European Journal of Obstetrics & Gynecology and Reproductive Biology 207 (2016) 188–192

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full lenght article

Misoprostol exposure during the first trimester of pregnancy: Is the malformation risk varying depending on the indication?

Marine Auffret[a,*], Nathalie Bernard-Phalippon[b], Joëlle Dekemp[a], Patrick Carlier[c], Marie Gervoise Boyer[d], Thierry Vial[b], Sophie Gautier[a]

[a] Centre Régional de PharmacoVigilance du Nord-Pas de Calais, CHRU de Lille, France
[b] Centre Régional de PharmacoVigilance de Lyon, Hospices Civils de Lyon, France
[c] Centre Régional de Pharmacovigilance Paris, Hôpital Fernand Widal, AP-HP, France
[d] Centre Régional de PharmacoVigilance de Marseille, AP-HM, France

ARTICLE INFO

Article history:
Received 6 September 2016
Received in revised form 3 November 2016
Accepted 10 November 2016

Keywords:
Misoprostol
Pregnancy
Voluntary abortion
Teratogenic risk
Congenital malformation

ABSTRACT

Objective: To report the prospective follow-up of pregnancies exposed to misoprostol during the first trimester and analyse the teratogenic risk depending on the indication for use.
Study design: Prospective observational study of 265 women exposed to misoprostol during the first 12 weeks of pregnancy and followed until the delivery. Women were included if they or their physician had contacted a French pharmacovigilance centre before 22 weeks of gestation (WG) to obtain information on the risk of misoprostol exposure, and if there had been misoprostol exposure before 13 WG. Data were collected at the time of the first contact, and the pregnancy outcome was recorded at follow-up. Women were prospectively enrolled from January 1988 to December 2013.
Results: The main indication for misoprostol was voluntary abortion (60.9%). Ten major malformations (5.5%) (95% CI 2.65–9.82%) were reported and five of them were consistent with the pattern of malformations attributed to misoprostol: Möbius sequence, hydrocephalus, terminal transverse limb reduction associated with a clubfoot, syndactyly, and complete posterior encephalocele. The rate of malformations was higher, but not significantly, in women exposed to misoprostol for voluntary abortion (7.9%) compared with women exposed to misoprostol for other or unknown indications (3.2%).
Conclusions: Our results confirmed a specific pattern of malformations due to misoprostol use in early pregnancy, even with low dose of misoprostol. Despite the small number of cases, we observed a higher proportion of major malformations in fetuses born to women who continued their pregnancy after a failed voluntary abortion with misoprostol. Further studies should be conducted to evaluate other potential factors, such as combination treatment with mifepristone and the socio-environmental characteristics in this group of women.

Introduction

Misoprostol is a synthetic prostaglandin E1 analogue used in the prophylaxis and treatment of peptic ulceration in patients taking non steroidal anti-inflammaroty drugs (NSAIDs), due to its gastric cytoprotective effects [1]. Misoprostol is also used in obstetrics for ripening the uterine cervix and stimulating uterine contraction at any stage of pregnancy. In France, misoprostol is given for voluntary abortion, alone or in combination with mifepristone, a synthetic steroid with potent antiprogesterone and antiglucocorticoid activities, until 14 weeks of pregnancy (i.e., weeks after the last menstrual period) [2].It is also used for incomplete miscarriage, induced abortion, intrauterine foetal death, induction of labour with a live fetus, and for the prevention and treatment of postpartum haemorrhage [3,4].

Misoprostol was not found to be teratogenic in rats and rabbits at 625 and 63 times the maximum recommended human doses, respectively [5]. However, birth defects were observed in the offspring of pregnant rabbits given doses of 300–1500 mcg/kg on days 7–19, including spina bifida, caudal vertebral defects, umbilical hernia and gastroschisis [6]. In humans, a variety of congenital malformations have been reported after a failed termination of pregnancy with exposure to misoprostol in early pregnancy. The mechanism by which misoprostol may cause malformations is based on the uterine contractions that it induced.

