5.8)	5 (3.7)	44 (8.4)
Hematological disease	10 (7.2)	7 (5.1)	7 (5.2)	38 (7.3)
Renal disease	11 (8.5)	7 (5.1)	10 (7.4)	31 (6.0)
Neoplastic disease	1 (0.8)	4 (2.9)	8 (5.9)	15 (2.9)
Asthma	7 (5.4)	1 (0.7)	5 (3.7)	14 (2.7)
Heart disease	5 (3.9)	3 (2.2)	4 (3.0)	12 (2.3)

The values are presented as mean ± standard deviation, or as n (%).
* Including cases whose age was not reported.

TABLE 3. Drug Exposure and Perinatal Outcomes

Variables	Maternal age			
	≤29 Years (n = 129)	30-34 Years (n = 138)	≥35 Years (n = 135)	Total* (n = 521)
Drug exposure				
Antihypertensives	11 (8.5)	9 (6.5)	23 (17.0)	46 (9.5)
ACE-I/ARB	2 (1.6)	3 (2.2)	6 (4.4)	14 (3.0)
Oral antidiabetics	2 (1.6)	1 (0.7)	3 (2.2)	6 (1.3)
Drugs for autoimmune disease				
Corticosteroids	28 (21.7)	15 (10.9)	18 (13.3)	66 (13.9)
Immunosuppressants	12 (9.3)	7 (5.1)	14 (10.4)	36 (7.6)
Biologics	3 (2.3)	4 (2.9)	7 (5.2)	15 (3.2)
Other drug categories				
Female hormone-related drugs	16 (12.4)	37 (26.8)	39 (28.9)	99 (20.9)
Psychotropic drugs	33 (25.6)	18 (13.0)	15 (11.1)	90 (18.7)
Antithyroid drugs	12 (9.3)	17 (12.3)	12 (8.9)	75 (14.9)
Antiepileptic drugs	23 (17.8)	10 (7.2)	10 (7.4)	55 (11.6)
NSAIDs	4 (3.1)	11 (8.0)	5 (3.7)	21 (4.4)
Antiallergic drugs	6 (4.7)	3 (2.2)	6 (4.4)	16 (3.4)
Vaccine	2 (1.6)	2 (1.4)	1 (0.7)	9 (1.9)
Warfarin	5 (3.9)	2 (1.4)	0 (0.0)	7 (1.5)
Perinatal outcomes				
Fetal and neonatal death	32 (24.8)	52 (37.7)	57 (42.2)	159 (30.5)
Miscarriage	22 (17.1)	46 (33.3)	46 (34.1)	130 (25.0)
Stillbirth	0 (0.0)	5 (3.6)	5 (3.7)	12 (2.3)
Neonatal death	2 (1.6)	0 (0.0)	2 (1.5)	4 (0.8)
Abortion for medical reasons	8 (6.2)	1 (0.7)	4 (3.0)	13 (2.5)
Cesarean section	52 (40.3)	37 (26.8)	53 (39.3)	162 (31.1)
Multiple pregnancy	6 (4.7)	12 (8.7)	11 (8.1)	34 (6.5)
Sex of infants (male/female)	40/34	27/24	18/31	101/103
Birth weight, g	2394 ± 722	2338 ± 842	2287 ± 814	2441 ± 782
Low birth weight (<2500 g)	33 (25.6)	28 (20.3)	31 (23.0)	106 (20.3)
Very low birth weight (<1500 g)	11 (8.5)	11 (8.0)	11 (8.1)	35 (6.7)
Gestational age, weeks	35.9 ± 3.5	35.5 ± 4.2	34.6 ± 4.5	35.7 ± 4.0
Preterm birth	35 (27.1)	31 (22.5)	37 (27.4)	117 (22.5)
Small for gestational age	16 (12.4)	12 (8.7)	13 (9.6)	45 (8.6)
Apgar score <7 at 5 min	12 (9.3)	10 (7.2)	7 (5.2)	43 (8.2)
Malformation	25 (19.4)	30 (21.7)	17 (12.6)	122 (23.4)
Multiple malformations	8 (6.2)	2 (1.4)	4 (3.0)	20 (3.8)
Cardiovascular	7 (5.4)	2 (1.4)	5 (3.7)	42 (8.1)
Cephalofacial	13 (10.1)	8 (5.8)	4 (3.0)	31 (6.0)
Aplasia cutis congenita	4 (3.1)	6 (4.4)	2 (1.5)	13 (2.5)
Cleft lip and palate	4 (3.1)	1 (0.7)	0 (0.0)	6 (1.2)
Digestive	7 (5.4)	11 (8.0)	6 (4.4)	30 (5.8)
Limb	3 (2.3)	3 (2.2)	5 (3.7)	18 (3.5)
Genitourinary	1 (0.8)	3 (2.2)	0 (0.0)	8 (1.5)
Neural	2 (1.6)	2 (1.4)	2 (1.5)	6 (1.2)

The values are presented as mean ± standard deviation, or as n (%). ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, NSAIDs = non-steroidal anti-inflammatory drugs.
* Including cases whose age was not reported.

