

Pregnancy outcomes after inadvertent exposure of anti-obesity drugs during pregnancy

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Backgrounds: To improve health, an increasing number of adults are attempting to lose weight. Moreover, the number of childbearing women targeting weight loss has increased, with a surge in pregnant women exposed to anti-obesity drugs. This study aimed to evaluate the ingredients, types, and trends of anti-obesity drugs and pregnancy outcomes among the exposures of anti-obesity drugs. Additionally, we reviewed their teratogenicity in literature. **Methods:** We performed a prospective cohort study and recruited pregnant women exposed to anti-obesity drugs in the Motherisk Database, from 2012 to 2018. We determined the frequency and type of anti-obesity drugs used. Furthermore, we compared the annual change in the frequency of anti-obesity drugs with that of total pregnancies. Overall, 30,704 pregnant women were enrolled during the study period. **Results:** The rate of pregnant women exposed to anti-obesity drugs was 4.8% (1487/30,704). The rate of pregnant women exposed to anti-obesity drugs significantly increased from 3.7% in 2012 to 7.4% in 2018 ($p < 0.001$). The most frequently used drugs were phentermine (33.0%) and phendimetrazine (25.9%). The number of pregnant women exposed to anti-obesity drugs has recently increased. There is no difference in pregnancy outcomes between the exposure and the un-exposure of anti-obesity drug except that birth weight and large for gestational age are significantly larger in the exposure group. Additionally, there are no difference of abnormalities between the exposure (3.1%) and the un-exposure of anti-obesity drugs (3.7%). **Discussion:** This study showed that the exposure of anti-obesity drug profoundly increased during the study period and there exist known teratogenic drugs. Therefore, childbearing women should be concerned with preventing teratogenic effects following anti-obesity drug exposure during pregnancy. Physicians should warn childbearing women about potential dangers of anti-obesity drug.

Keywords

Pregnancy; Anti-obesity drugs; Teratogen; Obesity; Overweight

1. Introduction

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health [1]. The World Health Organization has formally recognized obesity as a global epidemic [2], and as of 2008, it estimated that 650 million adults (greater than 10%) were obese, with higher rates among women than men [1]. Obesity in-

creases the likelihood of various diseases and conditions, particularly cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer, osteoarthritis, and depression [3, 4]. Furthermore, obese pregnant women are at an increased risk for maternal and perinatal complications, and the risks are amplified with increasing degrees of maternal obesity [5–7]. It has been estimated that one-quarter of pregnancy-related complications (e.g., gestational hypertension, preeclampsia, gestational diabetes, preterm birth) possibly occur due to maternal overweight/obesity, and almost one-third of large for gestational age infants are attributable to excessive gestational weight gain in pregnancy [7].

The prevalence of obesity and associated diseases is rapidly increasing among Korean adults [8]. The Korean Ministry of Food and Drug Safety has approved several anti-obesity drugs in the past decade, including phentermine, phendimetrazine, diethylpropion, mazindol, orlistat, lorcaserin, naltrexone/bupropion, liraglutide, and phentermine/topiramate [9]. In Korea, the rate of unintended pregnancy is 48%. A relative risk of inadvertent maternal medication exposure is 3.0 (95% CI, 2.0–4.5) in unintended pregnancy compared with that of intended pregnancy [10]. Therefore, some pregnant women are inadvertently exposed to anti-obesity drugs due to unintended pregnancies. Some drugs are known or potential teratogens. Therefore, we aimed to evaluate the ingredients, types, and trends of anti-obesity drugs and pregnancy outcomes in Korean pregnant women. In addition, we performed a literature review on the teratogenic effects of anti-obesity drugs.

2. Materials and methods

2.1 Data collection

This study protocol was approved by the institutional review board of the hospital for the Korean Motherisk Program, a teratogen information service that provides evidence-based information on the safety and risk of exposure to therapeutic and illicit drugs, smoking, chemicals and radiation during pregnancy and lactation. The study was prospectively performed between January 2012 and December 2018. We obtained information regarding the exposure of anti-obesity drugs and other drugs during pregnancy in the

Table 1. Characteristics of study subjects.