* Corresponding author at: Centre Régional de Pharmacovigilance, CHRU de Lille, 1 place de Verdun, 59037 Lille Cedex, France.
E-mail address: marine.auffret@chru-lille.fr (M. Auffret).

http://dx.doi.org/10.1016/j.ejogrb.2016.11.007
0301-2115/

These contractions cause flexion of the embryo, particularly at cranial nerves VI and VII. Haemorrhage and/or cell death of the nuclei in these cranial nerves may occur, causing Möbius sequence (characterised by paralysis of the eyes and facial muscles [7–11]).

Uterine contractions may also cause decreased blood flow, leading to hypoxemia and ischaemia, resulting in limb defects [12], defective vascularisation of the subclavian artery, and consequently to Poland sequence [7]. Syndactyly [13], club foot [13], cranial nerve anomalies (affecting nerves V, VI, VII and XII), encephalocele [14] have also been described. Some studies in the particular context of illegal abortion, raised the question of a dose-response effect, with higher doses being more susceptible to be toxic. However, a recent French study that included 246 pregnancies followed prospectively confirmed that malformations can occur even with low-dose exposure [15].

The main objective of our present study was to report the pregnancies exposed to misoprostol during the first trimester collected prospectively via the TERAPPEL system and to analyse the teratogenic risk according to the indication for use. We indeed hypothesize that misoprostol exposition may differ for time of exposure during pregnancy, dose, duration and associated drugs between women who intended voluntary abortion and women treated for other indications.

Methods

This prospective multicentre national study involved 20 French pharmacovigilance centres, which contributed to a shared database of drug exposure during pregnancy (TERAPPEL) using similar documentation and follow-up methodology [16]. This French system is independent from the Centre de Référence sur les Agents Tératogènes (CRAT) (a french public organization especially involved in the problem of drugs during pregnancy), with few overlap expected [17].

We used a method of analysis that has previously been described [18]. Pregnant women were enrolled if they had contacted, either themselves or via their physician, a pharmacovigilance centre between 1 January 1988 and 31 December 2013, for misoprostol exposure. In order to limit recruitment bias and to ensure prospective collection, the inclusion criteria were as follows: 1) exposure to misoprostol (all indications) before 13 weeks after last menstrual period, i.e., during the period of organogenesis, 2) first contact with the pharmacovigilance centre before 22 weeks of gestation (WG), i.e., before morphological ultrasound, and 3) known pregnancy outcome and examinable newborn or fetus. The exclusion criteria were concomitant exposure to a known major teratogen (*e.g.* isotretinoin, acitretin, mycophenolate, methotrexate, thalidomide, valproic acid) before 13 WG, and progressive cancer.

Maternal age, medical and obstetrical history, and detailed drug exposure (exact timing of exposure for all drugs, dose, and indication) since the beginning of pregnancy were obtained during the initial contact with the women or the health professional. Details on the course and outcome of pregnancy (gestational age at delivery, birthweight, congenital abnormalities and neonatal complications) were prospectively obtained by phone or mail within months after the expected delivery date.

The rate of major malformations, defined as those resulting in serious medical, surgical or cosmetic consequences, was the main outcome. Minor malformations were also described. Major or minor malformations were classified according to the EUROCAT classification with the help of a birth defect specialist [19]. The rate of major malformations was obtained by dividing the number of major malformations by the overall number of examinable live births and fetuses (resulting from miscarriages or termination of pregnancy with a pathological examination). Cases with chromosomal aberration or genetic disease were excluded from major malformations.

The population was analysed in two subgroups: the first group (group 1) consisted in women exposed to misoprostol for voluntary abortion, the main indication of misoprostol in the context of pregnancy and the second group (group 2) consisted of women exposed to misoprostol for other indications (i.e., uterine evacuation after incomplete miscarriage, medically-motivated termination of pregnancy, gastroprotective effect . . .) or unknown indications.

