Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy

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Abstract

Women with MS are advised to discontinue interferon-beta therapy before trying to conceive. Unplanned pregnancies occur and risks related to exposure remain unclear. To determine pregnancy outcomes following interferon-beta therapy, we examined pregnancies from a global drug safety database containing individual case safety reports received in the post-marketing setting and safety data from clinical trials of subcutaneous interferon beta-1a in MS. One thousand and twenty-two cases of exposure to subcutaneous interferon beta-1a during pregnancy were retrieved; 679 had a documented outcome. In cases for which exposure duration was available (n=231), mean time of foetal exposure to subcutaneous interferon beta-1a before treatment discontinuation was 28 days; most pregnancies (199/231; 86.1%) were exposed for ≤45 days. To avoid bias, only outcomes for prospective data (n=425) in pregnancies exposed to interferon beta-1a *in utero* were analysed further. Of these, 324 (76.2%) resulted in normal live births and 4 (0.9%) in live births with congenital anomalies (3 [0.7%] were 'major'). Four (0.9%) pregnancies resulted in stillbirths (1 [0.2%] with foetal defects). There were 5 (1.2%) ectopic pregnancies, 49 (11.5%) spontaneous abortions and 39 (9.2%) elective terminations. Most pregnancies exposed to subcutaneous interferon beta-1a *in utero* were associated with normal live births. The rates of spontaneous abortion and major congenital anomalies in live births were in line with those observed in the general population. These data should be taken into account when considering options for women with MS who become pregnant or who are planning pregnancy while on treatment with subcutaneous interferon beta-1a.

Keywords: Multiple sclerosis, subcutaneous interferon beta-1a, pregnancy, safety

Introduction

MS is twice as prevalent in women as in men, and has a typical onset between the ages of 20 and 40 years [1]. Accordingly, MS most commonly affects women of childbearing age. Interferon (IFN) beta is currently the most widely used therapy for MS [2-4]. There is no evidence that MS itself increases the risk of spontaneous abortion or congenital defects [5], and studies that have examined the effects of IFN-beta therapy on pregnancy have so far yielded inconclusive or conflicting findings [6-13]. In primates, human IFN beta is associated with abortifacient, but not teratogenic, effects [14].

In the absence of conclusive data addressing this issue, women with MS are currently advised to take appropriate contraceptive measures while receiving IFN-beta treatment and to discontinue therapy when trying to conceive [15]. Similar warnings are in place for other immunomodulatory and immunosuppressive therapies for MS [16,17]. Nevertheless, unexpected or unplanned pregnancies do occur, and the risks related to exposure to IFN beta during pregnancy remain unclear.

We aimed to further investigate the effects of IFN beta on pregnancy by evaluating exposure and pregnancy outcomes among women with MS who were receiving subcutaneous (SC) IFN beta-1a treatment before or during their pregnancy, using data from a global drug safety database that included prospective and retrospective post-marketing surveillance data and cases from controlled clinical trials.

Methods

Global drug safety database and database search

All individual case safety reports for SC IFN beta-1a administered 44 mcg or 22 mcg three times weekly (Rebif®; Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany), which were received in the post-marketing setting, as well as serious

case reports from clinical trials with SC IFN beta-1a, are recorded in the Merck Serono global drug safety database.

Data on all pregnancy cases were retrieved by searching the database for verbatim terms, including ‘utero’ or ‘pregnan’, and by using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class 10010331 (congenital, familial and genetic disorders) and 10036585 (pregnancy, puerperium and perinatal conditions).

All post-marketing surveillance data (n=984) received between 1 February 1998 (the date of first market authorisation for SC IFN beta-1a) and 3 November 2009, and case reports (n=38) from manufacturer-controlled clinical trials between 1 September 2004 and 3 November 2009 were included in this analysis. Details of included clinical trials in which a pregnancy occurred are documented in the online Supplementary Table. Reports were received from healthcare professionals, health authorities and patients, and from published case reports. Pregnancy cases were categorized according to status as follows: ‘medically confirmed’ if the case was received from a healthcare professional, health authority, literature case report or clinical trial; and ‘not medically confirmed’ if it was received from a patient or relative, either spontaneously or when solicited (i.e. provided in response to a call-out to patients from the manufacturer support network). Reports included patients exposed to any dose of SC IFN beta-1a.

