Congenital and Fetal Effects After Mifepristone Exposure and Continuation of Pregnancy: A Systematic Review

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Mifepristone is an anti-progestational drug that is the first component of the standard medical abortion regimen. For women who take mifepristone and then do not take misoprostol, which is the second component of the medical abortion regimen, it is possible that their pregnancy may continue to live birth. Since mifepristone is commonly used for medical abortion up to 9–10 weeks gestation, any adverse or teratogenic effects on the developing embryo/fetus must be considered, given exposure during the critical time of its development and organogenesis. Toxicology and teratology reports have cited studies demonstrating teratogenic effect of mifepristone in some animals. Current clinical guidelines for women exposed to mifepristone in the first trimester of pregnancy state that it is not known to be teratogenic based on limited published evidence from humans. The aim of this narrative systematic review was to investigate embryonic/fetal exposure to mifepristone and any association with congenital or fetal anomalies. This study was conducted by systematic searches of health databases from inception to February 2024. The references of relevant citations were manually searched to retrieve any additional citations not captured in database searching. Congenital anomalies and adverse outcomes were encountered at various doses of mifepristone exposure. A number of the congenital anomalies encountered in this review were explained by circumstances other than exposure to mifepristone. The present systematic review did not find data to support mifepristone being implicated as a teratogen.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Mifepristone is teratogenic in some animals. Reports and guidelines vary on whether mifepristone has teratogenic potential in humans.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In ongoing pregnancies in which there is exposure of the embryo/fetus to mifepristone, is there an increase in the rate of congenital anomalies compared with the baseline rate in the general population?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The risk of congenital anomalies after mifepristone exposure in pregnancy does not appear to be increased over the baseline rate in the general population.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Conclusions from this review lend support to existing clinical guidelines for women who take mifepristone for medical abortion but then proceed to having a viable pregnancy instead: that mifepristone is unlikely to cause congenital anomalies. This is becoming increasingly important as the number of medical abortions using mifepristone increases.

The combination of mifepristone followed by misoprostol is widely used for early medical abortion. A common, evidence-based regimen of mifepristone 200 mg followed by misoprostol 800 mcg buccally or intravaginally 36 to 48 hours later has successful pregnancy termination rates ranging from 95.2% to 97.7%.[1,2] Earlier clinical research and practice utilized a higher dose of mifepristone (600 mg).[3,4]

Progesterone is essential in initiation and maintenance of pregnancy.[5–7] Progesterone is primarily produced by the corpus luteum in early pregnancy, with levels increasing from about 7 weeks when

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production shifts to the placenta.[8] Mifepristone is an anti-progestin that has high affinity for progesterone and glucocorticoid receptors, and weak affinity for the androgen receptor. It is a competitive antagonist at progesterone receptors during pregnancy and exhibits reversible binding. While progesterone receptors predominate in the decidualized endometrium and cervix of the woman[9] there appears to be no direct effect of mifepristone on the trophoblast.[8] The anti-progestin effects of mifepristone halt progression of the pregnancy, initiate detachment of the placenta and embryo from the endometrium, and cause cervical dilation and softening.[5] After mifepristone exposure, the myometrium is sensitive to prostaglandins and the contractions they cause.[6] Misoprostol is a synthetic prostaglandin E1 analogue.[10] It can cause cervical dilation and softening, and initiates uterine contractions. Misoprostol has various other uses in gynecology including management of incomplete miscarriage, prevention, and treatment of postpartum hemorrhage, and induction of labor in the second trimester.[10]

There has been a global rise in unintended pregnancy rates ending in abortion from 51% to 61% between 1990 and 2019.[11] Recent figures from the United States noted medication abortions having increased from 247,557 in 2019[12] to 291,890 in 2020.[13] A small proportion of women commencing medical abortion do not complete the process and may continue their pregnancy instead (**Figure 1**). One study found that of the 3.4% of women with viable pregnancies after taking mifepristone then misoprostol, 10% of these decided to continue their pregnancy.[14] It has been reported that some women change their mind after taking mifepristone alone and seek to actively maintain their pregnancy.[15]

For women who take mifepristone and then decide not to take misoprostol, there is the possibility that their pregnancy will continue to live birth with or without intervention. Since mifepristone is commonly used for medical abortion up to 9–10 weeks of pregnancy, any adverse or teratogenic effects on the developing embryo/fetus must be considered since exposure to mifepristone occurs during the critical time of embryo development and organogenesis. The birth of a child with a congenital abnormality can have a devastating impact on the parents,[16] including engendering feelings of guilt and emotional difficulties.[17] Congenital anomalies also contribute to rates of miscarriage and stillbirth, and childhood morbidity and disability.[18]