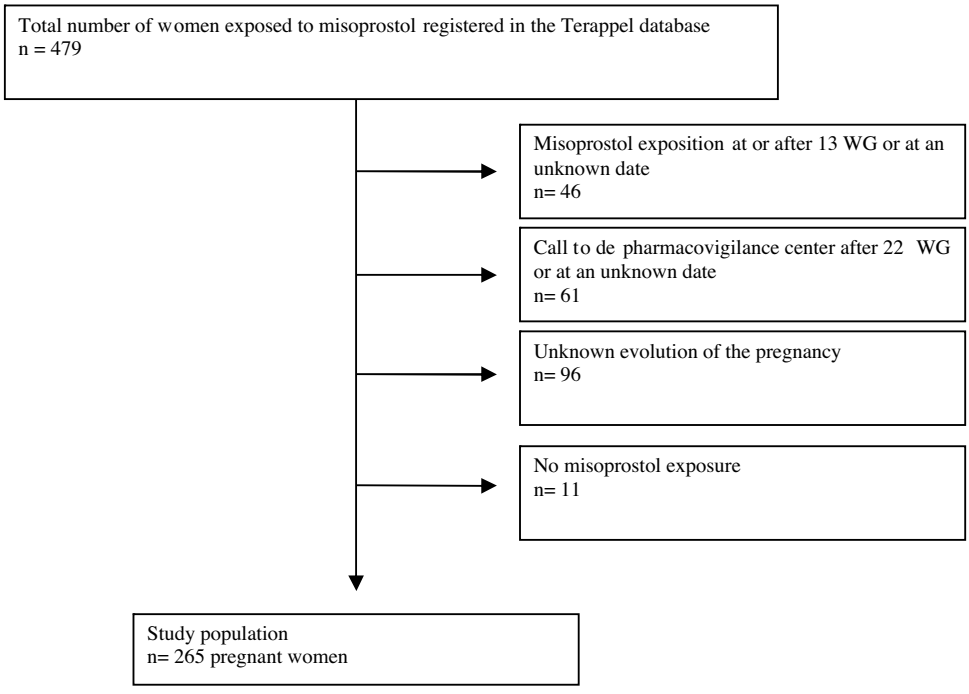

Fig. 1. Flow chart of the study population, with inclusion and exclusion of patients.

Apart from the prospective study, retrospective cases from TERAPPEL database will be briefly presented (calls after an adverse pregnancy outcome has been detected during prenatal diagnosis or after birth).

Statistical analysis

Qualitative variables (including ordinal variables) are expressed as frequency (percentage) and quantitative variables as mean ± standard deviation (SD) or median [interquartile (IQR)] in case of non-Gaussian distribution (normality of distribution was checked graphically and by using the Shapiro–Wilk test). Comparisons between the two groups (women who took misoprostol for voluntary abortion versus women who took misoprostol for another or an unknown indication) were made using the χ^2 test (or Fisher's exact test when expected cell frequency was <5) for qualitative variables, the Mantel-Haenszel trend test for ordinal variables and the Student *t* test (or Mann-Whitney *U* test for non-Gaussian distribution) for quantitative variables.

Statistical testing was done at the two-tailed α level of 0.05. Data were analysed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

Results

Data on 265 pregnancies were obtained from the collective French database TERAPPEL (Fig. 1). One hundred and ninety women were exposed to misoprostol alone and 75 to misoprostol and mifepristone. For all women exposed to misoprostol and mifepristone, misoprostol indication was voluntary abortion.

The indication of misoprostol was known for all but 40 cases. The main indication was voluntary abortion (137 women, 60.9%), followed by gastroenterological use (44 women, 19.5%), incomplete miscarriage (43 women, 19.1%) and one case of ectopic pregnancy.

Mean maternal age at inclusion was 29.5 years, sd 5.9. A previous history of voluntary abortion was found in 18.4% of women included. Women were included at a median gestational age of 9 WG [IQR: 7–13] and they were exposed to misoprostol at a median age of 6 WG [IQR: 5–8]. The misoprostol cumulative dose was 600 μg [400–1600].

Data on tobacco and alcohol consumption were available for 69 women. None were considered to be alcohol abusers (none consumed more than two drinks per day), nine women (13.0%) drank less than two drinks per day (13.2% in group 1 vs. 12.9% in group 2), 23 (33.3%) were smokers, with a higher rate in group 1 (44.9% vs. 19.4%); nine women (13.0%) were heavy smokers, with a higher rate in group 1 (31.1% vs. 3.2%).