	Unexposed-anti-obesity drugs	Exposed-anti-obesity drugs	p-value
	(n = 29,217)	(n = 1487)	
Age (year) (mean ± SD)	32.7 ± 8.4	32.4 ± 8.5	0.185
Gestational age (as of the call day) (mean ± SD)	9.6 ± 7.8	6.9 ± 3.3	<0.001
Gravidity (n) (mean ± SD)	1.2 ± 1.0	1.3 ± 1.0	<0.001
Parity (n) (mean ± SD)	0.3 ± 0.6	0.4 ± 0.6	<0.001
BMI (kg/m ²) (mean ± SD)	21.3 ± 3.0	22.1 ± 3.0	<0.001

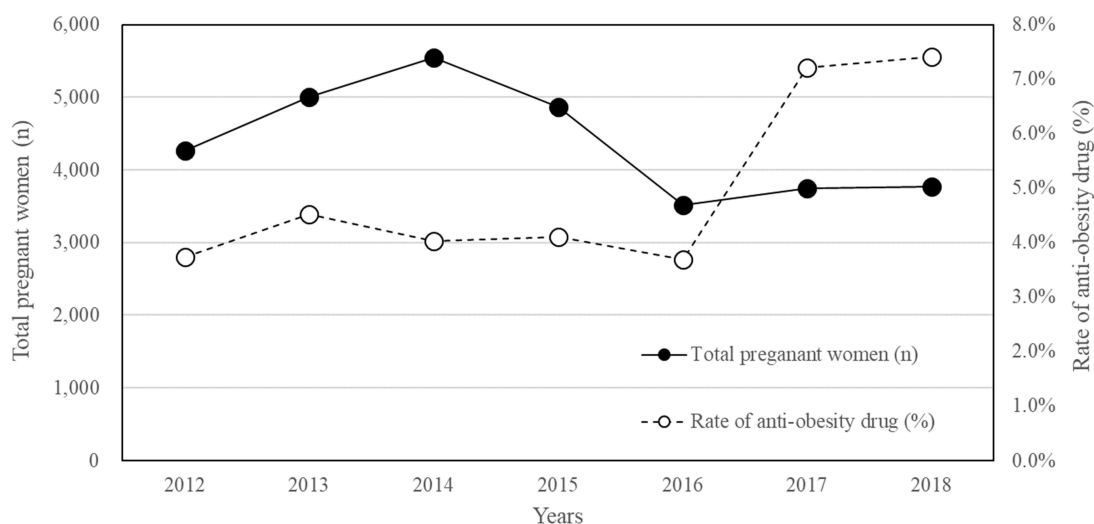


Fig. 1. Trends of calls for anti-obesity drugs compared with calls of total pregnant women. Solid circle = total pregnant women (non-exposed and exposed pregnant women); blank circle = rate of pregnant women exposed to anti-obesity drugs (exposed pregnant women/total pregnant women).

study period. All pregnant women were consulted for concerning inadvertent drug exposure during pregnancy. We conducted telephone interviews with pregnant women about exposure of general and anti-obesity medications.

2.2 Inclusion and exclusion criteria

The exposure of anti-obesity drug included the pregnant women inadvertently exposed to various anti-obesity drugs during early pregnancy for weight loss at the database of Korean Motherisk Program. Information on anti-obesity drug exposure from the study participants who called at call center of Korean Motherisk Program was obtained during telephone interviews with informed verbal consent. However, we excluded the exposure of anti-obesity drug before pregnancy and during breastfeeding and pregnant women with the insufficient information for the study at the database. The un-exposure of anti-obesity drugs as a control came from the same database of Korean Motherisk Program.

2.3 Definition of overweight and obesity

The definition of overweight and obesity is 18 kg/m² for overweight and 23 kg/m² for obesity. The threshold of the definition is calculated by Hood *et al.* [11].

The thresholds for BMI classification of overweight and obesity in the The Korean National Health and Nutrition Ex-

amination Survey database are BMI = 18 kg/m² (AUC = 0.97) and 23 kg/m² (AUC = 0.83) for females, respectively. These definition thresholds are lower than the current BMI cut-offs applicable to Caucasian population.