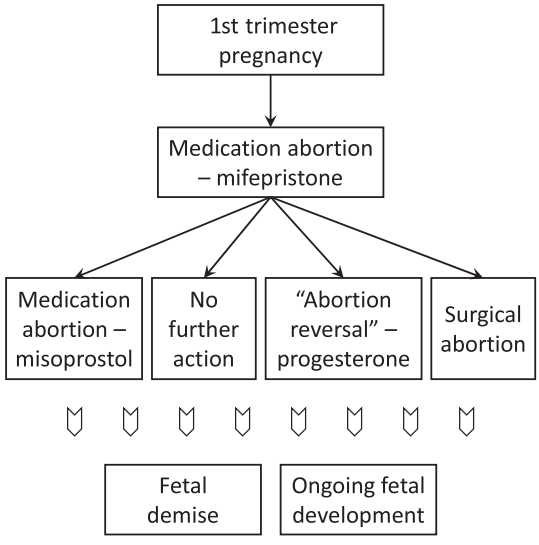

Figure 1 Timeline of mifepristone exposure and fetal outcome.

Toxicology[19] and teratology[20] reports have cited studies demonstrating teratogenic effect of mifepristone in rabbits, and some, but not all, monkey studies.[21,22] These reports provide caution about the unknown teratogenic potential of mifepristone in humans. Current clinical guidelines for women exposed to mifepristone in the first trimester of pregnancy state that it is not known to be teratogenic.[23] This is based on a single observational study of women exposed to mifepristone alone in the first 12 weeks of pregnancy. This prospective study did not demonstrate a significant increase in congenital anomalies in babies born to mothers exposed to mifepristone compared with the accepted rate of congenital anomalies found in the general population.[24] Birth defects, defined as any major structural anomalies present at birth, affect approximately 3% of all births in the general population.[25] There is lack of consensus regarding terminology in this field, with several terms being used interchangeably, including congenital disorders, defects, anomalies, and malformations. For the purpose of this review, the term congenital anomaly will be used.[26]

Given the increasing incidence of women exposed to mifepristone in the first trimester of pregnancy, there is an ongoing need for evidence to inform them of any teratogenic risk of such exposure. The aim of this narrative systematic review is to collate and analyze all studies reporting on embryonic/fetal exposure to mifepristone and any associated congenital or fetal anomalies.

METHODS

This review was registered on PROSPERO on June 28, 2021 (CRD42021255506). The study was conducted by systematic searches of the Medline (OVID), Embase (OVID), Cochrane Library (Wiley) and CINAHL (EBSCO) databases from database inception. Initial database searches were undertaken in May 2021. The search strategies for both Medline and Embase were constructed around the key concepts of congenital or fetal effects, mifepristone and pregnancy or termination. A broader search of the Cochrane and CINAHL databases, not restricting to particular outcomes, was undertaken to capture any additional fetal or congenital outcomes not identified in the Medline or Embase searches. Searches were limited to studies in English (**File S1**). Certain publication types including comments, editorials, letters, news, books, and book chapters as well as conference abstracts were excluded. Database searches were updated in February 2024 and the search strategies modified to include the publication type, letters.

Manual interrogation of reference lists of primary articles uncovered from initial search results were also conducted. A number of letters were found to be relevant for inclusion. Results were imported into Covidence and duplicates identified and removed. Title and abstract review were undertaken by two pairs of independent reviewers. Records were assessed as either eligible or ineligible. A record was excluded if both reviewers assessed it as ineligible after initial review. If there was a conflict, then a consensus was reached by discussion. Eligible records underwent full text review by two independent reviewers. Any conflicts were resolved by a third, independent reviewer. A study was included if both initial reviewers independently or jointly assessed it as eligible based on the inclusion criteria from the full text, or if the third reviewer so determined in the case of a disagreement. As a quality control measure, a random sample of 20 studies excluded at the full text stage were examined by fourth independent reviewer.

Quality assessment

Quality assessment of studies included in the current review was undertaken using an adaption of the Institute of Health Economics Quality Appraisal (IHA QA) for case series studies, a questionnaire that included 20 items.[27] Of these 20 items, 16 relevant questions were selected to evaluate the study quality in the present systematic review. A study was defined as high quality if 15 or more answers to these questions were positive, medium quality if 12 or more answers were positive, or low quality if less than 12 answers were positive. The four questions that were excluded from the IHA QA were irrelevant to the current review, and were: blinded interventions; outcome measured prior to the intervention; statistical tests used to assess relevant outcomes; and whether the study provided estimates of random variability in the data analysis of relevant outcomes or not. The removal of these four questions provided a quality assessment tool that was best suited to the literature identified for the current systematic review.