122cases, 24.6%). Six cases of chromosomal abnormalities in infants were reported, including translocation of the sex-determining region Y gene on the Y chromosome (n = 1), partial deletion of chromosome 15q (n = 1), abnormality of chromosome 12p (n = 1), trisomy 18 (n = 1), and trisomy 21 (n = 2). The mean maternal age of the cases with chromosomal abnormalities was 35.3 ± 4.8 years, and the drug categories used in those reports were psychotropic drugs (n = 2), female hormone-related drugs (n = 2), NSAIDs (n = 1), antithyroid drugs (n = 1), and vaccines (n = 1).

Maternal Drug Exposure and Perinatal Outcomes

Figure 2 presents the odds ratios (ORs) of perinatal outcomes for antihypertensive, oral antidiabetic, and autoimmune disease drugs. For antihypertensives (Figure 2A), the exposed group showed significant decreases in the ORs of fetal and neonatal death compared with the unexposed group (OR, 0.34; 95% confidence interval [CI], 0.15–0.79). The proportion of malformation also tended to be lower in the exposed group (OR, 0.42; 95% CI, 0.15–1.13). However, the ORs of outcomes such

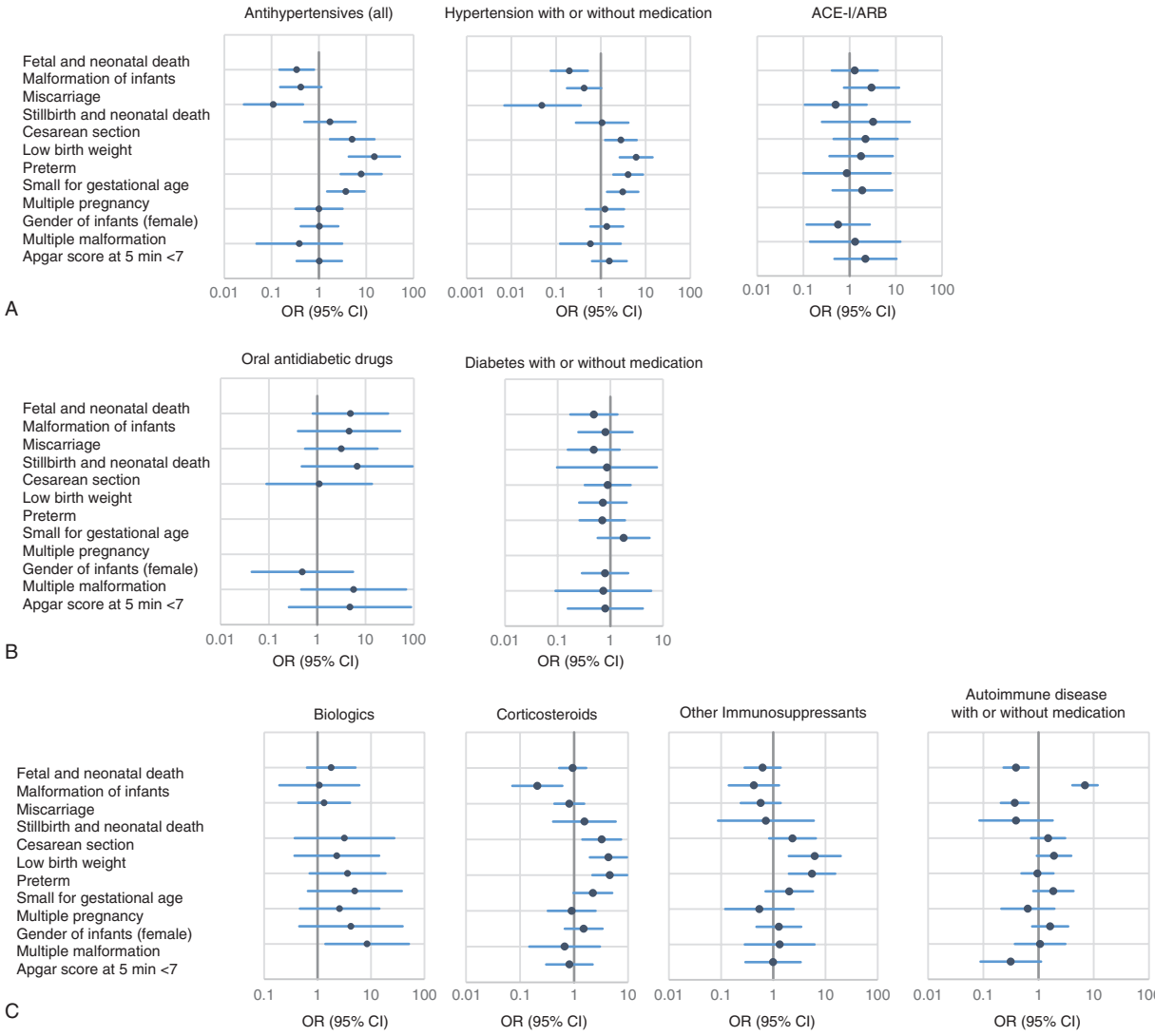

FIGURE 2. Odds ratios of perinatal outcomes according to antihypertensive, oral antidiabetic, and autoimmune disease drug use. (A) Association between perinatal outcomes and all antihypertensives, hypertension with or without medication, or angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB). Multiple pregnancy was not observed in cases exposed to ACE-I/ARB, and thus, the odds ratio (OR) was not calculated. (B) Associations between perinatal outcomes and oral antidiabetics or diabetes with or without medication. Low birth weight, preterm birth, small for gestational age, and multiple pregnancy were not observed in cases exposed to oral antidiabetics. Multiple pregnancy was not observed in cases of diabetes with or without medication. (C) Associations between perinatal outcomes and biologics, corticosteroids, other immunosuppressants, or autoimmune disease with or without medication. Biologics included infliximab, etanercept, tocilizumab, adalimumab, abatacept, golimumab, and certolizumab pegol, which have all been approved in Japan as of October 2013. Other immunosuppressants were defined as drugs other than biologics or corticosteroids among immunosuppressants approved in Japan. Stillbirths and neonatal deaths and Apgar scores at 5 min <7 were not observed in cases exposed to biologics.