Time of foetal exposure to SC IFN beta-1a

The duration (days) of exposure to SC IFN beta-1a during pregnancy before therapy was discontinued was determined for all pregnancies for which the last menstrual period (LMP) and IFN beta-1a stop date (at least month and year) were available (n=231, both prospective and retrospective cases). *In utero* exposure was calculated from the date of conception (day 0), which was estimated to be 15 days after the start of the LMP. Pregnancy cases where IFN beta-1a was discontinued before conception were not included in the calculation of exposure. Cases where the specific day of LMP and/or SC IFN beta-1a discontinuation was not recorded (n=84) were arbitrarily assigned as the 15th of the month reported.

Definitions of prospective/retrospective data for pregnancy outcomes

Classifications used to define pregnancy outcomes were based on European Medicines Agency (EMA) guidelines [18]. 'Prospective' data were defined as those acquired prior to either knowledge of the pregnancy outcome or the detection of a congenital malformation at prenatal examination (e.g. foetal ultrasound, serum markers). Conversely, data were classified as 'retrospective' if they were acquired only after the outcome of the pregnancy was known or after the detection of a congenital malformation on a prenatal test.

Pregnancies were categorised into one of the following outcomes: live birth (with or without congenital anomaly), spontaneous abortion (foetal defects/no foetal defects or unknown), elective termination (foetal defects/no foetal defects or unknown), stillbirth (foetal defects/no foetal defects or unknown), ectopic pregnancy. A congenital anomaly was classified as 'major' if it was either a life-threatening structural anomaly or one likely to cause significant impairment of health or functional capacity, and which would require medical or surgical treatment. Spontaneous abortion (comprising spontaneous abortion, miscarriage, missed abortion, incomplete abortion, or early foetal death) was defined as a pregnancy that ended spontaneously before 22 completed weeks of gestation (<24 weeks from the LMP). Stillbirth was defined as late foetal death (*in utero*, or during labour or delivery), ≥22 completed weeks of gestation (≥24 weeks from LMP). An elective termination with foetal defects was defined as a termination that had been medically induced because of a foetal defect. An elective termination without foetal defects was defined as a termination that had been medically induced for a reason other than a foetal defect (e.g. personal reason, medical condition in the mother). Miscarriage rates in the general population were derived from EMA guidelines [18].

Results

A total of 1022 cases of exposure to SC IFN beta-1a during pregnancy were retrieved from the database; of these, 679 pregnancies had a documented outcome, of which 23.9% (162/679) were medically confirmed (Table 1).

Time of foetal exposure to SC IFN beta-1a

For the exposed pregnancies for which the date of LMP and SC IFN beta-1a stop date were available (n=231, both prospective [n=187] and retrospective [n=44] cases), the mean (standard deviation) time of foetal exposure to SC IFN beta-1a was 28 (22) days (range 1 to 181 days) (Figure 1). In the vast majority of cases, women discontinued treatment as soon as they discovered that they were pregnant and only seven patients remained on treatment beyond the first trimester (Figure 1). Most (86.1% [199/231]) foetuses were exposed for ≤45 days.

Pregnancy outcomes

Retrospectively reported pregnancies exposed to SC IFN beta-1a were approximately three times more frequently associated with an adverse outcome than prospectively reported pregnancies (Figure 2). Adverse outcomes included spontaneous abortion (with or without foetal defects), all other outcomes with foetal defects (for non-live births) and congenital anomalies (for live births), and ectopic pregnancy. Conversely, prospectively reported pregnancies exposed to SC IFN beta-1a (n=425) were 1.5 times more likely to have an outcome of live birth without congenital anomaly (76.2% [324/425]) than the group with retrospectively reported data (49.6% [126/254]) (Figure 2).