Literature and outcome data

Studies were considered eligible if they included the following criteria:

1. Reported pregnancy outcomes,
2. Mifepristone exposure.

Main outcomes assessed were congenital anomalies (at birth) or fetal anomalies (in the case of miscarriages, stillbirths, and elective terminations of pregnancy). Congenital anomalies are defined as defects, disorders, or malformations identified before or at birth, that have developed prenatally. Major anomalies were defined as malformations having serious medical, surgical, or cosmetic consequences.[28] Descriptive analysis of numbers and types of anomalies was also undertaken. This was compared with the baseline rate of congenital anomalies present in the general population.

Additional outcomes considered were gestation at termination/delivery, and the means of pregnancy termination including delivery or abortion.

Data extracted included study dates and design, patient demographics, mifepristone exposure (including dose, route, duration, gestation at dosing), concomitant drug and other exposures. Outcome data was sought for: termination of pregnancy (livebirth, miscarriage, stillbirth, and iatrogenic termination), gestation at delivery (including preterm birth), congenital anomalies, neonatal birth weight (including low birth weight), and need for special care nursery, respiratory distress syndrome of the newborn, and other neonatal morbidity and mortality.

RESULTS

The initial searches identified 5533 citations. Six records were excluded since they were unable to be located on any accessible Australian or international databases. After deduplication, 3484 citations remained, and 10 articles met the inclusion criteria. Three articles were then added via an independent reference list search (**Figure 2**). After the updated search, 939 additional citations were identified, of which 681 individual records were assessed, with none being included for data extraction.

The 13 publications analyzed consisted of case reports (majority), observational studies containing both retrospective and prospective data, a systematic review, and a non-peer reviewed scientific/medical report.

Two of the included reports were assessed as being high quality, with more than half assessed as low quality (**Table 1**). Studies tended to score lower in questions 1–8 in which population and intervention details were assessed, and scored higher in questions 10–15 which involved assessment of outcomes.

A total of 361 cases of pregnant women exposed to mifepristone alone were described in the literature (**Table 2**). One report did not clearly differentiate between women who were exposed to mifepristone plus a prostaglandin or mifepristone alone.[20] There were 21 fetuses/infants reported as having congenital anomalies, and 13 reported as having neonatal adverse outcomes. In the majority of cases reporting congenital defects, mifepristone was administered in the first trimester, with dosages ranging between 200 and 1200 mg.

Congenital anomalies/adverse neonatal outcomes

A high-quality prospective observational study conducted in France in 2013 examined data on 105 pregnancies that continued after a failed medical abortion or because the patient changed their mind.[24] Of these, 46 pregnancies were exposed to mifepristone only. Pregnancy outcomes comprised of: one repeated abortion (unknown if medical or surgical abortion), eight miscarriages, and 37 live births. Of the 37 livebirths, three were preterm deliveries. In two of the live births associated with mifepristone exposure, the babies had congenital anomalies. One neonate, exposed to 600 mg of mifepristone at 4 weeks gestation, was diagnosed with Claude-Bernard-Horner's syndrome with stridor at birth. This baby was also large for gestation (4010 g). Claude-Bernard Syndrome is recognized as a sequela of traumatic vaginal delivery of a high-birthweight newborn.[29] The second fetus was exposed to 400 mg of mifepristone at 7 weeks gestation and resulted in a spontaneous abortion at 18 weeks. Examination of the fetus revealed evidence of hydrocephalus with tri-ventricular dilatation and an adductus thumb. Subsequent pathological examination revealed streptococcus B chorioamnionitis, which may have contributed to the anomalies identified.

Henrion published a letter to the editor of *Nature* in 1989 clarifying the report of a single case of exposure to mifepristone and continuing pregnancy by the chair of the French Ministry of Health commission that was approving mifepristone for commercial use in France in 1988. After exposure to mifepristone in early pregnancy, the woman subsequently proceeded to a surgical termination of pregnancy at 18 weeks for severe oligohydramnios. The only description provided was that of a "case of fetal malformation." It was also noted for this case that "embryological examination did not allow any conclusions to be drawn regarding the role of RU 486."[30]

In 1991, Pons reported on a fetus exposed to 400 mg of mifepristone after 5 weeks amenorrhea.[31] It is unclear[32] if this is the same case as the one discussed by Henrion 1989.[30] At 17 weeks gestation, an ultrasound scan showed a complete lack of amniotic sac, while stomach, gallbladder, and urinary tract were also not seen. The pregnancy was then terminated at 18 weeks by administration of a prostaglandin. Examination of the fetus showed sirenomelia, cleft palate and cleft lip. The study also reported on another case that described a 3030 g baby born at term with no congenital anomalies after exposure to mifepristone "at 6 weeks of amenorrhea."