as cesarean section (OR, 5.06; 95% CI, 1.71–14.9), LBW (OR, 14.9; 95% CI, 4.28–51.8), preterm birth (OR, 7.83; 95% CI, 2.88–21.3), and SGA (OR, 3.72; 95% CI, 1.50–9.26) were significantly higher in the antihypertensives-exposed group compared with the unexposed group. When cases of maternal hypertension and nonmaternal hypertension were compared, regardless of antihypertensive exposure, the association between hypertension and the outcomes was similar to that observed for antihypertensive exposure. When limited to only ACE-I/ARB among the antihypertensives, the proportion of malformation tended to be greater in the drug-exposed group (OR, 2.98; 95% CI, 0.76–11.7), whereas the opposite trends were observed for the overall antihypertensives (OR, 0.42; 95% CI, 0.15–1.13) and hypertension itself (OR, 0.42; 95% CI, 0.18–1.02), regardless of drug exposure.

For oral antidiabetics (Figure 2B), the OR of fetal and neonatal death showed an increasing trend in the exposed group (OR, 4.86; 95% CI, 0.81–29.2). However, regardless of exposure to oral antidiabetics, the OR of fetal and neonatal death showed a decreasing trend in mothers with diabetes (OR, 0.49; 95% CI, 0.17–1.36). Diabetes and hypertension frequently occur together, and drugs for both diseases may hence

be administered simultaneously. Accordingly, we next investigated the changes in the OR of perinatal outcomes due to combination therapy of antihypertensives and oral diabetics, as well as drug combinations of ACE-I/ARB. However, no significant increases in the ORs owing to those combinations were observed (data not shown).

Figure 2C shows the associations between exposure to autoimmune disease drugs and perinatal outcomes. Biologics exposure showed no significant association with the risk of fetal and neonatal death or malformation. However, a significant increase was observed in the OR of multiple malformations (OR, 8.46; 95% CI, 1.40–51.1). In contrast, no significant increases were observed in the ORs of multiple malformations due to exposure to corticosteroids (OR, 0.67; 95% CI, 0.15–3.01) and other immunosuppressants (OR, 1.32; 95% CI, 0.29–6.15) or the presence of autoimmune disease (OR 1.07; 95% CI, 0.37–3.06). As these drug categories are commonly used in combination to treat autoimmune diseases, we next investigated the potential OR changes due to combination therapies. However, no specific combinations showed increases in the ORs of different perinatal outcomes (data not shown). It should be noted that autoimmune disease itself was associated with an increased OR of malformation (OR, 6.95; 95% CI, 4.10–11.8); however, this association showed a trend opposite to that for exposure to corticosteroids and other immunosuppressants. The increased OR of malformation in the category of autoimmune disease may be due to inclusion of cases of Graves disease treated with antithyroid drugs, which are known to be associated with congenital malformation of infants. Therefore, cases treated with antithyroid drugs were excluded to reevaluate the association between autoimmune disease and malformation. As a result, no significant increase in the OR was observed (OR, 1.40; 95% CI, 0.48–4.09).