2.4 Pregnancy outcomes

Pregnancy outcomes were evaluated from singleton pregnant women exposed to anti-obesity drugs or un-exposed of anti-obesity drugs at the obstetrics and gynecology clinic of Korean Motherisk Program. Four hundred forty-eight among the exposures of anti-obesity drug and 4304 among the un-exposures of anti-obesity drugs were followed until the end of pregnancy or neonatal period. Pregnancy outcomes include birth weight, low birth weight, large for gestational age, gestational weeks of delivery, preterm birth, Apgar score of 1 min and 5 min, Apgar score of 1 min <7, Apgar score of 5 min <7. The above pregnancy outcomes were analyzed in 240 pregnant women exposed to anti-obesity drugs and 3804 pregnant women un-exposed to anti-obesity drugs who delivered after 28 weeks of gestation. Additionally, pregnancy with abnormalities including anomaly, intrauterine fetal death, and neurologic sequence was evaluated. The abnormalities were identified in prenatal or postnatal period.

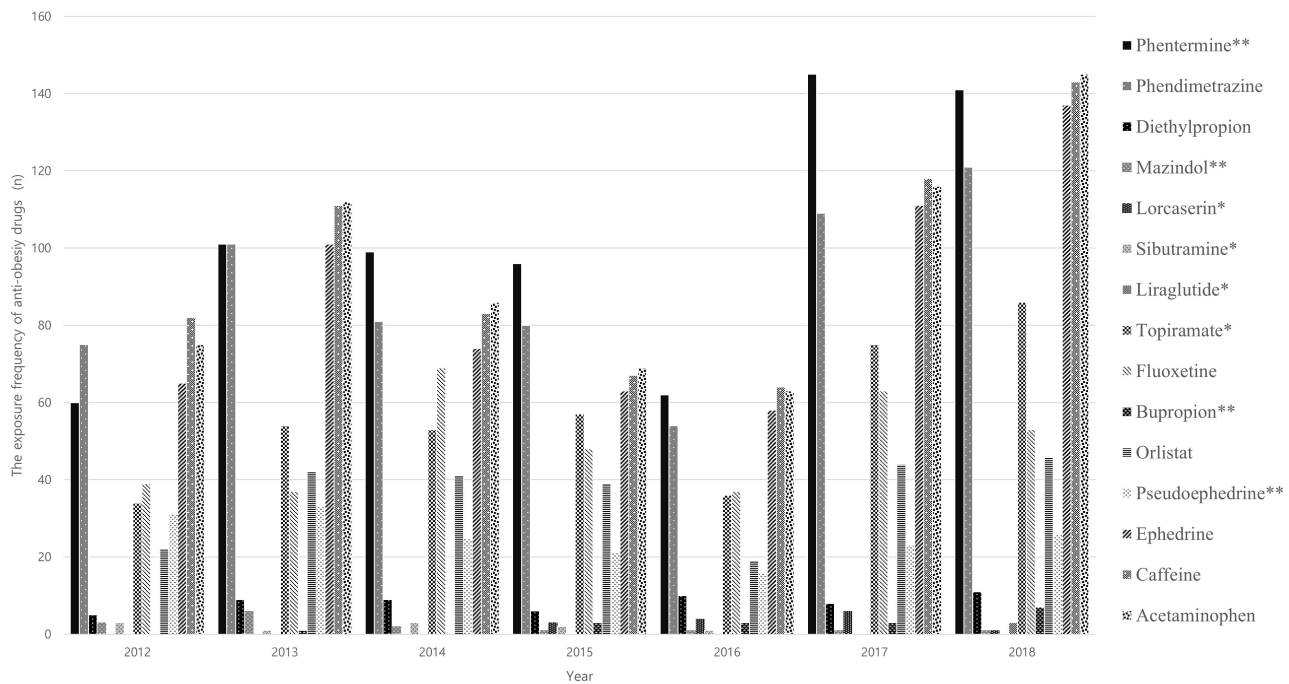


Fig. 2. Trends of calls for anti-obesity drugs.

Chi-square test (linear by linear association): * p -value < 0.05; ** p -value < 0.01.

2.5 Statistical analyses

The statistical significance was calculated using the chi-square test (linear-by-linear association) for time-trend differences, the t -test for differences in continuous variables and chi-square test for association between two categorical variables. A two-tailed p value of <0.05 was considered significant. Statistical analysis was performed using IBM SPSS Statistics (version 22; IBM Corporation, Armonk, NY, USA).