A low-quality retrospective observational study published by Sitruk-Ware in 1998 presented data on 71 cases of continuing pregnancy after failed early medical termination of pregnancy that occurred between 1987 and 1998 in the UK, France, and Sweden.[33] The study analyzed data on cases where mifepristone

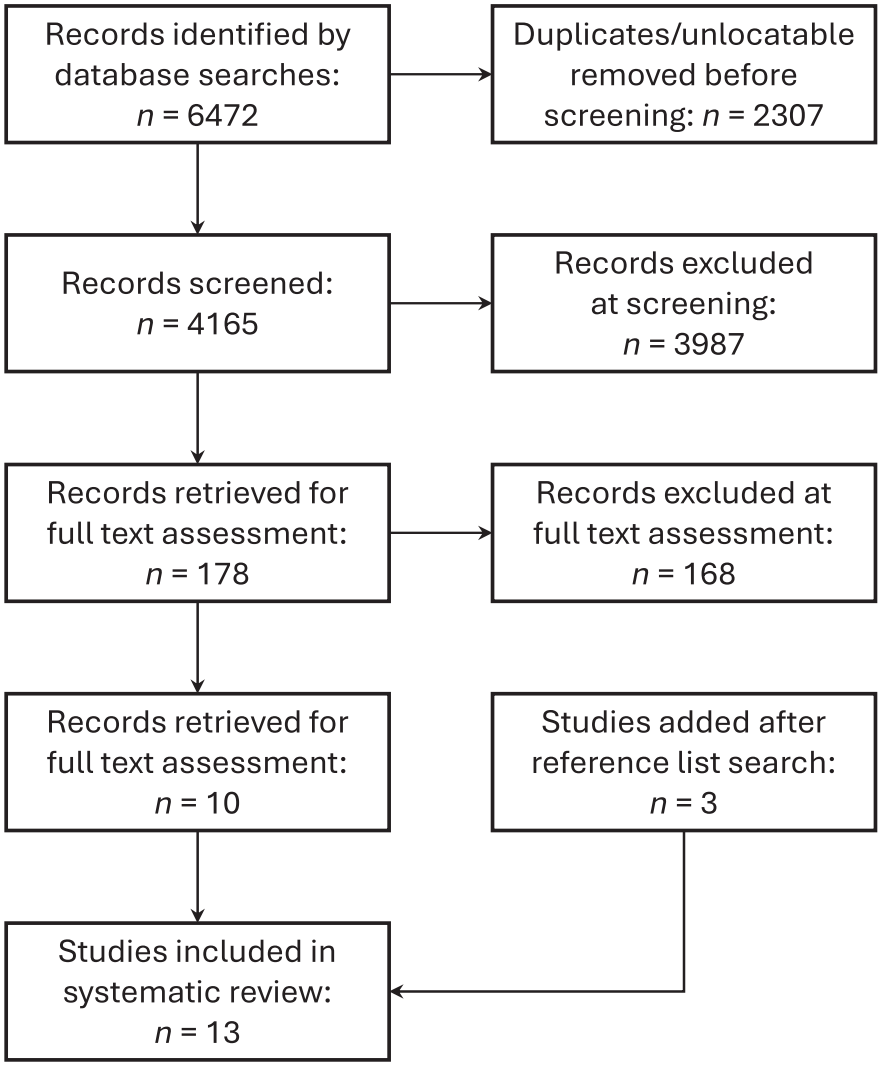

Figure 2 PRISMA flow diagram of article selection.

was used alone as well as when associated with a prostaglandin analogue. There was one case of fetal anomaly documented with mifepristone only exposure. The fetus was exposed to 400 mg of mifepristone and was subsequently surgically aborted at 7 weeks gestation.