Pregnancy outcomes consisted in 174 live births including one twin pregnancy (65.4%). A voluntary abortion occurred in 59 cases (22.2%), a miscarriage in 24 cases (9.0%) (including two with anatomopathological examination) and a medically motivated abortion for 9 cases (3.4%) (including seven with anatomopathological examination). For the nine medically-motivated termination of pregnancy there were six cases of malformation (five major and one minor) and one case of chromosomal aberration detected by ultrasound examination after drug exposure. In one case, medically-motivated termination of pregnancy was motivated by an ectopic pregnancy and in one other case the reason was unknown.

After exclusion of two chromosomal aberrations or genetic disease, ten major malformations were observed in 183 newborns or examined fetuses (174 live births and nine fetuses examined).

Table 1
Major malformations reported and characteristic of interest between the two groups of indication.

	Total	Group 1	Group 2	p
Maternal age, years (mean ± SD) (*n = 247*)[a]	29.5 ± 5.9	28.6 ± 6.5	30.6 ± 5.0	0.007
Gestational age at drug exposure, weeks (median [IQR]) (*n = 231*)[a]	6 [5–8]	7 [6–9]	6 [4–7]	< 0.0001
Misoprostol cumulative dose, μg (median [IQR]) (*n = 183*)[a]	600 [400–1600]	400 [400–800]	1200 [400–2400]	< 0.0001
Rate of major malformations (*n = 183*)[a]	10 (5.5)	7 (7.9)	3 (3.2)	0.20
Type of major malformations		**Asymmetric lower limb reduction defects, club foot, scoliosis, macrocrania, single pulmonary lobe** *Misoprostol 400 μg and mifepristone 200 mg at 6 WG (issue: therapeutic abortion)*	**Large vessel transposition** *Misoprostol 1200 μg before 13 WG for an unknown indication (issue:birth)*	–
		Möbius syndrome *Misoprostol 400 μg and mifepristone 600 mg between 5 and 7 WG (issue:birth)*	**Hexadactyly** *Misoprostol (unknown dose) at 7 WG for suspected miscarriage (issue:therapeutic abortion)*	–
		Complete posterior encephalocele *Misoprostol 400 μg and mifepristone 600 mg dose at 9 WG (issue:therapeutic abortion)*	**Cerebellar hypoplasia** *Misoprostol 200 μg and diclofenac at 4 WG for gastroenterology indication (issue:therapeutic abortion)*	–
		Laparoschisis *Misoprostol 400 μg and mifepristone 600 mg at 5 WG (issue:birth)*	–	–
		Hydrocephalus *Misoprostol 800 μg and mifepristone 200 mg before 13 WG (issue:therapeutic abortion)*	–	–
		Pituitary stem interruption syndrome *Misoprostol 400 μg at 11 WG (issue:birth)*	–	–
		Limb defect, syndactyly *Misoprostol 200 μg and mifepristone 600 before 13 WG (issue:birth)*	–	–

Group1: women exposed to misoprostol for voluntary abortion – Group 2: women exposed to misoprostol for other indications or unknown indications.
μg: microgram, IQR : Interquartile range mg: milligram, WG: weeks of gestation.
[a] Number of patients with available data.

Table 2
Major malformations retrospectively collected.

