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ORIGINAL RESEARCH ARTICLE

Pregnancy Loss Signal from Prostaglandin Eye Drop Use in Pregnancy: A Disproportionality Analysis Using Japanese and US Spontaneous Reporting Databases

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Abstract

Background There is limited research regarding the use of glaucoma medicines during pregnancy. Prostaglandins contract uterine smooth muscle; however, it is not clear whether prostaglandin eye drops are associated with pregnancy loss in pregnant women.

Objectives We conducted a pharmacovigilance study using spontaneous report databases from Japan and the USA to evaluate the association between pregnancy loss and the use of prostaglandin eye drops during pregnancy.

Methods The Japanese Adverse Drug Event Report database and the Food and Drug Administration Adverse Event Reporting System were used for analysis. Disproportionality analyses and a review of individual case safety reports were conducted.

Results As for prostaglandin eye drops in pregnancy-related reports, there were eight reports involving latanoprost in the Japanese Adverse Drug Event Report database and no reports of pregnant women using other prostaglandin eye drops. In the Food and Drug Administration Adverse Event Reporting System, there were 25 reports involving latanoprost, 23 involving bimatoprost, 13 involving travoprost, and three involving tafluprost. The drug safety signal was detected during latanoprost usage and pregnancy loss. In the Japanese Adverse Drug Event Report database, there were five reports of pregnancy loss related to latanoprost, with a reporting odds ratio of 12.84 (95% confidence interval 3.06–53.86), and in the Food and Drug Administration Adverse Event Reporting System, pregnancy loss was reported in 12 cases of latanoprost usage with a reporting odds ratio of 4.35 (95% confidence interval 1.98–9.54). Uterine contractions were observed as concomitant adverse events in one case.

Conclusions Although a disproportionality analysis cannot determine causality, we need to keep an eye on the signal detected in this study. This signal should be validated using a causal design study.

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Key Points

Our study suggests the presence of a drug safety signal that use of latanoprost eye drops, a prostaglandin analog, during pregnancy may be associated with pregnancy loss.

Given that signal detection is a hypothesis-generating study, future efforts to accumulate cases and confirm/refute the hypothesis is desirable.

1 Introduction

Spontaneous reporting is a fundamental source of information in pharmacovigilance. To study drug safety in pregnant women, spontaneous reporting of adverse events related to the use of drugs during pregnancy is required [1]. Usually, the risk of adverse drug reactions in pregnant women is examined in study designs such as cohort studies to compare against a control group. However, these studies require a system to collect pregnant women and a sufficient number of cases to be conducted. Given the possibility that safety information for pregnant women can be obtained earlier by using spontaneous reports, some reports using the spontaneous reporting database have been reported [2–6]. Lareb, a pharmacovigilance center in the Netherlands, is also developing a toolkit for monitoring drug safety in pregnant women under the guidance of the World Health Organization, in which the use of a spontaneous reporting database is discussed [7].

Glaucoma in pregnancy is relatively rare, and intraocular pressure (IOP) generally decreases with pregnancy [8]. An epidemiological study conducted in Japan reported that the prevalence of open-angle glaucoma in women aged 15–44 years was less than 1% [9]. Therefore, there are limited instances of using glaucoma medicines during pregnancy, and there is limited evidence for their safety [10]. It has been reported that about 2–3% of pregnant women aged over 40 years have glaucoma [11]. The number of pregnant women with glaucoma is expected to increase in the future because of the aging of mothers. If evidence for the effect of drug on the mother or fetus is available, action can be taken, such as reviewing the drug therapy before pregnancy. As a general glaucoma treatment, prostaglandin eye drops have strong antihypertensive effects and are used as first-line drugs in open-angle glaucoma [12]. In a survey in the UK, 71% of ophthalmologists who had treated pregnant women with glaucoma said they continued with the medication they were already using [13]. Therefore, it is possible that prostaglandin eye drops are used by pregnant women. However, prostaglandin $F_{2\alpha}$ analogs result in the contraction of uterine smooth muscle in vitro [14], which could theoretically cause miscarriages. On the contrary, some experts claim that the active ingredients in prostaglandin eye drops are unlikely to be absorbed in large amounts to cause miscarriage. Although the amount of topical eye drops absorbed is indeed expected to be small, it has been reported that topical eye drops with beta-blockers can cause serious adverse events in the fetus [15]. No conclusions have been reached regarding this concern [10]. This argument may stem from the limited data available on human studies, in which prostaglandins were used in pregnant women. Thus, we conducted a pharmacovigilance study using spontaneous report databases from Japan and the USA in order to evaluate the association between prostaglandin eye drops and pregnancy loss.