A systematic review published by Gary in 2006 on Adverse Event Reporting (AER) to the Food and Drug Administration presented information on continuing pregnancy after medical abortion in the United States of America.[34] Thorough analysis of AER cases was not able to be made due to lack of detail in the original reports. Thus, AERs involving mifepristone-only and mifepristone/misoprostol exposure were not able to be differentiated. For the 22 second, trimester pregnancies that were ongoing after failed medical abortion, nine pregnancies proceeded to elective termination, one was enrolled in a fetal registry, three were documented to have major congenital anomalies, and nine pregnancies were lost to follow-up.

A case study from France reported by Sentilhes in 2007, discussed a fetus that was exposed to 200 mg mifepristone at 10 weeks gestation and ultimately resulted in a termination of pregnancy following abnormal morphology findings on ultrasound at 22 weeks gestation.[35] The findings were of an amputation of the right arm above elbow, bilateral talipes of equinovarus, and severe cerebellum atrophy. Prior to the 22-week scan, ultrasounds performed at 10 and 12 weeks showed no abnormal findings. Pathological examination of the placenta showed an amniotic band which was thought unlikely to have been directly associated with mifepristone. The authors postulated that amniotic rupture after mifepristone exposure possibly contributed to the amniotic band syndrome and cerebellar atrophy.

The report by Delgado published in 2012 reported on six cases where women commenced early medical abortion but then changed their mind after taking mifepristone. They were subsequently administered progesterone to try to maintain pregnancy viability.[36] One baby delivered at term with no birth defects had neonatal complications including neonatal physiologic jaundice and circumcision wound infection. Three of the cases reported no neonatal complications or birth defects. The two other cases included in the study resulted in spontaneous abortions, without detail on any birth defects being commented upon.

Table 1 Quality analysis scoring

Henrion 1989	Lim 1990	Pons 1991	Sitruk-Ware 1998	Hunter 2002	Sorenson 2005	Gary 2006	Sentilhes 2007	Delgado 2012	Bernard 2013	UKTIS 2016	Garratt 2017	Delgado 2018	
0	1	1	1	0	1	1	1	1	1	0	1	1	1. Was the hypothesis/aim/objective of the study clearly stated?
0	0	0	0	1	1	0	0	0	1	0	0	0	2. Was the study conducted prospectively?
0	1	0	1	0	0	1	0	1	1	1	1	1	3. Were the cases collected in more than one center?
0	1	0	0	1	1	0	1	0	1	1	1	1	4. Were the patients recruited consecutively?
0	1	1	1	1	1	1	1	1	1	0	1	0	5. Were the characteristics of the patients included in the study described?
0	0	0	0	1	1	0	1	0	1	0	0	1	6. Were the eligibility criteria for entry into the study clearly stated?
0	1	1	1	1	1	0	1	1	1	0	1	1	7. Did the patients enter the study at a similar point?
0	0	1	1	0	1	1	1	0	1	1	1	1	8. Was the intervention of interest clearly described?
1	0	1	1	0	1	0	1	1	1	0	1	1	9. Were the additional interventions (co-interventions) clearly described?
1	1	0	1	1	1	1	1	0	1	1	1	1	10. Were relevant outcomes measures established *a priori*?
1	1	1	1	1	1	1	1	0	1	1	1	1	11. Were the relevant outcomes measured using appropriate objective/subjective methods?
1	1	1	0	1	1	1	1	1	1	1	1	1	12. Was follow-up long enough for important events and outcomes to occur?
1	1	1	0	1	1	1	1	1	0	1	1	1	13. Were losses to follow-up reported?
1	1	1	1	1	1	1	1	1	1	1	1	1	14. Were the adverse events reported?
1	1	1	1	1	1	1	1	1	1	1	1	1	15. Were the conclusions of the study supported by the results?
0	0	0	0	1	1	1	1	1	1	0	1	0	16. Were both competing interests and sources of support for the study reported?
7	11	10	10	12	15	11	14	10	15	9	14	13	Quality score
Low	Low	Low	Low	Med	High	Low	Med	Low	High	Low	Med	Med	Quality rating: Low <12; Medium 12–14; High 15–16