3. Results

The total number of pregnant women was 30,704. The pregnant women of unexposed anti-obesity group were exposed to other drugs except anti-obesity drugs and the rate was 95.1% (29,217/30,704). The rate of pregnant women exposed to anti-obesity drugs was 4.9% (1487/30,704). The rate of women exposed to anti-obesity drugs increased 50% between 2012 and 2018 (3.7% in 2012, 7.4% in 2018) (Fig. 1). The increased rate during the period demonstrated a significant linear-by-linear association ($p < 0.01$). Table 1 show that some variables except maternal age between exposed and unexposed to anti-obesity drugs are statistically significant difference.

Anti-obesity drugs are classified according to their ingredients and type, and are categorized into three groups (drugs suppressing food intake, drugs inhibiting intestinal fat absorption, drugs increasing energy consumption and thermogenesis) based on their mode of action [12]. The frequency and trends of anti-obesity drugs have been analyzed for each ingredient. The most commonly prescribed

anti-obesity drugs were phentermine (15.5%) and phendimetrazine (13.6%), with a 29.1% proportion of all drugs. The order of the other anti-obesity drugs was caffeine (14.7%), acetaminophen (14.6%), ephedrine (13.4%) (Table 2). Fig. 2 demonstrates that from 2012 to 2018, the use of phentermine and phendimetrazine was more substantially increased than the other drugs. In addition, anti-obesity drugs that significantly increased each year were phentermine ($p = 0.001$), bupropion ($p = 0.004$), topiramate ($p = 0.013$), liraglutide ($p = 0.019$), and lorcaserin ($p = 0.039$). Anti-obesity drugs that significantly decreased each year were pseudoephedrine ($p = 0.001$), mazindol ($p = 0.009$), and sibutramine ($p = 0.017$). The other anti-obesity drugs did not change during the study period.

Table 3 show the pregnancy outcomes. In the anti-obesity drug exposure, birth weight and large for gestational age (≥ 4000 g) are significantly larger than those of un-exposure of anti-obesity drugs. However, there are no difference of other pregnancy outcomes between both groups. In addition, there are no difference of abnormalities between exposure of anti-obesity drugs (14/448, 3.1%) and un-exposure of anti-obesity drugs (161/4304, 3.7%). There are no chromosomal abnormality and 6 spontaneous abortions among the exposures of anti-obesity drugs. And there are 14 chromosomal abnormalities and 66 spontaneous abortions in un-exposure of anti-obesity drugs. Table 4 shows the abnormalities in pregnancy exposed to anti-obesity drugs. There are no characteristic patterns in the abnormalities.

Table 2. Exposure frequency of anti-obesity drugs.

