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Safety of Oseltamivir in Pregnancy
A Review of Preclinical and Clinical Data

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Abstract

Pregnant women with influenza are at increased risk of morbidity, particularly due to respiratory complications. A high excess mortality rate among pregnant women has been observed in previous influenza pandemics and healthcare agencies have provided recommendations on the use of oseltamivir to treat pregnant women who are infected with the pandemic (H1N1) 2009 virus. This article reviews pre-clinical and clinical data to assess the safety of oseltamivir administered during pregnancy, in the context of the effects of influenza on adverse pregnancy outcomes and fetal malformations.

The effects of influenza during pregnancy, whether mediated directly by the virus or by fever or other events secondary to the underlying infection, are not yet well understood, but some data indicate an increased risk of birth defects in women infected with influenza during the first trimester. Animal and toxicology studies do not suggest that clinically effective dosages of oseltamivir have the potential to produce adverse effects on fetal development. Additionally, transplacental transfer of the drug and its active metabolite was very limited and not detectable at normal therapeutic doses in an *ex vivo* human placenta model.

To investigate the safety of oseltamivir in pregnancy, the Roche oseltamivir safety database was searched for all exposures to oseltamivir during

pregnancy in the 9 years up to 14 December 2008. In addition, a search of the literature was carried out. Of 232 maternal exposures to oseltamivir in the Roche database, pregnancy outcomes were known for 115 of these exposures. The incidence of adverse pregnancy outcomes was as follows: spontaneous abortions 6.1% (7/115), therapeutic abortions 11.3% (13/115) and pre-term deliveries 2.1% (2/94 live births), values that are not higher than background incidence rates. Fetal outcomes were known in 100 of the 232 exposures. For the nine cases of birth defect that were reported, the timing of oseltamivir exposure in relation to the sensitive period for inducing the birth defect was analysed. Two cases of ventricular septal defect, a more common birth defect, and one case of anophthalmos, an uncommon birth defect, were consistent with exposure to oseltamivir during the sensitive period for these birth defects. For other birth defects, there was either no exposure to oseltamivir during the sensitive period for the defect or insufficient information for assessment. These findings were consistent with other reports in the published literature, including a series of 79 Japanese women exposed to oseltamivir during the first trimester.

Together with the other evidence reviewed herein, review of the company safety database suggests that oseltamivir is unlikely to cause adverse pregnancy or fetal outcomes, but available data are limited. Clinicians who use oseltamivir in pregnant women should consider the available safety information, the pathogenicity of the circulating influenza virus strain, the woman's general health and the guidance provided by health authorities. Roche will continue to monitor all reports of oseltamivir use during pregnancy.

Influenza is an acute respiratory illness that is caused by influenza A or B viruses, and is characterized by local and systemic symptoms such as cough, sore throat, fever, headache, myalgia and weakness.[1] Outbreaks of influenza result in significant morbidity in the general population, and can cause secondary illnesses such as pneumonia that carry an increased mortality risk.[2] Influenza pandemics are caused by the emergence of a novel influenza virus to which populations have little or no immunity. Pregnant women have been disproportionately affected in previous influenza pandemics; this was particularly evident during the 1918–9 and 1957–8 outbreaks, when excess influenza-associated deaths among pregnant women were reported.[3] In the 1918 'Spanish flu' pandemic, very high rates of spontaneous abortion and pre-term birth (>50% of cases in some reports) were seen, especially among women with pneumonia.[4,5]

Oseltamivir (Tamiflu®; F. Hoffmann-La Roche Ltd) is an antiviral medication of the neuraminidase inhibitor class that is used for the treatment and prophylaxis of influenza A and B infections. It is taken orally as a pro-drug and metabolized to the active form oseltamivir carboxylate, which is a potent and selective inhibitor of influenza virus neuraminidase.[6] The efficacy and safety profile of oseltamivir in children aged ≥1 year and adults of all ages is well established, and the drug is widely approved for use in these populations. Experience of the drug's use in pregnant women has been limited thus far, because recommendations for using oseltamivir during pregnancy in, for example, the European summary of main product characteristics, suggest that oseltamivir should be used only if the potential benefit justifies the potential risk to the fetus.[7]