Table 2 Studies with pregnancy continuation after mifepristone exposure

Study	Pregnancies reported on	Mifepristone		Pregnancy outcomes (*n*)	Congenital anomalies (*n*)	Neonatal adverse outcomes (*n*)
		Timing	Dose			
Henrion (1989) France Case Report	1	Not reported	Not specified	Abortion at 18 weeks	Severe oligohydramnios (1)	N/A
Lim (1990) United Kingdom Case Report	3	48 days, >63 days	Not specified	Live birth (3)	Nil	Nil
Pons (1991) France Case Report	2	>42 days, 35 days	400 mg	Live birth (1) Medical abortion at 18 weeks (1)	Nil (1) Major (1) 1. Sirenomelia, cleft palate and cleft lip	Nil
Sitruk-Ware (1998) France Retrospective observational study/Letter to the Editor	21	Not reported	200–600 mg	Surgical abortion at 49 days (1)	Nil (20) Major (1) 1. Sirenomelia, cleft palate	Not reported
Hunter (2002) United Kingdom Case Report	1	77 days	Not specified	Medical abortion after 19 weeks	Major (1) 1. Congenital High Airways Obstructive Syndrome (CHAOS) Minor (1) 1. Syndactyly	N/A
Sorensen (2005) Norway Case report	1 (Twins)	57 days	200 mg	Live birth (2)	Nil	Low Birth Weight (2390 g)—Twin 1
Gary (2006) USA Systematic Review	22	Not specified	Not specified	Elective termination (9) Enrolled in fetal registry (1) Documented fetal anomaly (3)	Major (3) 1. Mobius syndrome 2. Neural tube defect, 3. Oligodactylia, monodactylia, facial dysmorphia, and meningo-encephalocele	Not reported
Sentilhes (2007) France Case Report	1	70 days	200 mg	Induction of labor/termination after 22 weeks (1)	Major (1) 1. Amputation of the right arm above elbow, bilateral talipes of equinovarus and severe cerebellum atrophy	N/A
Delgado (2012) America Case report	4	≤56 days	Not specified	Live birth (4)	Nil (4)	Neonatal jaundice (1)
Bernard (2013) France Observational Prospective Study	46	60 days ± 18 days (SD)	200–1200 mg	Live birth (37) Miscarriage (8) Elective termination (1)	Nil (36) Major (2) 1. Claude Bernard Horner Syndrome with stridor and possible cytomegalovirus (CMV) infection 2. Hydrocephalus with triventricular dilatation and adductus thumb	Preterm delivery (3)
UKTIS (2016) United Kingdom Observational—Retrospective and prospective study	73[a,b]	Not specified	Not specified	Live birth (42)[a,b] Abortion/miscarriage / intrauterine death (26+1+4=31)[a,c]	Nil—live birth (39)[a,c] Major (4)[d] 1. Trisomy 21 and atrioventricular septal defect (AVSD) 2. Bowel atresia 3. Congenital High Airways Obstructive Syndrome (CHAOS) (33) 4. Hypoplastic heart and pulmonary atresia with intraventricular septum	Neonatal jaundice (1)[d]

(Continued)

Table 2 (Continued)

Study	Pregnancies reported on	Mifepristone		Pregnancy outcomes (*n*)	Congenital anomalies (*n*)	Neonatal adverse outcomes (*n*)
		Timing	Dose			
Garratt (2017) Australia Case Report	2	43 days, 61 days	200 mg	Live birth (2)	Nil (2)	None reported
Delgado (2018) USA, other countries Retrospective case series/observational report	257	≤63 days	Likely 200 mg	Live births (257)	Nil (250) Minor (7) 1. Port wine stain 2. Bilateral absent toe 3. Unilateral two absent fingers 4. Choroid plexus cyst 5. Cystic kidney 6. Unilateral failed hearing test 7. Heart murmur	Preterm delivery (7)

[a]Combined figure for pregnancies exposed to mifepristone + prostaglandin, and mifepristone alone. [b]Two sets of twins. [c]One set of twins. [d]Exposed to mifepristone only.

The UK Teratology Information Services (UKTIS) published a report in 2016 following up 73 cases of mifepristone exposure during pregnancy. This was done both retrospectively and prospectively.[20] Data included cases with exposure to mifepristone only, as well as cases with both mifepristone and prostaglandin exposure. In the prospective data, there were 44 pregnancies having had mifepristone exposure in the first trimester, including two sets of twins, with detail on exposure to prostaglandin not provided. There were 25 live births with 20 infants (one set of twins) reported as being "normal." One infant had neonatal jaundice and required phototherapy. There were no infants born with congenital malformations who were exposed to mifepristone alone during either the first or second trimesters. There were nine cases for which time of mifepristone exposure was unknown, with five live births. Four of these were reported as "normal" while the other, which had been exposed to mifepristone only, had trisomy 21 and an atrial septal defect.