Exploratory Analyses on the Association Between Maternal Age and Perinatal Outcomes

Table 4 shows the associations between maternal age ($\leq$29 vs 30–34 and $\geq$35 years) and perinatal outcomes evaluated by logistic regression analyses adjusted for BMI. Significant increases in the ORs of fetal and neonatal death, miscarriage, and cesarean section were observed in women aged $\geq$35 years, compared with those aged $\leq$ 29 years. Similar trends were observed for the risk of stillbirth and neonatal death, multiple pregnancy, and female birth rate, although these were not significant. Moreover, significant increases were seen in the ORs of malformation and Apgar score $<$7 at 5 minutes in women aged 30 to 34 years, compared with those aged $\leq$ 29 years. Similar trends were observed for the risk of miscarriage and multiple pregnancy, although these were not significant.

TABLE 4. Associations Between Perinatal Outcomes and Maternal Age Evaluated by Logistic Regression Analysis

Outcomes	Age Category	OR (95% CI)*
Fetal and neonatal death†	≥35	2.24 (1.32–3.80)
	30–34	1.14 (0.670–1.85)
	≤29	1.00 [Reference]
Malformation	≥35	0.84 (0.41–1.72)
	30–34	2.50 (1.41–4.29)
	≤29	1.00
Miscarriage	≥35	2.60 (1.44–4.68)
	30–34	1.59 (0.92–2.75)
	≤29	1.00
Stillbirth and neonatal death	≥35	4.21 (0.85–20.9)
	30–34	1.81 (0.37–8.91)
	≤29	1.00
Cesarean section	≥35	2.61 (1.23–5.51)
	30–34	0.69 (0.39–1.23)
	≤29	1.00
Low birth weight	≥35	1.44 (0.72–2.84)
	30–34	0.83 (0.46–1.51)
	≤29	1.00
Preterm birth	≥35	1.61 (0.83–3.13)
	30–34	0.99 (0.55–1.78)
	≤29	1.00
Small for gestational age	≥35	0.98 (0.42–2.27)
	30–34	0.72 (0.33–1.56)
	≤29	1.00
Multiple pregnancy	≥35	2.58 (0.90–7.38)
	30–34	2.55 (0.96–6.80)
	≤29	1.00
Sex of infants (female)	≥35	2.00 (0.96–4.20)
	30–34	1.03 (0.55–1.94)
	≤29	1.00
Multiple malformation	≥35	0.63 (0.18–2.18)
	30–34	0.67 (0.24–1.88)
	≤29	1.00
Apgar score <7 at 5 min	≥35	0.77 (0.28–2.15)
	30–34	2.39 (1.01–5.40)
	≤29	1.00

CI = confidence interval; OR = odds ratio.
* Each OR was adjusted by maternal body mass index.
† Miscarriage, stillbirth, neonatal death, and abortion due to medical reasons.

DISCUSSION

The present study, which analyzed the Japanese regulatory database of ADRs in terms of perinatal drug exposure, was a relatively large-scale study. We here revealed detailed information on the perinatal outcomes associated with drug administration for chronic disease during pregnancy. In this database review, the primary outcome of fetal and neonatal death was one of the most frequently reported perinatal outcomes (30.5%). The other primary outcome, malformation, was observed in 23.4% of cases, which is a seemingly high proportion. This finding may be because clinicians tend to associate malformations with prescriptions during pregnancy. Among the secondary outcomes, cesarean section was performed in 31.1% of all analyzed reports. In contrast, according to the health statistics of the MHLW of Japan,[19] cesarean section is performed on only 23.3% of pregnant women in the general population. Moreover, the mean birth weight was 2441 g and the proportion of LBW ($<$2500 g) was 20.3% in the present study, whereas the mean birth weight was 3020 g, and the proportion of LBW was 8.3% in the birth statistics from the MHLW.[20] These results indicate that the frequencies of cesarean section and LBW are higher in cases registered in the perinatal adverse reaction database than in the general population.