An influenza pandemic, hereafter referred to as pandemic (H1N1) 2009, was declared by the WHO in June 2009. Although current evidence suggests that most patients infected with pandemic (H1N1) 2009 have had mild disease,[8,9] the virus is readily transmissible between humans

and has caused severe illness and death in high-risk populations, including pregnant women.[9-15] Several health authorities have provided guidance on the use of oseltamivir and other antivirals to treat pandemic (H1N1) 2009 in high-risk groups: the WHO and the US Centers for Disease Control and Prevention (CDC) recommend treatment for all high-risk patients, including pregnant women,[16,17] and the European Medicines Agency advises that the benefit of treating pregnant women with these drugs outweighs the risk.[18]

The aim of this review is to summarize data on pregnancy and fetal outcomes following oseltamivir exposure during pregnancy by reviewing the currently available evidence from pre-clinical studies and single case reports in the Roche oseltamivir safety database (up to a cut-off date of 14 December 2008), and reviewing the published literature. To set this evidence in context, the article briefly reviews relevant background information in two sections: adverse pregnancy and fetal outcomes in general, and the effect that influenza and/or fever have on pregnancy and its outcomes.

1. Adverse Pregnancy and Fetal Outcomes

The important adverse outcomes of pregnancy are fetal loss, resulting from spontaneous abortion (during the first 20 weeks of gestation) or stillbirth (after 20 weeks) and therapeutic (induced) abortion. In the US, 64.4% of pregnancies in 2004 resulted in a live birth, 16.5% resulted in spontaneous abortions or stillbirths and 19.1% of pregnant women had induced abortions.[19] The rate of spontaneous abortions and stillbirths is similar to that reported 10 years earlier (1994 value, 15.6%) and the rate of induced abortions has fallen over the same period (1994 value, 22.3%).[19] More than 80% of spontaneous abortions happen in the first 12 weeks of gestation and the majority are due to chromosomal abnormalities.[20] Another important adverse pregnancy outcome is preterm delivery: in 2006, approximately one in eight live births in the US (12.8%) was delivered preterm, i.e. before the end of the 37th week from last menstrual period.[21] Three important risk factors for pre-term delivery are medical and obstetric complications, chorioamnionitis and genetic factors, but lifestyle factors such as smoking also play a part.[22]

Adverse fetal outcomes may be birth defects or low birthweight. The Metropolitan Atlanta Congenital Defects Program found that between 1978 and 2005, major birth defects occurred with a frequency of 2.8% of all live births;[23] such defects most frequently affect the cardiovascular, musculoskeletal and genitourinary systems.[24] Exposure to drugs at various stages of embryonic and fetal development can cause birth defects. The embryonic period (weeks 3–8 from conception) is the most sensitive for induction of birth defects, e.g. by exposure to teratogenic drugs or to infections such as rubella and cytomegalovirus. Another common fetal disorder is low birthweight, defined as a birthweight of <2.5 kg – this affected 8.3% of live births in the US in 2006.[21]

2. Effect of Influenza on Pregnancy

To provide background information and context to the Roche safety database search, a literature search of English-language articles in PubMed and DataStar (the latter specifically for MEDLINE articles published from 1993 onwards) was conducted in January 2009. The term 'influenza' was searched for in the abstract and title fields in combination with any of the following terms: 'birth defect', 'pregnancy', 'congenital', 'malformation', 'anomaly', 'parturition', 'prematurity', 'low birth weight', 'IUGR (intrauterine growth retardation)', 'abortion' and 'pregnancy complications'. Titles and abstracts were screened and all potentially relevant articles reviewed for inclusion in this section.