2 Methods

2.1 Data Sources

In this study, we used the Japanese Adverse Drug Event Report (JADER) database, a spontaneous reporting database in Japan, and the Food and Drug Administration Adverse Event Reporting System (FAERS), a spontaneous reporting database in the US Food and Drug Administration. Both databases have a data structure compliant with International Conference on Harmonisation E2B. The JADER database consists of reports from pharmaceutical companies and medical institutions. It is divided into four tables and contains the following information: patient demographic information (DEMO), drug information [including indication for the use of the reported drugs] (DRUG), adverse events (REAC), and patient disease (HIST). Adverse events, indications for the use of the reported drugs, and patient diseases are coded in preferred terms (PTs) of the *Medical Dictionary for Regulatory Activities* (MedDRA). Age information is recorded in increments of 10 years, or by category names such as a child or elderly. The FAERS consists of reports from pharmaceutical companies, medical institutions, and consumers. This is divided into seven tables, which contain the following information: patient demographic information (DEMO), drug information (DRUG), indications for the use of the reported drugs (INDI), therapy information [start dates and end dates] (THER), adverse events (REAC), outcomes for the event (OUTC), and report sources (RPSR). The JADER database included cases reported from April 2004 to June 2019; the FAERS included cases reported from the fourth quarter of 1997 to the third quarter of 2018. We used the FAERS, which has been processed by the Japan Pharmaceutical Information Center, to remove duplicate cases, unify drug names, give PT codes to adverse events and indications for the use of the reported drugs, and convert age information

consisting of numbers and units to years. The JADER database and the FAERS are coded in MedDRA version 22.1 and version 21.1, respectively, and the corresponding MedDRA was used in this study.

Table 1 PTs of exposure-related pregnancy

PT code	PT name
10073513	Exposure during pregnancy
10071415	Maternal exposure timing unspecified
10071409	Fetal exposure during delivery
10071408	Maternal exposure during pregnancy
10071407	Maternal exposure during delivery
10071406	Maternal exposure before pregnancy
10071405	Fetal exposure timing unspecified
10071404	Fetal exposure during pregnancy
10064998	Drug exposure before pregnancy[a]
10050425	Maternal drugs affecting fetus

[a]Available as a PT only at *Medical Dictionary for Regulatory Activities* Version 22.1, *PT* preferred term

2.2 Extraction of Pregnancy-Related Reports

Subgroup disproportionality analyses have been reported because of the possibility of bias when analyzing the association between drugs and pregnancy outcomes in datasets in which the majority of reports are from non-pregnant women [4, 16]. Given that there is no dedicated field to identify pregnant women's reports from the spontaneous reporting database, attempts are being made to identify such reports using the standard MedDRA query (SMQ) [3, 5, 17]. Therefore, in this study, we modified our previously reported method and used the following extraction method [3, 17].

All sub-SMQs of the SMQ "Pregnancy and neonatal topics" except "Lactation related topics (incl neonatal exposure through breast milk)" were used to identify cases containing pregnancy-related terms as candidates for reporting pregnant women. From these reports, cases that included PTs