Voluntary abortion	Other or unknown indication
Anencephaly, cervicodorsal myelomeningocele, radial club hand, single umbilical artery	**Congenital megaureter**
Misoprostol (unknown dose) and mifepristone (unknown dose) before 13 WG (issue: therapeutic abortion)	Misoprostol 1600 μg at 5 WG for suspected miscarriage (issue:birth)
Möbius syndrome	**Brain malformation (isolated bilateral germinolytic cysts)**
Misoprostol 400 μg and mifepristone 600 mg at 8 WG (issue:birth)	Misoprostol 400 μg at 7 WG for an unknown indication (issue: therapeutic abortion)
Hydrocephalus	
Misoprostol 200 μg at 11 WG (issue:therapeutic abortion)	
Potter sequence: dysmorphia, lung hypoplasia, multicystic kidney	
Misoprostol 400 μg at 6 WG (issue:therapeutic abortion)	
Oligodactyly of inferior and superior limb, large meningoencephalocele, facial dysmorphia	
Misoprostol 400 μg and mifepristone 600 mg at 7 WG (issue:therapeutic abortion)	
Club foot, syndactyly	
Misoprostol 400 μg at 11 WG (issue:birth)	
Cerebellar vermian agenesis	
Misoprostol (unknown dose) and mifepristone (unknown dose) (issue:therapeutic abortion)	
Bilateral hexadactyly	
Misoprostol 800 μg and mifepristone (unknown dose) at 5 WG (issue:birth)	
Left hand hypoplasia	
Misoprostol 400 μg and mifepristone 600 mg at 7 WG (issue:therapeutic abortion)	
Corpus callosum agenesis	
Misoprostol 600 μg and mifepristone 600 mg at 8 WG (issue:therapeutic abortion)	

μg: microgram, mg: milligram, WG: weeks of gestation.

The resulting rate of major malformations was 5.5% (CI 95% 2.65–9.82%) in our study population.

When we compared the two groups (Table 1), women exposed to misoprostol for voluntary abortion significantly received a smaller cumulative dose of misoprostol (400 μg vs. 1200 μg $p < 0.0001$) and were exposed statistically later during pregnancy (7 WG [6–9] vs. 6 WG [4–7] $p < 0.0001$). The rate of major malformations was slightly increased in group 1 (7.9% vs. 3.2% in group 2) but did not reach statistically significance ($p = 0.20$) All the major malformations compatible with the spectrum of malformation of misoprostol were reported in the group 1.

Major malformations retrospectively collected are summarized in Table 2.

Discussion

We found a 5.5% rate of major malformations after exposure to misoprostol during the first trimester of pregnancy, which is slightly higher than the expected rate in the general population (2%) [19]. Among the reported major malformations, five (50.0%) were consistent with the pattern of malformations attributed to misoprostol in the literature (Table 1). In addition, among the 13 major malformations reported retrospectively after exposure to misoprostol (Table 2) collected during the study, six were consistent with the specific pattern of malformations described for misoprostol. All these data confirm the rare but specific risk related to misoprostol after exposure in the first trimester of pregnancy.

When we compared the two groups based on misoprostol's indications of use, the rate of major malformations was higher, but not significant, for women exposed to misoprostol for voluntary abortion. Five of the seven malformations reported in women exposed to misoprostol for voluntary abortion were consistent with the typical pattern of malformations described for misoprostol whereas none in the other group. Mifepristone was systematically associated with misoprostol for these five major malformations.

The role of mifepristone deserves debate. No risk of malformation associated with mifepristone had previously been demonstrated. The largest study published on this subject included 105 pregnancies exposed to mifepristone for voluntary abortion during the first trimester of pregnancy where the patients were followed prospectively [18]. The rate of major malformation was 4.2%, which was slightly higher than that in the general population. In that study, the four major malformations may be explained by factors other than mifepristone exposure: in two cases, associated medical conditions could explain the birth defects and in the other two cases, the women had also been exposed to misoprostol, and the malformations corresponded to the specific malformation pattern previously described for that drug. If mifepristone is not teratogenic alone, the role of its combination with misoprostol must be evaluated specifically. This is supported by the fact that the antiprogesterone activity of mifepristone results in uterine contractions and enhances the sensitivity of the myometrium to the contraction-inducing activity of prostaglandins (i.e., misoprostol) [20].

Major malformations were observed for median cumulative doses ranging from 200 to 1400 μg. Moreover, half of the major malformations observed in our study occurred after exposures to a misoprostol dose of 400 μg. A possible dose-effect has been evocated, especially in studies conducted in countries where voluntary abortion is illegal. Indeed, in these countries, the dose of misoprostol used was for some patients very high and there was not well-established procedures (i.e., other drugs may have been administered, other medical interventions may have been used, etc.) [14,21–27].