The present study indicated that the use of drug categories such as oral antidiabetics, ACE-I/ARB, and biologics during pregnancy may have undesirable effects on perinatal outcomes. Exposure to antihypertensives was associated with increases in the ORs of outcomes such as cesarean section, LBW, preterm birth, and SGA. However, the same result was obtained for the

presence of hypertension itself with or without drug exposure, indicating that drug exposure may not necessarily contribute to the increases in ORs. In fact, when a mother has hypertension, cesarean section is often chosen to avoid perinatal problems, and it has also been previously reported that LBW and preterm birth often occur in these women.[21] However, exposure to ACE-I/ARB tended to be associated with increases in the OR of malformation. This result was opposite to the trends observed for the overall antihypertensives and for hypertension itself. Therefore, we believe that this result supports the theory of teratogenic potential of ACE-I/ARB.[7] Exposure to oral antidiabetics tended to be associated with an increased risk of fetal and neonatal deaths, and this result was opposite to the trend observed for diabetes itself. With regard to the other outcomes, including malformation, the trend observed for exposure to oral antidiabetics was opposite to that of diabetes itself, although the width of the confidence interval was wide because of the low number of reports. At present, the safety of oral antidiabetic treatment during pregnancy is controversial, and insulin treatment is recommended, in principle.[8] The results of the present study appear to be largely consistent with the current recommendation. Among the oral antidiabetics, a previous study reported that metformin is not associated with any major problems when administered for gestational diabetes,[22] and further studies are needed to confirm this finding. The safety of drugs used during pregnancy to treat autoimmune diseases, biologics in particular, is not yet conclusive.[9,10] In this study, when the association between autoimmune disease itself and perinatal outcomes was compared with the association between biologics and perinatal outcomes, the OR point estimates of the biologics appeared to be more unfavorable. However, the width of the CI was wide because of the limited number of reports on the use of biologics, and only multiple malformations showed a significant difference.

We also performed exploratory analyses on the effects of maternal age. Compared with maternal age of $\leq$29 years, women aged 30 to 34 years and $\geq$35 years showed increased risks of various perinatal outcomes. These results are largely consistent with those of previous reports.[11–14] Interestingly, women aged $\geq$35 years showed a tendency to give birth to a higher proportion of female than male infants. Conversely, a previous large-scale epidemiological study reported that maternal age had no effect on the infant's sex.[23,24] However, one report concluded that female infants tended to be born more often when the father is older, compared with when the father is aged 25 to 29 years.[24] It is expected that, in general, when the mother is older, the father is older as well, which may have had a confounding effect on the results of the present study.

Our study has some limitations. First, the regulatory database was not originally designed to evaluate the causal associations between drug exposure and ADRs. The interpretations of the associations between drug exposure and perinatal outcomes require careful consideration of the effects of various forms of bias and confounding. The ADR reporting frequency is especially affected by the time when the drug product is released (Weber effect). If the drug has been newly brought to the market, ADRs may be more frequently reported. Additionally, this study was performed in Japan, which has the homogeneous East Asian population. Further studies are needed to generalize our findings. In the present study, maternal age and physique are also major confounders. A recent study reported that logistic regression analysis is more desirable as a method of signal detection than the traditional disproportional analysis.[25] Therefore, we evaluated the associations between drug exposure and perinatal outcomes by logistic regression, and included maternal age and BMI as adjustment factors. This method enabled controlling confounders to some degree. Furthermore, regarding the associations between drug exposure and perinatal outcomes, it is difficult to completely exclude the effects of maternal underlying diseases that necessitate the administration of a certain drug on the perinatal outcomes. Taking this problem into consideration, we presented both ORs in parallel in Figure 2 to compare the trends. This approach enabled us to more easily evaluate the effects of the investigated drugs on the perinatal outcomes.

CONCLUSION AND FUTURE PERSPECTIVE

The findings suggest that drugs of different categories such as oral antidiabetics, ACE-I/ARB, and biologics are likely to have undesirable effects when used during pregnancy. However, the limitations of the spontaneous reporting systems should be carefully taken into account. Further studies are needed to elucidate the effects of individual drugs in each category on perinatal outcomes. Additionally, to increase the safety of pregnant women and infants, health care providers are required to quickly and accurately report all ADRs potentially associated with drug exposure during pregnancy. The PMDA is currently establishing a new electrical ADR database system, which shall enable the use of clinical information held in medical institutions. Future studies may focus on developing an electronic linkage between the regulatory database and clinical information, to perform more detailed postmarketing research.

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