Pregnant women have a higher risk of influenza complications[25] and hospitalization for acute cardiopulmonary complications of influenza than non-pregnant women,[26] sometimes resulting in death.[27,28] This stems from physiological changes during pregnancy whereby the enlarging gravid uterus reduces expiratory reserve volume, residual volume and functional residual capacity, while the heart rate and stroke volume increase to meet the needs of the growing fetus.[27,29]

Reports received by the US CDC during the first 2 months of the pandemic (H1N1) 2009 outbreak indicated that, of 45 deaths from the disease, six were in pregnant women (all from primary viral pneumonia); the estimated rate of hospitalization in pregnant women was more than four times that of the general at-risk population.[15] A monovalent vaccine against pandemic (H1N1) 2009 is now widely approved for use, and women who expect to be pregnant during the influenza season are strongly advised to receive this vaccination.[30,31]

2.1 Pregnancy Outcome

A review of data from previous influenza pandemics concluded that the effects of influenza infection on pregnancy are not yet well understood.[28] Studies of the effects of influenza on pregnancy outcomes have produced inconsistent results; a possible reason for this is that pregnancies are usually diagnosed late in the first trimester, making it difficult to capture sufficient data for this critical period. During the 'Asian flu' pandemic of 1957–8, infection during the first trimester appeared to increase the rates of adverse pregnancy outcomes compared with both infections later in pregnancy and rates in non-infected pregnant women.[32] Women with respiratory illness during the influenza season were found to have increased odds of a co-diagnosis of pre-term labour compared with women hospitalized for delivery but without a respiratory illness.[33] However, in a birth registry survey, there were no differences in the incidence of pre-term birth in patients with and without an episode of influenza during pregnancy.[34]

2.2 Fetal Outcome

The methods used by some researchers who have evaluated associations between influenza in pregnancy and risk of birth defects make it difficult to draw firm conclusions about an association. For example, two studies by Griffiths et al.[35] and Irving et al.[25] that failed to show any significant effect of maternal influenza on congenital abnormalities assessed infections during the second or third trimester only, whereas weeks 3–8 after conception are a more critical period for any teratogenicity. In two other studies that investigated the effect of first trimester exposure to influenza on neural tube defects (suggesting an elevated risk) and low birthweight babies (suggesting no effect on risk), influenza infection was not serologically confirmed, thus limiting the value of the study findings.[34,36] A study of 611 pregnant women in the US who had serologically confirmed 'Asian flu' in 1957–8 suggested that birth defects were more likely when influenza occurred in the first trimester than later in gestation, although the statistical significance of this difference was not reported.[32] In contrast, serologically confirmed influenza in the first trimester did not appear to be associated with the development of anencephalic fetuses in 248 mothers in a Finnish birth registry analysis.[37]

Placental transmission of influenza virus is rare in seasonal influenza infection,[25] although it has been demonstrated in human avian influenza A (H5N1) infection.[38] Nevertheless, prenatal influenza infection in the mouse has been associated with histopathological changes in the brain in the absence of viral RNA.[39] This suggests that any effects of influenza on the fetus are unlikely to be direct and could be secondary to the maternal inflammatory response.[28]

2.3 Role of Hyperthermia (Fever)

Fever may be a cause of congenital defects of the CNS and other organs.[40] Birth defects associated with hyperthermia during pregnancy include neural tube defects, microcephaly, microphthalmia, cleft lip with or without cleft palate and conotruncal heart defects.[41] The most common febrile illnesses associated with these anomalies are influenza, pyelonephritis and streptococcal pharyngitis. The nature of the defects relates to the degree and duration of hyperthermia and the trimester of pregnancy during which it occurs.[41]

Retrospective studies in which mothers were asked to recall infections or fever in early pregnancy have shown an association with certain birth defects. Fever during early pregnancy was reported to be associated with an elevated risk of cardiac malformations.[42] A subsequent study

showed a higher risk of neural tube defects, such as anencephaly and spina bifida, in babies born to mothers in the US who had influenza (no serological confirmation) and fever during or just before the first trimester.[36] A more recent study, in which the influenza diagnosis was mostly based on clinical signs and not serologically confirmed, showed that women who gave birth to fetuses with congenital abnormalities were significantly more likely to have had influenza during pregnancy than controls, with cleft lip/palate, cardiovascular malformations and neural tube defects being strongly associated with first trimester infections.[43] The latter study found no such association, however, in those women who received antipyretic therapy, suggesting that the defects could have been caused by influenza-related hyperthermia. Other researchers have recently suggested a link between fever in the second and third months of pregnancy and the incidence of multiple congenital anomalies, in particular neural tube defects and orofacial clefts.[44]