In the retrospective UKTIS data, there were three cases with documented exposure to mifepristone alone that resulted in live birth. One fetus exposed at 9 weeks gestation had an emergency delivery at 34 weeks and 3 days and required surgical intervention for bowel atresia. The second case was exposed to mifepristone at 11 weeks gestation, and then proceeded to completed abortion with mifepristone and misoprostol at 18 weeks gestation. This fetus was diagnosed with congenital high airways obstructive syndrome (CHAOS) and syndactyly. In the third retrospective case, the fetus was exposed to mifepristone at 29 weeks gestation during attempted abortion for prenatally detected hypoplastic heart and pulmonary atresia with intraventricular septum. The woman changed her mind and did not proceed with the abortion and the infant was delivered at term. There were a further two healthy live births to women who took mifepristone, but it is unknown if there was also exposure to a prostaglandin.

A large retrospective report by Delgado in 2018 detailed 257 women who were exposed to mifepristone in early pregnancy and were then administered progesterone in order to maintain pregnancy viability.[37] Of these women who had live births, seven were preterm births, and there were nine sets of twins. There were seven infants with minor birth defects, which represented a congenital defect rate of 2.7% in this cohort.

No congenital defects/adverse outcomes

A case report by Lim in 1990 described three live births after exposure to mifepristone in early pregnancy.[38] This study had a notably longer follow up period than other studies. The first fetus was exposed to mifepristone at 8 weeks and was born at term with a birth weight of 4150 g and no congenital anomalies or adverse neonatal outcomes. Follow up at 15 months postnatally showed normal development. The second case was also exposed to mifepristone at 8 weeks and was born at term with a birth weight of 3930 g and no congenital anomalies or adverse neonatal outcomes. Follow up at 9 months postnatally showed normal development. The third fetus, which was exposed to mifepristone "at 9 weeks' amenorrhea," was a live birth at term weighing 3585 g and had no anomalies or adverse neonatal outcomes. Good development at 6 months postnatally was reported.

A twin pregnancy was described by Sorenson in 2005.[39] After exposure to 200 mg of mifepristone at 9 weeks gestation, the twins were delivered at 39 weeks with no congenital anomalies noted. Twin #1 weighed 2390 g at birth, meeting the criterion for low birth weight, while twin #2 had weight in the normal range at birth, being 2930 g. Low birth weight is known to be associated with multiple pregnancies.[40]

A case study by Garratt & Turner in 2017 presented details on three women who used progesterone to try and maintain pregnancy viability after commencing early medical abortion.[41] One woman proceeded to complete miscarriage. For the other two women, both had deliveries at term with no documented birth defects.

DISCUSSION

The current systematic review thoroughly examined the available evidence on mifepristone exposure and adverse congenital and fetal outcomes. Despite a sensitive search strategy, there were only

10 studies eligible for full text analysis, none of which included controlled studies. The paucity of data available did not permit statistical analysis, which would otherwise have been a desirable objective. Case reports and case series are low-level evidence and may not necessarily reflect actual clinical outcomes at the population level. Their inclusion in the present review may result in a higher risk of bias. Nevertheless, case-reports are known to be useful in reporting rare conditions.[42] Letters to the Editor may include brief reports of note, novel data, and peer-reviewed reports in some circumstances. Letters were included in the updated search due to the lack of formal studies found in the field, to increase the sensitivity of the search for data published in this format, and after initial interrogation of primary article reference lists identified potentially relevant articles published as letters. It is recognized that many clinical circumstances are not informed by randomized controlled trial (RCT) evidence since it is either not available or not appropriate. Conclusions presented by this research need to consider limitations such as the rigor of the evidence assessed and potential sources of bias. Nevertheless, this review provides an objective and open summary of the evidence to date.[42]

With predominantly case series and reports to analyze, the outcomes reported represent a small fraction of women, with many possible outcomes remaining unknown. To account for these limitations, additional cases and data could have been sought from national or international adverse event registers. This was not done in the current review due to limitations such as the fees for requesting data and translating reports presented in languages other than English.

Congenital anomalies and adverse outcomes were encountered at various doses of mifepristone exposure. It is possible that 200 mg of mifepristone had a higher absolute number of usages since it is the most common dose of mifepristone administered for this indication.

The publication providing the most useful data was the prospective study by Bernard et al., which described a rate of major congenital malformations fetuses exposed to mifepristone alone or with misoprostol was 4.2% (95% CI 1.2–10.4%).[24] Considering the baseline occurrence of congenital anomalies in the general population is around 3%,[25] this study concluded that their evidence did not support mifepristone being causative for the congenital anomalies occurring in their cohort.