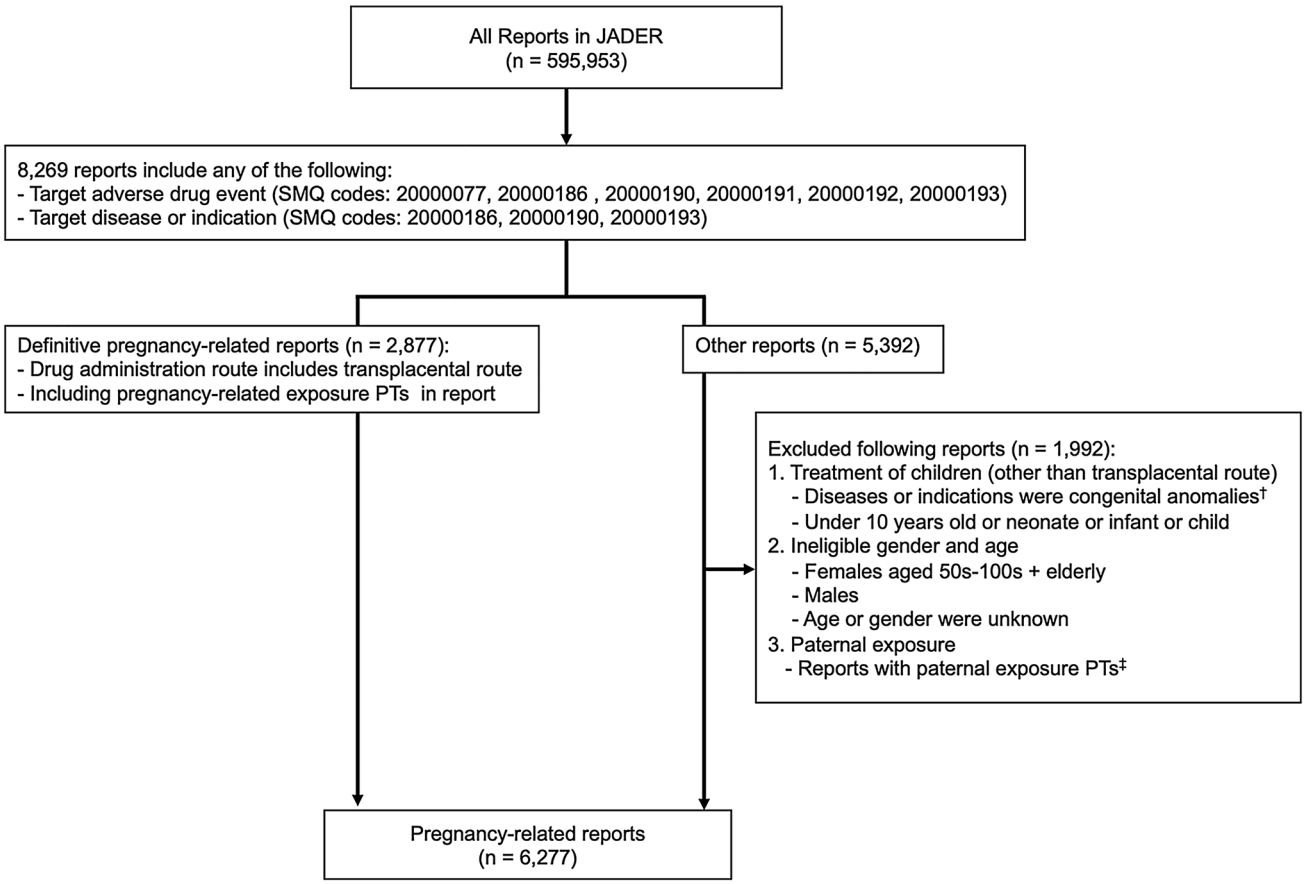

Fig. 1 Data extraction of pregnancy-related reports from the Japanese Adverse Drug Event Report (JADER) database. †Standard MedDRA queries (SMQs): congenital, familial, and genetic disorders (20000077). ‡Preferred terms (PTs): paternal drugs affecting the fetus (10050425), paternal exposure (10071403), paternal exposure during pregnancy (10080091), paternal exposure timing unspecified (10080092), and paternal exposure before pregnancy (10080093). *MedDRA* Medical Dictionary for Regulatory Activities