Our results, along with the results of the previous French study, are not in favour of a relation between the malformation risk and the dose of misoprostol, indicating that careful attention should be paid to all pregnancies exposed to misoprostol, regardless of the dose [15].

In our study, the lack of a control group for comparison is grounds for criticism. However, in this type of study using a database relying on the recording (and follow-up) of spontaneous questioning of women or healthcare professionals about the potential risk of drug exposure in pregnancy, it is obviously difficult to recruit an appropriate unexposed group. First of all, it is difficult to collect post-partum data in women exposed to drugs that are non-teratogenic, and who are less concerned about the importance of following-up the reports collected. This point may lead to an overestimation of the risk of misoprostol exposure on the pregnancy outcome. Moreover, the common characteristics of

these women, such as their initial disorders or conditions, the indications for treatment, the type of treatment (potentially non-teratogenic vs. teratogenic) and type of exposure (acute or chronic) may differ, because the use of misoprostol mainly takes place in the particular context of voluntary abortion.

Moreover, the short duration of follow-up may have led to an under-diagnosis of the moderate symptoms of Möbius sequence, such as feeding difficulties, expressionless faces and speech impediments that result in social disadaptation. This may have led to an underestimation of the risk of Möbius syndrome.

Conclusion

Our results are in accordance with previous findings on the teratogenic role of misoprostol, and showed for the first time that the risk may be different depending on misoprostol's indication and likely in a non-dose-dependent manner. The role of the combination of mifepristone and misoprostol, the time of exposure during pregnancy and the role of socio-environmental factors (for example tabacco and alcohol consumption) need to be further evaluated.

Disclosure of interests

None declared.

Contribution to authorship

All authors have contributed to the study and approved the final version of the article. MA, NB, TV and SG designed the study. MA and SG analysed the data. MA, NB and SG drafted the article. MA, NB, JD, PC, MGB, TV and SG contributed to data collection, data entry, data interpretation and article composition.

Ethical approval

The databse used for the purpose study has been declared to the French Commission nationale de l'informatique et des libertés (CNIL). As the study was only observational, according to the French legislation no ethics approval was required.

Funding

No funding was obtained for this study.

Acknowledgments

The participation of the network of French pharmacovigilance centers and the helpful contributions of Dr Sylvie Joriot (Lille) and Dr Emmanuelle Amar (Lyon) for their expertise on birth defects are acknowledged. The authors thank Pernelle Noize (Bordeaux) for her careful review of the article. Finally the authors thank Elodie Drumez and Julien Labreuche (Lille) for their help on statistical analysis.