Classification	Ingredients	Drug types	Frequency	Co-prescribed other anti-obesity drugs
Appetite suppressants	Phentermine	Anorexiant	704 (15.5%)	Acetaminophen 40.1%, Ephedrine 37.5%, Caffeine 38.9%, Topiramate 29.0%, Orlistat 17.6%, Fluoxetine 16.2%, Phendimetrazine 12.1%, Pseudoephedrine 6.3%, Diethylpropion 1.3%, Lorcaserin 1.3%, Bupropion 0.7%, Mazindol 0.3%, Sibutramine 0.1%, Liraglutide 0.1%
	Phendimetrazine	Anorexiant	621 (13.6%)	Caffeine 56.7%, Acetaminophen 56.0%, Ephedrine 51.2%, Fluoxetine 25.6%, Topiramate 24.0%, Orlistat 15.6%, Phentermine 13.7%, Pseudoephedrine 13.0%, Diethylpropion 4.2%, Bupropion 1.8%, Mazindol 0.8%, Lorcaserin 0.5%, Sibutramine 0.2%, Liraglutide 0.2%
	Diethylpropion	Anorexiant	58 (1.3%)	Caffeine 55.2%, Acetaminophen 48.3%, Phendimetrazine 44.8%, Fluoxetine 41.4%, Ephedrine 37.9%, Orlistat 32.8%, Pseudoephedrine 31.0%, Topiramate 27.6%, Phentermine 15.5%, Bupropion 6.9%
	Mazindol	Anorexiant	15 (0.3%)	Acetaminophen 46.7%, Ephedrine 40.0%, Caffeine 40.0%, Phendimetrazine 33.3%, Orlistat 26.7%, Fluoxetine 20.0%, Pseudoephedrine 20.0%, Topiramate 20.0%, Phentermine 13.3%
	Lorcaserin	Anorexiant	14 (0.3%)	Ephedrine 64.3%, Phentermine 64.3%, Acetaminophen 64.3%, Caffeine 57.1%, Orlistat 42.9%, Topiramate 35.7%, Phendimetrazine 21.4%, Pseudoephedrine 7.1%, Bupropion 7.1%
	Sibutramine	Anorexiant	10 (0.2%)	Phentermine 10.0%, Phendimetrazine 10.0%, Fluoxetine 10.0%, Caffeine 10.0%
	Liraglutide	Anorexiant	3 (0.1%)	Phentermine 33.3%, Phendimetrazine 33.3%, Acetaminophen 33.3%, Orlistat 33.3%, Ephedrine 33.3%, Caffeine 33.3%
	Acetaminophen	Analgesic	666 (14.6%)	Caffeine 93.5%, Ephedrine 88.0%, Phendimetrazine 52.3%, Phentermine 42.3%, Topiramate 29.4%, Fluoxetine 24.6%, Orlistat 16.7%, Pseudoephedrine 8.7%, Diethylpropion 4.2%, Lorcaserin 1.4%, Mazindol 1.1%, Bupropion 1.1%, Liraglutide 0.2%
Fat absorption inhibitor	Topiramate	Anti-convulsant	395 (8.7%)	Phentermine 51.6%, Acetaminophen 49.6%, Caffeine 49.1%, Ephedrine 48.9%, Phendimetrazine 37.7%, Fluoxetine 32.4%, Orlistat 21.8%, Pseudoephedrine 14.9%, Diethylpropion 4.1%, Lorcaserin 1.3%, Mazindol 0.8%, Bupropion 0.8%
	Fluoxetine	Anti-depressant	346 (7.6%)	Caffeine 48.0%, Acetaminophen 47.4%, Phendimetrazine 46.0%, Ephedrine 41.6%, Topiramate 37.0%, Phentermine 32.9%, Pseudoephedrine 26.6%, Orlistat 15.6%, Diethylpropion 6.9%, Bupropion 1.2%, Mazindol 0.9%, Sibutramine 0.3%
	Bupropion	Anti-depressant	17 (0.4%)	Phendimetrazine 64.7%, Ephedrine 41.2%, Acetaminophen 41.2%, Caffeine 35.3%, Phentermine 29.4%, Diethylpropion 23.5%, Fluoxetine 23.5%, Pseudoephedrine 23.5%, Topiramate 17.6%, Orlistat 11.8%, Lorcaserin 5.9%
	Orlistat	Lipase inhibitor	253 (5.6%)	Phentermine 49.0%, Acetaminophen 43.9%, Caffeine 41.9%, Ephedrine 39.1%, Phendimetrazine 38.3%, Topiramate 34.0%, Fluoxetine 21.3%, Pseudoephedrine 13.8%, Diethylpropion 7.5%, Lorcaserin 2.4%, Mazindol 1.6%, Bupropion 0.8%, Liraglutide 0.4%
Metabolic activators	Pseudoephedrine	Stimulant	175 (3.8%)	Fluoxetine 52.6%, Phendimetrazine 46.3%, Caffeine 34.3%, Topiramate 33.7%, Acetaminophen 33.1%, Phentermine 25.1%, Orlistat 20.0%, Ephedrine 15.4%, Diethylpropion 10.3%, Bupropion 2.3%, Mazindol 1.7%, Lorcaserin 0.6%
	Ephedrine	Stimulant	609 (13.4%)	Acetaminophen 96.2%, Caffeine 97.0%, Phendimetrazine 52.2%, Phentermine 43.3%, Topiramate 31.7%, Fluoxetine 23.6%, Orlistat 16.3%, Pseudoephedrine 4.4%, Diethylpropion 3.6%, Lorcaserin 1.5%, Bupropion 1.1%, Mazindol 1.0%, Liraglutide 0.2%
	Caffeine	Stimulant	668 (14.7%)	Acetaminophen 93.3%, Ephedrine 88.5%, Phendimetrazine 52.7%, Phentermine 41.0%, Topiramate 29.0%, Fluoxetine 24.9%, Orlistat 15.9%, Pseudoephedrine 9.0%, Diethylpropion 4.8%, Lorcaserin 1.2%, Mazindol 0.9%, Bupropion 0.9%, Sibutramine 0.1%, Liraglutide 0.1%
Total			4554 (100.0%)	

Table 3. Pregnancy outcomes between the exposures and the un-exposures of anti-obesity drugs.