The majority of prospectively reported pregnancies (76.2% [324/425]) in which the foetus was exposed to SC IFN beta-1a were associated with normal, live births. Four live births had congenital anomalies (Figure 2a). Outcomes of live-birth pregnancies with congenital anomalies are further detailed in Table 2. There were 92 non-live births in prospectively reported pregnancies (49 spontaneous abortions, 39 elective terminations, four stillbirths),

which included three foetal defects. The incidence of spontaneous abortion, with or without foetal defects, was 11.5% (49/425) (Figure 2a). In all cases in which foetal defects were present, they did not cluster around any specific body system or organ (Table 3). The majority of congenital anomalies or foetal defects occurred singly, regardless of whether they were prospectively or retrospectively reported (Tables 2 and 3).

Discussion

This study assessed outcomes in women with MS who became pregnant while receiving SC IFN beta-1a therapy, using data from a global drug safety database.

It has been shown that rates of adverse outcomes are higher when ascertained retrospectively rather than prospectively [19]. To avoid any potential reporting bias generated by over-reporting of adverse outcomes, this discussion focuses only on prospectively reported pregnancies, unless otherwise specified.

The majority of pregnancies exposed to SC IFN beta-1a (76.2%) were associated with normal, live births. The percentage of pregnancies resulting in spontaneous abortions (11.5%), with or without foetal defects, was in line with the reported rate in the general population (known to be relatively common, 10–20% before 20 weeks of pregnancy) [20], suggesting that an association between SC IFN beta-1a and spontaneous abortion is unlikely.

The proportion of live births resulting in a major congenital anomaly after exposure to IFN beta-1a (0.9%) was lower than the incidence of major anomalies among live births in the general population in many published studies (2–4%) [18]. Among non-live births with reported outcomes there were three with foetal defects. The reported defects did not cluster around any specific body system or organ, suggesting a coincidental occurrence, rather than the involvement of an IFN beta-1a-induced mechanism. Taken together, these results suggest that an association between IFN beta-1a and the incidence of congenital anomalies

or foetal defects is unlikely. Recent findings from a prospective registry of pregnant women exposed to intramuscular IFN beta-1a during the first trimester of pregnancy also showed that the rate of spontaneous abortions and major/serious birth defects was not increased when compared with rates in the general population [21].

Results from previous studies [6-13] of pregnancy outcomes in women with MS receiving other immunomodulatory or immunosuppressive therapies have been inconclusive and, consequently, exposure to these agents during pregnancy is not advised. Use of mitoxantrone during pregnancy is contraindicated due to its mechanism of action. Post-marketing surveillance studies of glatiramer acetate have reported an incidence of spontaneous abortion of 21% [22]. Animal studies involving the immunosuppressive agent natalizumab have also demonstrated harmful effects on foetuses [17]. In a recent prospective evaluation of pregnancy outcomes in women, preliminary data showed that the rate of spontaneous abortions with natalizumab treatment was comparable with the rate in the general population [23].

Currently, advice against use of IFN beta during pregnancy is based on findings from animal studies, which report higher-than-expected abortion rates in primates exposed to human IFN beta during pregnancy [16,17]. However, it should be noted that across the IFN beta drugs assessed, these studies used up to 40 times the recommended human dose, based on surface area [24].

The analyses presented here were subject to several limitations. Outcomes were unavailable for 111 pregnancies collected prospectively that were subsequently lost to follow-up, which may have introduced bias. Further, estimation of time of exposure to IFN beta-1a may have been inaccurate; patients may have been uncertain of the date of LMP or the date when IFN beta-1a treatment was discontinued.

General population data were used for comparisons, although patients with MS who were not receiving disease-modifying drugs may have been a more accurate control population.

However, treated patients with MS are closely monitored and comparative data from monitored but untreated patients would be difficult to obtain.