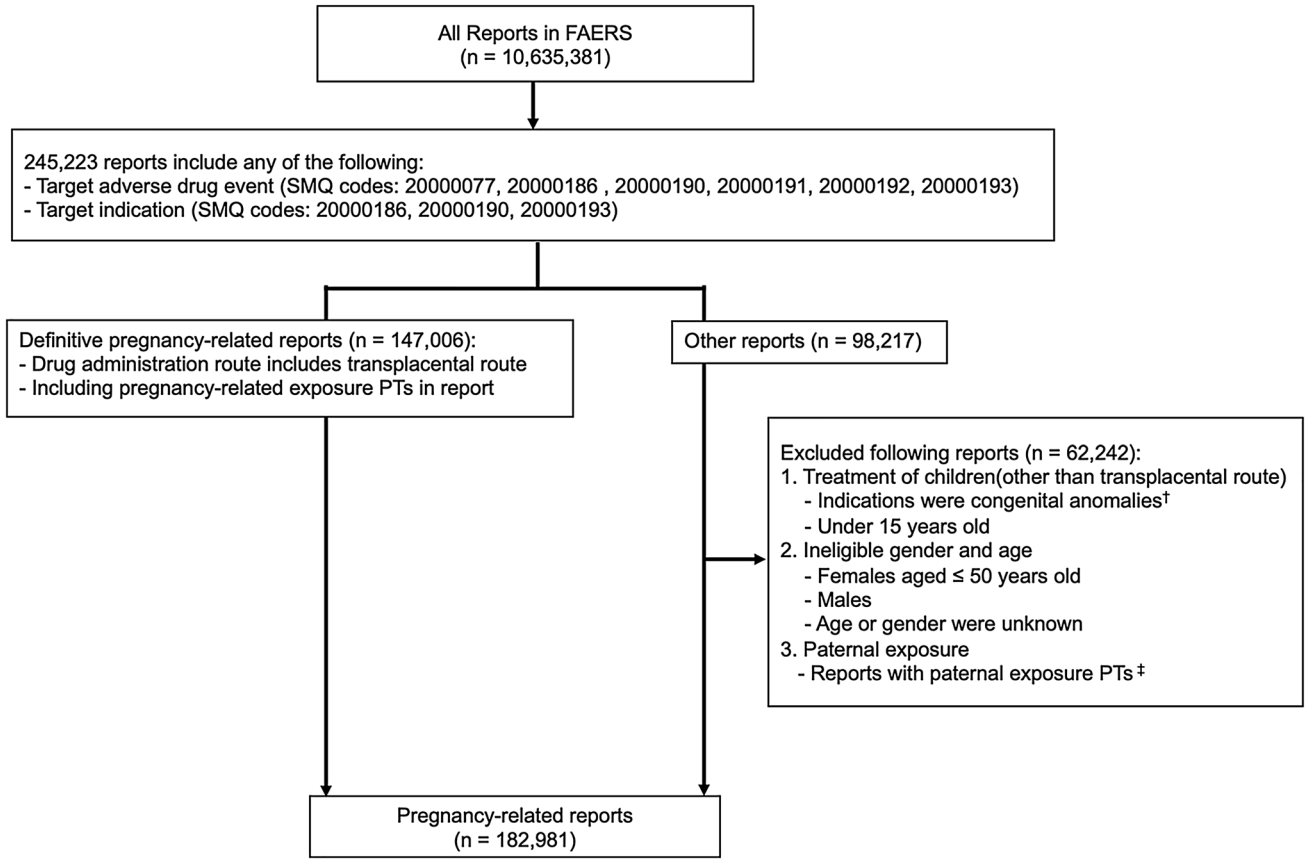

Fig. 2 Data extraction of pregnancy-related reports from the Japanese Adverse Drug Event Report (JADER) database. †Standard MedDRA queries (SMQs): congenital, familial, and genetic disorders (20000077). ‡Preferred terms (PTs): paternal drugs affecting the fetus (10050425), paternal exposure (10071403), paternal exposure during pregnancy (10080091), paternal exposure timing unspecified (10080092), and paternal exposure before pregnancy (10080093). *FAERS* Food and Drug Administration Adverse Event Reporting System, *MedDRA* Medical Dictionary for Regulatory Activities

in Table 1 or cases in which the administration route was transplacental were defined as definitive pregnancy-related reports. Except for definitive pregnancy-related reports, we excluded treatment of medical condition in children, ineligible gender and age, and paternal exposure (Figs. 1 and 2). The reports obtained through these processes were considered pregnancy-related reports.