Outcomes	Unexposed anti-obesity drugs	Exposed anti-obesity drugs	p-value
	(n = 3804)	(n = 240)	
Birth weight (g) (mean ± SD)	3282 ± 422	3400 ± 452	<0.001
Low birth weight	2.9%	2.1%	0.464
Large for gestational age (≥4000 g)	4.8%	10.0%	<0.001
Gestational weeks of delivery (mean ± SD)	39.4 ± 1.4	39.2 ± 1.5	0.127
Preterm birth (<37 weeks)	4.1%	6.3%	0.101
Apgar score 1 min (mean ± SD)	8.3 ± 1.7	8.1 ± 1.1	0.879
Apgar score 1 min (score ≤7)	10.0%	11.7%	0.463
Apgar score 5 min (mean ± SD)	9.0 ± 1.8	9.0 ± 0.8	0.840
Apgar score 5 min (score ≤7)	1.3%	1.7%	0.643
Abnormality ^a	3.7%	3.1%	0.510

^a Unexposed anti-obesity drugs (n = 4304), exposed anti-obesity drugs (n = 448).

Table 5 (Ref. [13–44]) shows teratogenic effects of anti-obesity drugs included in this study. Teratogenic effects of topiramate are cleft lip and/or palate. And sibutramine has cardiovascular defects. Furthermore, other anti-obesity drugs possess potential teratogenic risks, such as cryptorchidism, gastroschisis, hemifacial macrosomia, embryonic death, fetal growth restriction.

4. Discussion

Anti-obesity drugs are categorized into three groups based on the mechanism of action as follows: drugs inhibiting intestinal fat absorption, drugs suppressing food intake (appetite suppressants), drugs increasing energy consumption, and thermogenesis (metabolic activators) [12]. Orlistat is the only approved anti-obesity medication that inhibits intestinal fat absorption. The appetite suppressants include medications that modulate the production of neurotransmitters or act on their receptors in the central nervous system. Metabolic activators are composed of various ingredients, such as ephedrine, caffeine, and other agents [45]. Although the scientific evidence was insufficient, paracetamol (acetaminophen) was used for systemic administration as an appetite depressant [46]. Furthermore, weight loss was found among people who take Tylenol and Excedrin (acetaminophen, aspirin, and caffeine), especially for female [47, 48].

In this study, BMI of exposed group of anti-obesity drugs is in below the agreed cutoff, 23.0 kg/m², of overweight in Asia-pacific countries including Korea [49]. However, Hood *et al.* [11] calculated BMI thresholds for South Korean females, as 18 kg/m² for overweight and 23 kg/m² for obesity. These thresholds are lower than the current BMI cut-offs applicable to Caucasian population. This is due to increased insulin resistance in Asians [50].

So, the indications of prescription of anti-obesity drugs might be more related to medical issues such as cardiometabolic risk factors or body fat for weight loss.

In addition, we observed that pregnant women exposed to anti-obesity drugs were increased by approximately two-fold

(from 3.7% to 7.4%) in 2018 when compared to 2012. In pregnant women, phentermine and phendimetrazine composed over 50% of the exposed anti-obesity drugs. The other drugs included topiramate, liraglutide, locaserin, and bupropion. As seen in Fig. 2, during the study period, exposure trends of phentermine and phendimetrazine were more profoundly increased than in the case of other anti-obesity drugs. The increased exposure to phentermine and phendimetrazine was estimated to result due to the changes in drug regulations in the Korean Ministry of Food and Drug Safety during 2016. These drugs were amended from narcotics to non-narcotics [51]. In addition, it is related the increase of prevalence of obesity in Korea. Nam *et al.* [52] reported that according to the National Health Insurance Service, the prevalence of obesity from 29.7% in 2009 to 35.7% in 2018 in Korea.