The mean foetal exposure time for both prospectively and retrospectively reported pregnancies (for cases for which duration of exposure was available; n=231) was 28 days (range 1 to 181 days). For the vast majority of these pregnancies (86.1%), foetal exposure time was short, ranging from 1 to 45 days, and nearly all cases of foetal exposure occurred during the first trimester. Other studies have reported a mean foetal exposure time of 4–9 weeks (28–63 days) [7,11,12]. It is possible that the difference in length of exposure to IFN beta-1a may account for differences in pregnancy outcomes between different studies. In the current analysis, the vast majority of women were not exposed to IFN beta-1a during the whole period of foetal organogenesis or in later trimesters. However, although the length of exposure was short, exposure occurred during a critical period of foetal development.

It should be noted that in a previous study of pregnancy outcomes occurring during controlled clinical trials in women with MS, a case of hydrocephalus was described in a live birth after the foetus had been exposed to a low dose of IFN beta-1a throughout the pregnancy [12]. However, the overall results of the study showed that there was no overall risk associated with use of SC IFN beta-1a [12].

The apparent lack of detrimental effect of IFN beta-1a on pregnancy outcomes could be attributed to the large size of the IFN molecule (approximately 23 kDa for IFN beta-1a), which may inhibit the degree to which IFN crosses the placental barrier. The degree of transferral across the placenta is not known, although the related molecule IFN alpha (19.5 kDa) was not detectable in the foetal blood or amniotic fluid in one study involving two women [25].

In conclusion, no increased risk was found for a detrimental effect of SC IFN beta-1a treatment on pregnancy outcomes in women with MS when compared with pregnancy outcomes in the general population. The women who did not discontinue IFN beta before

conception, but who stopped therapy as soon as pregnancy was recognised, were not at a higher risk of adverse pregnancy outcomes. The analyses described here add to previous research [7-13,26] and should be taken into account when considering options during pregnancy and exposure to SC IFN beta-1a. Future analyses of long-term safety should come from large, prospective registries, ideally with adjustment for potential confounders such as maternal age and prior miscarriages.

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Conflicts of interest

MS-W has received honoraria from Serono Symposia International Foundation (lectures); from Merck Serono (lectures, work in data safety monitoring boards [DSMB]); from Genentech and Roche (DSMB); from Elan (advisory board); from the Swedish bank SEB Enskilda (lectures); from sanofi-aventis (lectures); and from Bayer Health Care (contribution of articles to Swedish health website). She has also received honoraria for serving on the board of directors of Active Biotech, Lund, Sweden, and as an external reviewer of a PhD thesis at the University of Copenhagen. EA, MSM and GK are salaried employees of Merck Serono S.A. – Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

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Table 1 Number of individual case safety reports for pregnancy, by confirmation status, data collection type, and presence of outcome

Confirmation status	Data collection				Total, n (%)
	Prospective		Retrospective		
	With outcome	Without outcome[a]	With outcome	Without outcome[a]	
Medically confirmed, n (%)	116 (50.4)	66 (28.7)	46 (20.0)	2 (0.9)	230 (100)
Not medically confirmed, n (%)	309 (39.0)	269 (34.0)	208 (26.3)	6 (0.8)	792 (100.1)[b]
Total, n (%)	425 (41.6)	335 (32.8)	254 (24.9)	8 (0.8)	1022 (100.1)[b]

[a]Denotes that when data were collected, either the pregnancy had not ended or the patient/reporting physician was lost to follow-up.

[b]Percentages do not sum to 100% due to rounding.