2.3 Target Drugs and Adverse Events

The target drugs were the following prostaglandin eye drops used for glaucoma [10, 18]: latanoprost, travoprost, tafluprost, bimatoprost, and unoprostone. For adverse events, we first examined the number of reports of the PT included in the SMQ (termination of pregnancy and risk of abortion). The SMQ "Termination of pregnancy and risk of abortion" includes adverse events such as induced abortion and infectious miscarriage, which are unlikely to have been directly caused by the drug. Therefore, a definition of "Pregnancy Loss" was created excluding these adverse events, and these were used as the target adverse events (Table 2).

2.4 Disproportionality Analysis

A 2 × 2 contingency table was created from pregnancy-related reports, and the reporting odds ratio (ROR) was calculated. The ROR was calculated using the following formula: (N (target adverse event | target drug)/N (other adverse events | target drug))/(N (target adverse event | other drugs)/N (other adverse events | other drugs)), in which N means the number of reports [5]. The detection criteria were the lower limit of the 95% confidence interval (CI) of the ROR > 1 and at least three reported cases of the target adverse event, based on the criteria of the European Medicines Agency [5, 19]. We also conducted a sensitivity analysis of the disproportionality of using PT "abortion spontaneous" and PT "stillbirth" as the only target adverse events and using definitive pregnancy-related reports. Because miscarriage and maternal

Table 2 Definition of pregnancy loss in this study

PT code	PT name
10000209	Aborted pregnancy
10000210	Abortion
10000212	Abortion complete complicated
10000217	Abortion incomplete
10000218	Abortion incomplete complicated
10000230	Abortion missed
10000234	Abortion spontaneous
10000236	Abortion spontaneous complete complicated
10000238	Abortion spontaneous complicated
10000239	Abortion spontaneous incomplete complicated
10042062	Stillbirth
10052846	Abortion early
10052847	Abortion late
10055690	Fetal death
10061614	Abortion complete
10061615	Abortion complicated
10061616	Abortion spontaneous complete
10061617	Abortion spontaneous incomplete

PT preferred term

Table 3 Adverse events related to termination of pregnancy and risk of abortion (SMQ)

	JADER	FAERS
Latanoprost	$n = 8$	$n = 25$
Abortion spontaneous	2	7
Abortion	2	2
Fetal death		2
Abortion missed	1	2
Abortion induced		1
Stillbirth		1
Bimatoprost	$n = 0$	$n = 23$
Abortion spontaneous		1
Stillbirth		1
Travoprost	$n = 0$	$n = 13$
Abortion spontaneous		5
Abortion induced		1
Tafluprost	$n = 0$	$n = 3$
Abortion		1

FAERS Food and Drug Administration Adverse Event Reporting System, *JADER* Japanese Adverse Drug Event Report database, *MedDRA* Medical Dictionary for Regulatory Activities, *SMQ* standard MedDRA queries

age are generally associated, we also aggregated the ages in reports of pregnancy loss in the FAERS for the target drugs and in the entire pregnancy-related reports. To exclude reports in which "0" was entered as the age of the child who was not born and reports in which the age was clearly misentered, we aggregated reports in which the age was entered as 15–50 years. In the JADER database, age information could not be aggregated because it is recorded in increments of 10 years or by category names such as "child" or "elderly." Statistical analysis was performed using the open-source R software (version 3.6.2).

2.5 Review of Individual Case Safety Reports

For the drugs for which signals were detected, individual case safety reports were investigated for further study of causality. The survey items were age, drug, indication, adverse events, and reporting period.

3 Results

3.1 Extraction of Pregnancy-Related Reports

A total of 6273 and 182,981 reports of pregnant women were extracted from the JADER database and from the FAERS, respectively. Pregnancy loss was reported in 725 cases in the JADER database and 32,037 cases in the FAERS. As for the use of prostaglandin eye drops in pregnancy-related reports, there were eight reports of latanoprost in the JADER database, and no reports of pregnant women using other prostaglandin eye drops. There were 25 reports involving latanoprost, 23 reports involving bimatoprost, 13 reports involving travoprost, and three reports involving tafluprost in the FAERS; there were no pregnancy-related reports using unoprostone in any of the spontaneous report databases. The reported adverse events of "Termination of pregnancy and risk of abortion" (SMQ) for each drug are shown in Table 3.