The growing prevalence of obesity has become a global public health concern. Maternal obesity is associated with an increase in neural tube defects (NTDs) [53]. During early pregnancy, weight loss or lower weight gain increases the risk of NTDs [54, 55]. Moreover, in overweight and obese women, a weight loss or weight gain of less than 5 kg during pregnancy increases the risk of a small for gestational age (SGA) newborn and decreases fetal growth when compared with infants whose mothers had a gestational weight gain of greater than 5 kg [56]. Globally, the use of anti-obesity drugs for weight loss is increasingly common. In particular, these drugs are disproportionately used by women of childbearing potential. A large portion of childbearing women are inevitably exposed to these drugs during pregnancy due to unintended pregnancy.

Maňáková *et al.* [57] have demonstrated that there is an increasing tendency for weight control among fertile women in the Czech Republic. Furthermore, they reported that the number of calls for anti-obesity drug exposure, such as sibutramine and phentermine, was rare until 2005. However, their number started to increase up to 2009, and later decreased as both drugs were withdrawn from the market.

Table 4. Abnormality in pregnancy exposed to anti-obesity drugs.

No.	Abnormality	Anti-obesity drugs exposed
1	Cleft lip and palate (right paramedian)	Sibutramine HCl
2	Lateral ventriculomegaly (left)	Phentermine HCl, Ephedrine HCl, Anhydrous caffeine, Acetaminophen, Pseudoephedrine HCl
3	Bilateral lacrimal duct cyst, lateral ventriculomegaly (left)	Phentermine HCl
4	Large nevus of face	Phentermine HCl, Ephedrine HCl, Anhydrous caffeine, Acetaminophen, Pseudoephedrine HCl, Magnesium hydroxide
5	Ventricular septal defect	Sibutramine HCl
6	Secundum atrial septal defect	Phentermine HCl, Pseudoephedrine HCl
7	Choledochal cyst	Phendimetrazine tartrate, Fluoxetine HCl, Cimetidine, Aspirin, Ephedrine HCl, Anhydrous caffeine
8	Cloacal exstrophy	Furosemide
9	Bilateral inguinal hernia	Pseudoephedrine HCl, Aminophylline, Sodium hyaluronate, Ephedrine HCl, Anhydrous caffeine, Acetaminophen, Phendimetrazine tartrate, Orthosiphon powder
10	Micro-penis with right smaller testis	Phendimetrazine tartrate, Acetaminophen, Anhydrous caffeine, Ephedrine HCl, Bisacodyl, Docusate sodium
11	Both club foot	Phentermine HCl, Pseudoephedrine HCl
12	Both leg deformity	Phentermine HCl
13	Atonic seizure	Phentermine HCl, Acetaminophen, Anhydrous caffeine, Ephedrine HCl, Fluoxetine HCl
14	Intrauterine fetal death	Phendimetrazine tartrate, Ephedrine HCl, Anhydrous caffeine, Anhydrous caffeine

According to the Swedish Medical Birth Register, during 1998–2011, among the 392,126 infants born, 509 had been exposed to anti-obesity drugs during early pregnancy, with 248 exposed to orlistat, 242 to sibutramine, 12 to rimobant, and 13 to unspecified anti-obesity drugs [27]. The most frequently exposed drugs differ among Swedish and Korean pregnant women. In Korean pregnant women, exposure to phentermine and phendimetrazine is more frequent, with a marked increase in exposure observed between 2012 and 2018 when compared to other anti-obesity drugs.

In this study, there are no difference in pregnancy outcomes except birth weight and large for gestational age between exposure and un-exposure of anti-obesity drugs. Birth weight and large for gestational age are larger in the exposure of anti-obesity drugs than the un-exposure of anti-obesity drugs. Those are not possibly associated with anti-obesity drugs, but larger BMI among the exposure of anti-obesity drugs. In additionally, there is no difference of abnormalities including anomaly, intrauterine fetal death, and neurologic sequence of neonate between both groups. There are no characteristic patterns of abnormalities in pregnancy exposed to anti-obesity drugs.

Conversely, pregnant women are also concerned regarding the teratogenicity of anti-obesity drugs. Reportedly, there some studies on the teratogenic effects of anti-obesity drug exposure. In a prospective observational study conducted by the UK pregnancy registry, a significantly higher rate of oral clefts was observed following topiramate exposure [58]. Furthermore, an increased number of oral clefts was reported in the offspring of mothers prescribed am-

phetamines during the first 56 days from the last menstrual period [59].