References

[1] Misoprostol, Martindale, Pharmaceutical Press, London, 38th edition (2014).
[2] de Santé Haute Autorité. Interruption médicamenteuse de grossesse. Les protocoles à respecter. .
[3] Collège National des gynécologues et Obstétricien de France (CNGOF), Interruption médicale de grossesse. Processus décisionnel et pris en charge (2008).
[4] Elati A, Weeks AD. The use of misoprostol in obstetrics and gynaecology. BJOG Int J Obstet Gynaecol 2009;116(Suppl. 1):61–9.
[5] Product information, Cytotec. G.D. Searle (2001).
[6] Clemens GR, Hilbish KG, Hartnagel Jr. RE, Schluter G, Reynolds JA. Developmental toxicity including teratogenicity of E1 prostaglandins in rabbits. Toxicol 1997 36260.
[7] Pachajoa H, Isaza C. First case of Moebius-Poland syndrome in child prenatally exposed to misoprostol. Neurol Barc Spain 2011;26(8):502–3.
[8] Pirmez R, Freitas MET, Gasparetto EL, Araújo APQC. Moebius syndrome and holoprosencephaly following exposure to misoprostol. Pediatr Neurol 2010;43(5):371–3.
[9] Sánchez O, Guerra D. Moebius syndrome due to the use of misoprostol. Case report. Investig Clínica 2003;44(2):147–53.
[10] Bos-Thompson M-A, Hillaire-Buys D, Roux C, Faillie J-L, Amram D. Möbius syndrome in a neonate after mifepristone and misoprostol elective abortion failure. Ann Pharmacother 2008;42(6):888–92.
[11] Gonzalez CH, Vargas FR, Perez AB, Kim CA, Brunoni D, Marques-Dias MJ, et al. Limb deficiency with or without Möbius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. Am J Med Genet 1993;47(1):59–64.
[12] Genest DR, Di Salvo D, Rosenblatt MJ, Holmes LB. Terminal transverse limb defects with tethering and omphalocele in a 17 week fetus following first trimester misoprostol exposure. Clin Dysmorphol 1999;8(1):53–8.
[13] Gonzalez CH, Marques-Dias MJ, Kim CA, Sugayama SM, Da Paz JA, Huson SM, et al. Congenital abnormalities in Brazilian children associated with misoprostol misuse in first trimester of pregnancy. Lancet Lond Engl 1998;351(9116):1624–7.
[14] Barbero P, Liascovich R, Valdez R, Moresco A. Misoprostol teratogenicity: a prospective study in Argentina. Arch Argent Pediatr 2011;109(3):226–31.
[15] Vauzelle C, Beghin D, Cournot M-P, Elefant E. Birth defects after exposure to misoprostol in the first trimester of pregnancy: prospective follow-up study. Reprod Toxicol Elmsford N 2013;36:98–103.
[16] Vial T, Gouraud A, Bernard N. Terappel: description of a computerised database and examples of studies. Thérapie 2014;69(1):31–8.
[17] Bellet F, Beyens M-N, Bernard N, Beghin D, Elefant E, Vial T. Exposure to aripiprazole during embryogenesis: a prospective multicenter cohort study. Pharmacoepidemiol Drug Saf 2015;24(4):368–80.
[18] Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG Int J Obstet Gynaecol 2013;120(5):568–74.
[19] EUROCAT website database, EUROCAT prevalence data tables, (Internet), Available from: http://www.eurocat-network.eu/prenatalscreeninganddiagnosis/generalinformation/introduction.
[20] Sitruk-Ware R, Spitz IM. Pharmacological properties of mifepristone: toxicology and safety in animal and human studies. Contraception 2003;68(6):409–20.
[21] Opaleye ES, Coelho HLL, Schüler-Faccini L, de Almeida PC, dos Santos EC, Ribeiro AJV, et al. Evaluation of the teratogenic risks in gestations exposed to misoprostol. Rev Bras Ginecol E Obstetrícia Rev Fed Bras Soc Ginecol E Obstetrícia 2010;32(1):19–35.
[22] Schüler L, Pastuszak A, Sanseverino TV, Orioli IM, Brunoni D, Ashton-Prolla P, et al. Pregnancy outcome after exposure to misoprostol in Brazil: a prospective, controlled study. Reprod Toxicol Elmsford N 1999;13(2):147–51.
[23] Orioli IM, Castilla EE. Epidemiological assessment of misoprostol teratogenicity. BJOG Int J Obstet Gynaecol 2000;107(4):519–23.
[24] Dal Pizzol T da S, Sanseverino MTV, Mengue SS. Exposure to misoprostol and hormones during pregnancy and risk of congenital anomalies. Cad Saúde Pública 2008;24(6):1447–53.
[25] Pastuszak AL, Schüler L, Speck-Martins CE, Coelho KE, Cordello SM, Vargas F, et al. Use of misoprostol during pregnancy and Möbius' syndrome in infants. N Engl J Med 1998;338(26):1881–5.
[26] Vargas FR, Schuler-Faccini L, Brunoni D, Kim C, Meloni VF, Sugayama SM, et al. Prenatal exposure to misoprostol and vascular disruption defects: a case-control study. Am J Med Genet 2000;95(4):302–6.
[27] Brasil R, Lutéscia Coelho H, D'Avanzo B, La Vecchia C. Misoprostol and congenital anomalies. Pharmacoepidemiol Drug Saf 2000;9(5):401–3.