3. Oseltamivir in Pregnancy

3.1 Pre-Clinical Studies

In pre-clinical studies, oseltamivir at a dosage of 500 mg/kg/day in rats had no adverse effect on reproduction parameters such as duration of gestation, the number of pups born (alive or dead), the live birth index and survival.[45] In addition, a dosage of 250 mg/kg/day in rabbits had no effect on fetal survival or weight or sex ratio, and did not cause any treatment-related abnormalities.[45] At higher dosages, the only reproductive toxicity seen was prolongation of parturition in rats (at 1500 mg/kg/day of oseltamivir) and abortion associated with maternal toxicity in rabbits (at 500 mg/kg/day).[45]

Teratology studies with oseltamivir at dosages of up to 1500 mg/kg/day in rats and 500 mg/kg/day in rabbits showed no direct effects on embryonic or fetal development, despite the estimated fetal exposure to drug being 15–20% of the systemic exposure to parent drug and metabolites in the mother.[45] Minor skeletal changes in some rat and rabbit fetuses observed in these studies were not considered to be of toxicological concern as they were morphologically different in the two species and the incidence rate was no higher than in historical controls.[45] In an *ex vivo* study of a human placental model by Worley et al.,[46] neither oseltamivir nor oseltamivir carboxylate could be detected in the fetal compartment after administration of the phosphate salt at up to six times the normal therapeutic dose. At 30 times the normal therapeutic dose, fetal compartment concentrations of oseltamivir and oseltamivir carboxylate were 1.4% and 3.6%, respectively, of those in maternal plasma.[46] It is known that oseltamivir is a substrate of the p-glycoprotein transporter[47] that is present in the placenta.[48] The very low oseltamivir concentrations found by Worley et al.[46] in the fetal compartment can be explained by active export of the compound from the fetal to the maternal site via this pathway.

In mutagenicity tests (Ames test, human lymphocyte chromosome analysis, mouse micronucleus test and mouse lymphoma cell mutation), no evidence was seen of any mutagenic potential of oseltamivir and/or oseltamivir carboxylate.[45] Studies of fertility in male and female rats showed no adverse effect of dosages of oseltamivir 1500 mg/kg/day on either fertility, mating performance or the number of estrous cycles.[45]

3.2 Safety Database Analysis

3.2.1 Methods

All reports received by Roche of women who have been exposed to oseltamivir during pregnancy are coded into the Roche oseltamivir safety database; these reports may be obtained through spontaneous reporting, clinical trials (despite routine exclusion of pregnant and lactating women), surveillance studies or literature reports. In the current analysis, the search and selection method was to include all exposures to oseltamivir in pregnant women reported before a cut-off date of 14 December 2008.

3.2.2 Results

Maternal Exposures to Oseltamivir; Distribution

By the cut-off date, 232 maternal exposures to oseltamivir were retrieved from the oseltamivir safety database. The breakdown of these exposures

by country, age and source (i.e. reporting method) is shown in table I; the majority were from Japan (169 [72.8%]) and most were spontaneously reported (153 [65.9%]). For 151 exposures with known maternal age, the age group of 26–35 years was most prevalent; for the other 81 exposures, the maternal age was unknown. The timing of maternal exposure to oseltamivir was unknown in 36 of the 232 women. For the remainder, the majority of exposures (115/196 [58.7%]) occurred during the first trimester.

The therapeutic indication for oseltamivir was unknown for 59 (25.4%) of the maternal exposures. Of the remaining 173, the indication in the greatest majority (158) was influenza, with ten being for 'prophylaxis' and five for 'other' indications.