In the literature review on the teratogenic effects of anti-obesity drugs included in our data, topiramate is cleft lip and/or palate and sibutramine has cardiovascular defects. Other anti-obesity drugs possess potential teratogenic risks, such as cryptorchidism, gastroschisis, limb abnormalities, abnormalities of the viscera, hemifacial macrosomia, embryonic death, fetal growth restriction. Phendimetrazine is a racemic mixture of the trans configuration, producing both trans isomers of phenmetrazine when metabolized in vivo. The biologic effects of phendimetrazine are due primarily to the effects of the metabolite phenmetrazine on central norepinephrine and/or dopamine release [60]. The teratogenic effects of phendimetrazine were replaced with the data of phenmetrazine. Additionally, maternal weight loss in early pregnancy following anti-obesity drugs use associated with neural tube defects [55].

There are limitations to our study. Our data were not based on the population. Therefore, this data cannot be generalized. Despite this limitation, our data were collected prospectively from pregnant callers exposed to anti-obesity drugs based on teratogen information service. And the number of pregnant women followed up pregnancy outcome in the exposure to the anti-obesity drugs is not enough for adequately evaluating adverse pregnancy outcomes including birth defects. Additionally, there are loss of many pregnant women on follow-up of pregnancy outcome among the study subjects enrolled.

Table 5. Teratogenic effects of anti-obesity drugs.

Drug	In human	In animal
Phentermine	A case of bilateral porencephalic cysts [13]	Thickened mitral valves [14]
Phendimetrazine	Abnormalities of the viscera [15]; Limb abnormalities(web fingers, missing little finger) [16]	No animal teratology studies
Fluoxetine	Persistent pulmonary hypertension of the newborn [17]	Pulmonary hypertension [18]; Increased perinatal mortality [19]
Acetaminophen	Cryptorchidism [20]; Wheezing/asthma [21]	Reduced anogenital distance [22]
Pseudoephedrine	Gastroschisis [23]; Hemifacial macrosomia [24]	No animal teratology studies
Topiramate	Cleft lip and/or palate [25]	Craniofacial malformations including cleft palate [26]
Orlistat	No increase of birth defects [27]	No increase of developmental toxicity [28]
Diethylpropion	A report of congenital anomalies [29]; Withdrawal symptoms in neonate [30]	Non-teratogenic in the rat and mouse [31]
Ephedrine	A case of limb reduction defects [32]; Fetal acidosis [33]	Cardiovascular anomalies [34]
Caffeine	Miscarriage [35]; Low birth weight [36]	Decreased fetal birth weight and skeletal ossification [37]
Mazindol	No epidemiological studies	Increased perinatal mortality, Decreased fetal growth [38]
Lorcaserin	No epidemiological studies	Increase in stillbirth and pup deaths [39]
Sibutramine	Cardiovascular defects [27]	Increase in embryonic death [40]
Liraglutide	No epidemiological studies	Increase in birth defects [41]
Bupropion	Left ventricular outflow track heart defects [42]; Fetal arrhythmia [43]	Kyphosis, retroverted rear legs, incomplete ossification of occipital bone [44]

However, despite these limitations, our study demonstrated that pregnant women are exposed to various anti-obesity drugs. The most frequently used anti-obesity drugs are phentermine and phendimetrazine. In addition, pregnancy outcomes were evaluated in pregnancy exposed to anti-obesity drugs even though we couldn't identify the characteristic patterns of abnormalities among the exposures.

5. Conclusions

Our data showed that the exposure of anti-obesity drug profoundly increased during the study period. In addition, there are no difference in pregnancy outcomes between the exposure and the un-exposure of anti-obesity drug except that birth weight and large for gestational age are significantly larger in the exposure group. However, among the anti-obesity drugs there exist known teratogenic drugs. Therefore, childbearing women should be concerned with preventing teratogenic effects following anti-obesity drug exposure during pregnancy. Physicians should warn childbearing women about potential dangers of anti-obesity drug.

Author contributions

EJC: data collection/data analysis and manuscript writing. JYH: project development/manuscript editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving patients were approved by the Medical Ethical and Institutional Review Board at the Cheil General Hospital & Women's Healthcare Center, Seoul, Korea (approval number: CGH-IRB-2010-21). The patient's written consent was obtained.

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Conflict of interest

The authors declare no conflict of interest.

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