Table 2 Congenital anomalies detected in live birth pregnancies exposed to IFN beta-1a

Medically confirmed	MedDRA preferred term	Time exposed to IFN beta-1a	Comments	Minor or major anomaly
Prospective pregnancies				
Yes	VACTERL syndrome, congenital anomaly, rib hypoplasia, pulmonary hypoplasia, congenital musculoskeletal anomaly, spine malformation, limb malformation	5 weeks	Fatal Baby died 5 hours after birth; normal karyotype; mother with type 2 diabetes	Major
Yes	Tetralogy of Fallot	Possibly for 1 month	None	Major
Yes	Microtia right ear	Unknown	None	Minor
No	Solitary kidney	2 months	None	Major
Retrospective pregnancies				

Yes	Sturge–Weber syndrome	Unknown[a]	Mother with birthmarks	Major
No	Hydrocephalus, anomaly of orbit, congenital cleft palate, harelip, respiratory arrest, cardiac arrest	17 weeks	Fatal; high levels of mercury, cobalt and lead in father	Major
No	Congenital corneal anomaly	9 weeks	None	Minor
No	Down's syndrome[b]	8 weeks	None	Major
No	Possible genetic mitochondrial defect	2 months	Baby was pre-term (35 weeks' gestation) and had *Escherichia coli* infection in peripherally inserted catheter site	Major (to be conservative)

IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities.

[a]Case notes do not specify clearly the time of foetal exposure to IFN beta-1a.

[b]Mother's age: 32 years.

Table 3 Foetal defects detected in non-live birth pregnancies[a] exposed to IFN beta-1a

Medically confirmed	MedDRA preferred term[b]	Pregnancy outcome (with foetal defect)		
		Stillbirth	**Spontaneous abortion**	**Elective termination**
Prospective pregnancies				
No	Heart disease (congenital), dwarfism	Yes	–	–
No	Partial molar pregnancy	–	Yes	–
No	Foetal growth retardation	–	–	Yes
Retrospective pregnancies				
Yes	Hydrops foetalis not due to isoimmunisation, multiple congenital anomalies, clubfoot (congenital), congenital hand malformation, finger deformity,	Yes	–	–

	curvature of spine			
Yes	Gross abnormality	–	Yes	–
Yes	Anencephaly	–	Yes[c]	–
Yes	Sex chromosome abnormality NOS, Down's syndrome	–	–	Yes
Yes	Agenesia corporis callosi, hydrocephalus, polymicrogyria	–	–	Yes
Yes	Neural tube defect myelomeningocele, severe secondary cranial abnormality, hydrocephalus, club foot	–	–	Yes
No	Chromosomal abnormality	–	Yes	–
No	Chromosomal abnormality	–	Yes	–
No	Turner syndrome with a missing chromosome	–	Yes	–

No	Spina bifida	–	Yes	–
No	Malformation foot, malformation hand	–	–	Yes
No	Cleft palate, skull malformation, limb malformation	–	–	Yes

IFN, interferon; LMP, last menstrual period; MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified.

[a]Non-live births comprised stillbirths (late foetal death after 22 completed weeks of gestation [≥24 weeks from LMP]; foetus that has died in the uterus, or during labour or delivery); spontaneous abortion (when the pregnancy spontaneously ends before 22 completed weeks of gestation [<24 weeks from LMP]; comprises spontaneous abortion, miscarriage, missed abortion, incomplete abortion and early foetal death); and elective termination.

[b]For non-medically confirmed cases, MedDRA terms were attributed based on verbal reports from the patient.

[c]Outcome assigned as 'spontaneous abortion (with foetal defect)' as anencephaly is a non-viable condition.

Figure 1 Length of foetal exposure to interferon (IFN) beta-1a, from time of conception (day 0) to treatment discontinuation in prospectively and retrospectively collected pregnancies. Pregnancy cases where IFN beta-1a was discontinued before conception were excluded from the calculation of exposure.