3.2 Disproportionality Analysis

In the JADER database, there were five reports of pregnancy loss related with latanoprost use, with an ROR of 12.84 (95% CI 3.06–53.86). However, because of the limited number of cases, a sensitivity analysis could not be performed.

In the FAERS, pregnancy loss was reported in 12 cases of latanoprost use, two cases of bimatoprost use, five cases of travoprost use, and one case of tafluprost use (Table 4). Latanoprost met the detection criteria, with an ROR of 4.35 (95% CI 1.98–9.54), as did the results of the sensitivity analysis. Travoprost also met the detection criteria, with an ROR of 2.95 (95% CI 0.96–9.00), and the results of the sensitivity analysis were similar. In the FAERS, the age (mean ± standard deviation [number of age available cases]) of pregnancy loss reported cases was 30.78 ± 6.56 ($n = 21,808$) for the entire pregnancy-related reports, 34.82 ± 5.29 ($n = 11$) for

Table 4 Disproportionality analysis using the US Food and Drug Administration Adverse Event Reporting System

	Pregnancy loss		PT "abortion spontaneous" only		PT "stillbirth" only		Pregnancy loss-restricted definitive pregnancy-related reports	
Drug	*n*	ROR [95% CI]	*n*	ROR [95% CI]	*n*	ROR [95% CI]	*n*	ROR [95% CI]
Latanoprost	12	4.35 [1.98–9.54]	7	2.96 [1.24–7.09]	1	2.58 [0.35–19.10]	7	4.90 [1.82–13.15]
Bimatoprost	2	0.45 [0.11–1.91]	1	0.35 [0.05–2.57]	1	2.82 [0.38–20.91]	2	1.40 [0.30–6.47]
Travoprost	5	2.95 [0.96–9.00]	5	4.76 [1.56–14.55]	0	NA	5	4.50 [1.43–14.17]
Tafluprost	1	2.36 [0.21–25.98]	0	NA	0	NA	0	NA

CI confidence interval, *NA* not available, *PT* preferred term, *ROR* reporting odds ratio

Table 5 Individual case safety reports about pregnancy losses by latanoprost

Case number	Age, years	Drugs	Indications	Adverse events	Report year and quarter
JADER 1	20s	Latanoprost (S) Betamethasone (C), carteolol (C), tropicamide/phenylephrine (C)	Glaucoma, uveitis	Abortion missed	2004 Q4
JADER 2	20s	Latanoprost (S), timolol (C)	NA	Abortion	2005 Q2
JADER 3	30s	Latanoprost (S), timolol (C)	Intraocular pressure increased	Abortion	2006 Q1
JADER 4	30s	Dorzolamide/timolol (S), latanoprost (S)	Glaucoma	Abortion spontaneous	2016 Q2
JADER 5	30s	Latanoprost (S), dorzolamide/timolol (S)	Glaucoma	Abortion spontaneous	2016 Q4
FAERS 1	43	Latanoprost (PS)	NA	Abortion spontaneous	2001 Q2
FAERS 2	38	Latanoprost (PS)	Angle-closure glaucoma	Abortion spontaneous, uterine contractions during pregnancy, maternal drugs affecting fetus, pregnancy	2002 Q2
FAERS 3	31	Latanoprost (PS)	Glaucoma	Fetal death, maternal drugs affecting fetus	2003 Q4
FAERS 4	27	Latanoprost (PS), timolol (SS)	Ill-defined disorder	Abortion spontaneous, exposure during pregnancy, pregnancy	2005 Q2
FAERS 5	39	Latanoprost (PS), metformin (SS), bisoprolol (SS), dorzolamide/timolol (SS), insulin (SS), timolol (SS)	Ill-defined disorder	Abortion spontaneous, exposure during pregnancy	2006 Q1
FAERS 6	36	Latanoprost (PS), timolol (C)	Intraocular pressure increased	Abortion, exposure during pregnancy, pregnancy	2006 Q1
FAERS 7	NA	Latanoprost (PS)	Open-angle glaucoma	Abortion missed, stillbirth, exposure during pregnancy, pregnancy	2006 Q3
FAERS 8	35	Latanoprost (PS)	Open-angle glaucoma	Abortion missed, exposure during pregnancy, pregnancy	2006 Q3
FAERS 9	29	Latanoprost (PS), prednisolone (C)	Glaucoma, dermatomyositis	Abortion spontaneous, insomnia, abdominal pain upper	2010 Q2
FAERS 10	28	Latanoprost (PS), heparin (SS), acetylsalicylic acid (C)	Ocular hypertension, coagulopathy	Abortion, fetal death, coagulopathy, thrombosis, hemorrhage	2011 Q1
FAERS 11	38	Latanoprost (PS)	Glaucoma	Abortion spontaneous	2011 Q3
FAERS 12	39	Latanoprost (PS), dorzolamide/timolol (SS)	Glaucoma	Abortion spontaneous	2016 Q4