The largest study, with 257 women exposed to mifepristone, similarly found a congenital defect rate comparable with that in the general population.[37] This medium-quality study retrospectively analyzed sequential cases from a number of countries, predominantly the USA. The approved dose of mifepristone by the FDA was 200 mg when used in conjunction with misoprostol for medical abortion. A weakness was that data for congenital anomalies was not recorded for women exposed to mifepristone who did not have live births, which accounted for >50% of the cohort with analyzable data.

The 2006 review of FDA adverse events reporting[34] presented data related to mifepristone use, however did not delineate if there was collateral misoprostol use. This is an important consideration since it is known that misoprostol is linked to teratogenic outcomes including Mobius syndrome,[43,44] which was one of the three congenital anomalies found in that review. Other congenital anomalies have a known relationship with exposure to certain teratogens, for example, cleft palate, and exposure to nicotine and antiepileptic drugs.[45,46]

A number of the congenital anomalies encountered in this review can be explained by circumstances other than exposure to mifepristone. For example, sirenomelia[31,33] is a condition of sacral agenesis and fusion of the lower extremities which is thought to be caused by dysfunction of the vitelline artery very early in pregnancy. Sirenomelia results from a primary defect in the mid-posterior axis mesoderm. The embryonic defect dates back to the primitive streak stage during the third week of gestation, before the development of the allantois.[47] The sirenomelia and cleft palate reported by Sitruk-Ware[33] may have occurred prior to mifepristone exposure, similar to the case in Pons 1991,[31] although actual timing of mifepristone ingestion was not specified in the former study.

Other circumstances to consider in cases of congenital anomalies:

- neural tube defects (NTD)[34] have a known link to folate deficiency[48];
- limb amputation can be caused by an amniotic band[35];
- bowel atresia,[20] which occurs after failure of the bowel to restore patency around weeks 8–10 of gestation, is often linked to a chromosomal abnormality[49];
- trisomy 21[20] is an aneuploidy which exists prior to implantation of the embryo[50]; and
- atrioventricular septal defect (AVSD) has a high correlation with Trisomy 21.[51]

For other congenital anomalies there is no concrete link to the timing or dosage of mifepristone exposure alone. The fetus with CHAOS syndrome and syndactyly was exposed to mifepristone at 11 weeks gestation.[20,52] CHAOS syndrome is a clinical spectrum seen as a result of deficient recanalization of the upper airways around the 10th week of gestation.[53] Tracheal development and separation of the toes is complete before 11 weeks of gestation, so both these anomalies were unlikely to be temporally related to the failed medical abortion.

A woman choosing to continue her pregnancy after attempted medical abortion is an exceptional clinical circumstance. It is the responsibility of the prescribing clinician to provide informed consent regarding the use of the mifepristone and misoprostol for medical abortion—this includes providing information that may be significant to the patient.[54] Although continuing pregnancy after mifepristone alone is uncommon, an outcome of congenital anomaly resulting from this would be considered serious and significant. While previous research outlines cases of adverse outcomes, none of these studies are rigorous enough to provide definitive conclusions. This review has not found reliable evidence that demonstrates a causal relationship between mifepristone exposure and adverse congenital or fetal outcomes. Therefore, in clinical practice, if a woman wants to continue a pregnancy after taking mifepristone alone, concern about potential congenital abnormality due to mifepristone exposure should not be the deciding factor when enacting her reproductive autonomy. Clinicians consenting women for cessation of medical abortion need to consider what information regarding congenital anomalies would be reasonably expected for them to provide to the woman,[55] and if this would

satisfy the failure-to-warn principle[54] should such an adverse event occur.

With the increasing number of medical abortions occurring worldwide, there is likely to be an increasing number of women who may ingest mifepristone but then continue their pregnancy instead of completing the abortion. The risks associated with mifepristone exposure need to be thoroughly understood for clinicians to provide evidence-based care for women in this circumstance. It would not be ethical to undertake a controlled study on mifepristone to precisely determine rate of congenital anomalies caused by this drug. Therefore, other research designs should be utilized if seeking future evidence for this scenario. Observational studies have been shown to provide clinical evidence comparable to those achieved by randomized controlled trials.[56] Another direction may be accessing real world data from national registries such as those in the Nordic countries.[57] In light of the evidence analyzed to date, this systematic review did not find data to support mifepristone being implicated as a teratogen.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

LM was the principal investigator for a number of randomized placebo-controlled trials using progesterone. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.V.T. wrote the manuscript. J.V.T. and A.S. designed the research. J.V.T., D.G., L.A.M., A.B., M.J.S., and A.S. performed the research. J.V.T., L.A.M., and M.J.S. analyzed the data.

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