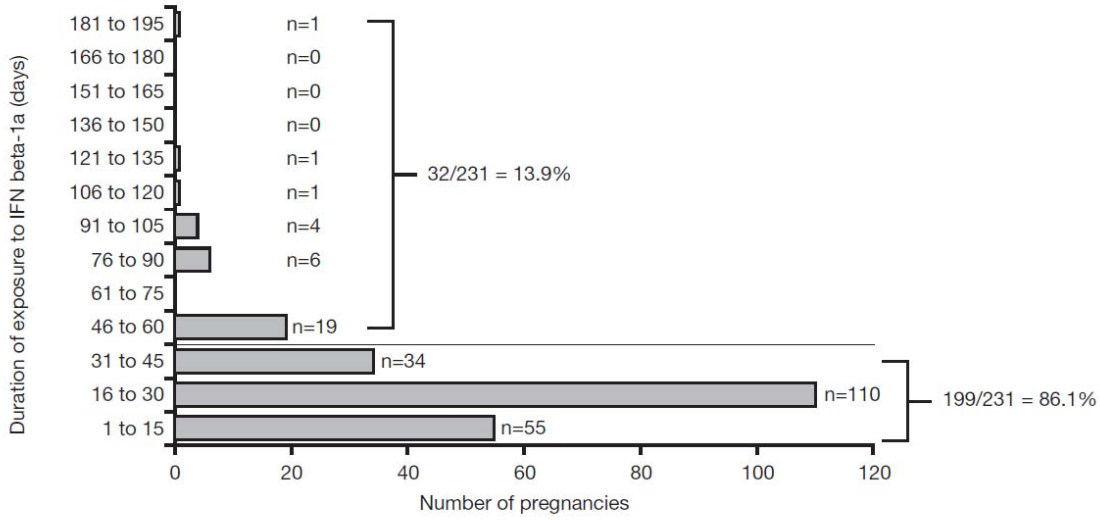
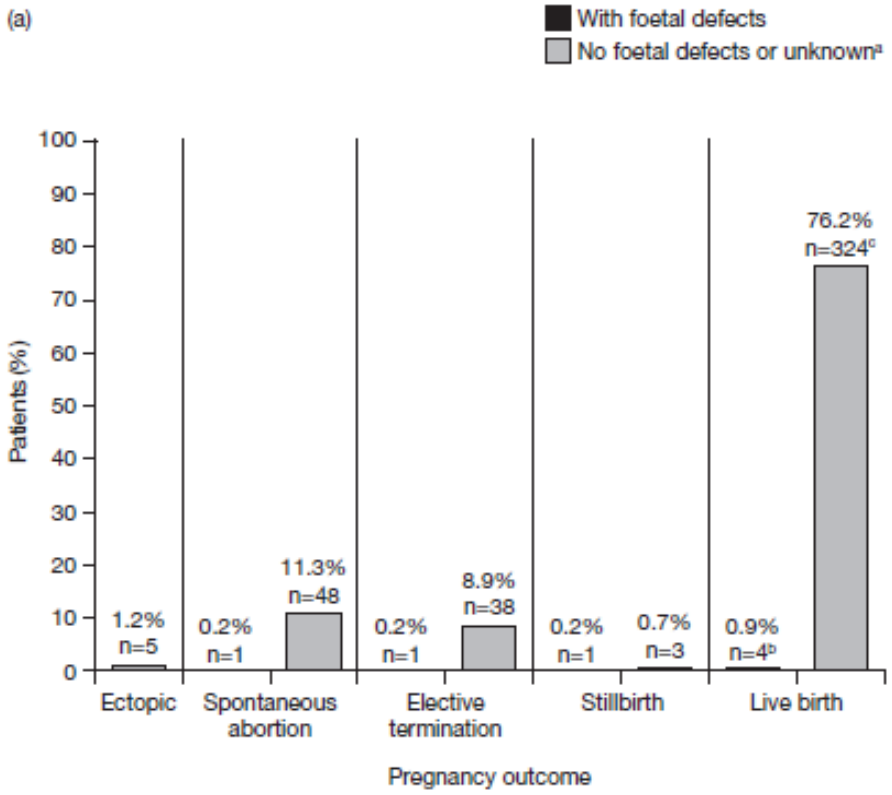
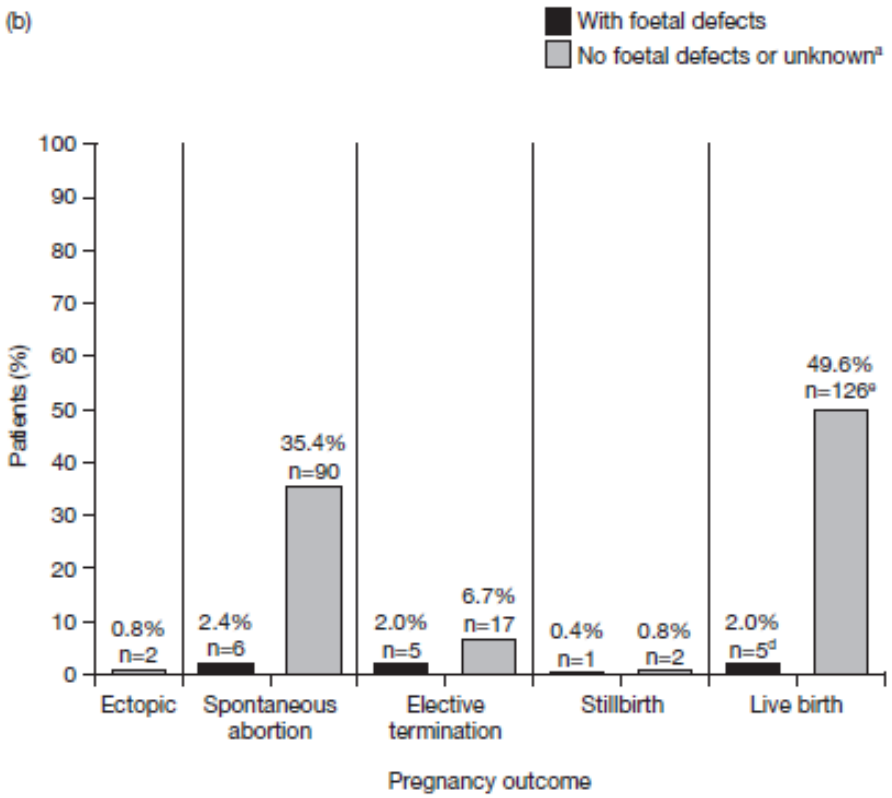