C concomitant, *FAERS* Food and Drug Administration Adverse Event Reporting System, *JADER* Japanese Adverse Drug Event Report database, *NA* not available, *PS* primacy suspect drug, *S* suspected drug, *SS* secondary suspect drug

Table 6 Individual case safety reports about pregnancy losses by travoprost

Case number	Age, years	Drugs	Indications	Adverse events	Report year and quarter
FAERS 1	36	Travoprost (PS), levothyroxine (C)	Ocular hypertension	Abortion spontaneous, exposure during pregnancy	2006 Q4
FAERS 2	NA	Travoprost/timolol (PS)	Glaucoma	Abortion spontaneous, exposure during pregnancy	2014 Q4
FAERS 3	NA	Travoprost/timolol (PS)	Glaucoma	Abortion spontaneous, exposure during pregnancy	2014 Q4
FAERS 4	NA	Travoprost/timolol (PS)	Glaucoma	Abortion spontaneous, exposure during pregnancy	2014 Q4
FAERS 5	NA	Travoprost/timolol (PS)	Glaucoma	Abortion spontaneous, exposure during pregnancy	2014 Q4

C concomitant, *FAERS* Food and Drug Administration Adverse Event Reporting System, *NA* not available, *PS* primacy suspect drug, *SS* secondary suspect drug

latanoprost, 36 ($n = 1$) for travoprost, and 33 ($n = 1$) for tafluprost; ages were unavailable for bimatoprost.

3.3 Review of Individual Case Safety Reports

The data of individual cases of pregnancy loss in latanoprost and travoprost are shown in Tables 5 and 6. In the latanoprost case reports, the patient age was in the 20s in two cases and in the 30s in three cases in the JADER database; in the FAERS, the age was in the 20s for three cases, in the 30s for seven cases, in the 40s for one case, and unknown in one case. In each case, the other suspected drugs did not include any classified as "X" in the Australian Therapeutic Goods Administration Classification. Adverse events other than pregnancy loss included "uterine contractions" in one case and "coagulopathy, thrombosis and hemorrhage" in another case. Four of the five cases of travoprost were similar to those reported in the same period.

4 Discussion

This study provides a drug safety signal for latanoprost-induced pregnancy loss. To the best of our knowledge, there have been few cases of latanoprost-induced pregnancy loss, with only 11 cases from the Teratology Information Service in Italy [20]. Of the 11 cases reported, one failed the follow-up and one miscarriage were observed in one of the ten cases that could be followed up. The frequency of reporting is such that the incidence of miscarriage in this report was 10%, which is not higher than the general incidence, but the very small number of cases is mentioned as a limitation. Although miscarriages occur frequently, exposure to prostaglandin eye drops during pregnancy is relatively rare. Thus, individual center studies are expected to be difficult, and we used a large database of spontaneous reports for our study. A previously reported case was 46 years old, and advanced age was considered to be one of the reasons for the miscarriage [20]. The results of age aggregation of pregnancy loss reports in the FAERS also showed that the age for the target drug was higher than that for the entire pregnancy-related reports. The possibility that age may have been a confounding factor cannot be ruled out. On the contrary, pregnancy loss was also reported in a relatively young pregnant woman in her 20s in this study. Moreover, the suspect drugs did not include drugs that are harmful to pregnant women, such as those classified as "X" in the Australian Therapeutic Goods Administration Classification. It is believed that latanoprost is a topical agent and is unlikely to affect the uterus. However, one of the reported spontaneous abortions occurred during uterine contractions during pregnancy. It is possible that trace amounts of latanoprost exerted the uterine contractile effects of prostaglandins. The signals obtained from the disproportionality analysis are not conclusive and do not necessarily lead to the discontinuation of latanoprost eye drop prescriptions for pregnant women with glaucoma. However, we believe that an important potential risk has been shown. Recently, an association between IOP-lowering therapy during pregnancy and pregnancy outcome was reported in Japan using a claims database, but the association remains unclear because pregnancy loss was excluded in the algorithm for extracting pregnant women [21]. Therefore, we believe that the signals presented in this study should be validated by a higher quality study design, such as a maternal registration cohort.

The next most frequently reported drug in the FAERS was bimatoprost, and there were few reports of pregnancy loss with this drug, with no signal detected. However, when the contents of individual cases were checked, eyelash growth was listed as an indication, and about half of the cases were used for conditions other than glaucoma (data not shown). In order to investigate the safety of the use of this drug in

pregnant women with glaucoma, it would be necessary to conduct an analysis of only those cases in which it is known that the drug is being used for glaucoma; however, there were many cases in which the indication was not specified, and therefore could not be examined in this study.

Given that the metabolite of travoprost, fluprostenol, has been used as an abortifacient in animals, some people, including healthcare professionals who prepare the drug, should be careful about exposure to travoprost [22], but there is limited evidence in humans. Although the signal was detected in this study, the content of individual cases was checked, and several cases were reported with the same suspect drug and PT at the same time. Although the FAERS identifiers, the PRIMARYID (a unique number for identifying a FAERS report) and CASEID (a number for identifying a FAERS case), were different in all four reports, the possibility that the same case was reported in duplicate cannot be denied.

More cases will likely need to be accumulated to examine the risk of pregnancy loss. For tafluprost, the number of cases was even more limited, and for unoprostone, there were no reports involving pregnant women. Therefore, it is not clear from this study whether the signal observed with latanoprost is a class effect, and drug safety monitoring activities will be necessary in the future.

4.1 Strength and Limitations

To our knowledge, this is the first study to report the possibility of pregnancy loss in humans related to the use of prostaglandin eye drops during pregnancy. Moreover, it is important to note that a common signal was detected in the database of spontaneous reports collected from two different countries. However, this study had several limitations. First, it is well known that signals from a disproportionality analysis often show false positives, owing to the effects of various reporting biases [5]. Because of the lack of denominator information in the spontaneous reporting database, the incidence rate cannot be calculated. The value of the ROR does not necessarily reflect the magnitude of the risk. Nevertheless, because of the limited number of cases in this study, its statistical estimate was unstable, showing a wide range of values. Given that signal detection is a hypothesis-generating study, future efforts to accumulate cases and confirm/refute hypotheses are desirable. In addition, information available on individual case safety reports is limited [23]. In particular, spontaneous reports do not include information on which term of pregnancy the drug was used, which is essential for assessing the causal relationship between drug exposure and pregnancy outcome. However, given that IOP-lowering therapy is usually administered on an ongoing basis and that IOP generally decreases during pregnancy [8], it is expected that the patient is likely to have been using the drug continuously since before pregnancy.

5 Conclusions

Both spontaneous reporting databases in the two different countries consistently showed a drug safety signal for latanoprost-induced pregnancy loss. Although a disproportionality analysis could not determine the causality, we need to keep an eye on the detected signals. It is desirable to use data sources where the incidence can be examined and to investigate whether there is an increased risk compared to an appropriate control group.

Declarations

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Conflicts of interest/Competing interests TS, CM, HK, RY, KT, and FO have no conflicts of interest directly relevant to the content of this study.

Ethics approval This study used a published dataset and no personally identifiable information is included in the paper. Ethics approval is not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions TS, KT, and FO were involved in the conception and design of the study; TS, CM, HK, and RY contributed to the data extraction; TS, HK, and RY conducted the analyses; and all authors contributed to interpreting the data and reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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