Figure 2 Number of individual case reports for all pregnancies documented by outcome in a) prospectively collected pregnancies, and b) retrospectively collected pregnancies. Multiple pregnancies, e.g. triplet pregnancy counted only once as one pregnancy outcome. The following outcomes from individual case safety reports were discarded: 'Not reported' (pregnancy was still ongoing) and 'Unknown' (patient was lost to follow-up).

[a]Unknown indicates no information was available on whether a foetal defect was noticed.
[b]Three of four were major anomalies (classified as life-threatening structural anomaly or one likely to cause significant impairment of health or functional capacity, and that required medical/surgical treatment): VACTERL syndrome, solitary kidney, tetralogy of Fallot.
[c]One baby died shortly after birth (lived for 20 minutes).
[d]All were single occurrences. Four of five were major anomalies: Sturge-Weber syndrome, Down's syndrome, hydrocephalus, possible genetic mitochondrial defect ('major, to be conservative'). Minor anomaly (classified as a relatively frequent structural anomaly not likely to cause any medical or cosmetic problems): congenital corneal anomaly.

[e]One baby died shortly after birth (lived for 'minutes to hours').


(a)
With foetal defects
No foetal defects or unknown[a]
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
1.2% n=5
0.2% n=1
11.3% n=48
0.2% n=1
8.9% n=38
0.2% n=1
0.7% n=3
0.9% n=4[b]
76.2% n=324[c]
Ectopic
Spontaneous abortion
Elective termination
Stillbirth
Live birth
Pregnancy outcome


(b)
With foetal defects
No foetal defects or unknown[a]
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0.8% n=2
2.4% n=6
35.4% n=90
2.0% n=5
6.7% n=17
0.4% n=1
0.8% n=2
2.0% n=5[d]
49.6% n=126[e]
Ectopic
Spontaneous abortion
Elective termination
Stillbirth
Live birth
Pregnancy outcome