Adverse Pregnancy Outcomes

Pregnancy outcome was evaluable in 115 of the 232 maternal exposures, and in 44 of these 115, exposure to oseltamivir occurred during the first trimester. Women for whom pregnancy outcome was not evaluable were categorized as 'pregnancy ongoing' (81), 'lost to follow-up' (13) or 'unknown' (23). Of the 115 known outcomes, 95 were 'delivery', comprising 94 live births and one stillbirth. Two of the 94 live births were preterm, giving an incidence of 2.1% for this outcome. Seven spontaneous abortions (6.1% of known outcomes) occurred, with exposure during the first trimester in all except one woman, for whom the time of exposure was not known. There were 13 therapeutic abortions (11.3% of known outcomes). The outcome rates, expressed for first trimester exposures and for all exposures, are compared with background reporting rates for adverse pregnancy outcomes from the published literature[19,21,49,50] in table II; the reporting rates in the database were no higher than background rates for these outcomes. Therapeutic abortions associated with a birth defect are analysed by case in the following section.

Table I. Distribution of maternal oseltamivir exposure cases and number of birth defects and other disorders by country, reporting method and age, as of 14 December 2008

Parameter	Cases of maternal exposure (n = 232) [n (%)]	Birth defect or other disorder[a] (n = 12) [n]
Country		
USA	25 (10.8)	1
EU + EFTA[b]	27 (11.6)	0
Japan	169 (72.8)	9
Rest of the world[c]	11 (4.7)	2
Reporting method		
Literature	2 (0.9)	2
Spontaneous	153 (65.9)	4
Study	77 (33.2)	6
Maternal age (y)		
16–25	32 (13.8)	4
26–35	101 (43.5)	4
36–45	18 (7.8)	1
Unknown	81 (34.9)	3

a Other disorders (3) were disseminated intravascular coagulation, premature birth and spontaneous abortion.

b Split by country: Denmark (1), France (11), Germany (6), Greece (2), Ireland (1), the Netherlands (2), Norway (1), Switzerland (1), UK (2).

c Split by country: Canada (5), China (4), Israel (1), New Zealand (1).

EFTA = European Free Trade Area.

Adverse Fetal Outcomes

Of the 232 maternal exposures before the cut-off date, fetal outcomes were unevaluable for 132 (ongoing pregnancy, 76; lost to follow-up, 14; and unknown, 42) and 100 pregnancies had known fetal outcomes (normal baby, 85; normal fetus, 3; birth defect, 9; and other disorders, 3). One of the three outcomes listed as 'other disorders' was a baby with disseminated intravascular coagulation, which is not considered to be a birth defect. The other two, a premature birth and a spontaneous abortion, are included in the statistics reported in the previous section. For 15 maternal exposures for which the pregnancy outcome was known (two deliveries, six spontaneous abortions and seven therapeutic abortions), the fetal outcome was unknown.

Summarized case descriptions for the nine birth defects are shown in table III. For seven of the nine pregnancies resulting in birth defects, maternal exposure occurred in the first trimester; in the cleft palate case, exposure was in the third trimester, and the time of exposure was unknown for the hydrocele case. In the two cases of ventricular septal defect (VSD) and one case of anophthalmos, exposure to oseltamivir occurred during the

Table II. Reporting rates for adverse pregnancy outcomes in the Roche oseltamivir safety database compared with background reporting rates, as of 14 December 2008

Adverse pregnancy outcome	Reporting rates from safety database, pregnancies with known outcomes [n (%)]		Background reporting rates at any stage of pregnancy (%)
	oseltamivir exposure at any stage of pregnancy (n = 115)	oseltamivir exposure during the first trimester (n = 44)	
Spontaneous abortion	7 (6.1)	6 (13.6)	12–14[a]
Therapeutic abortion	13 (11.3)	8 (18.2)	19.1–22.3[b]
Fetal loss[c]	8 (7.0)	7 (15.9)	15.6–16.5[b]
Pre-term delivery	2 (2.1)[d]	No cases	11.0–12.8 (of live births)[e]

a From US and UK cohort studies.[49,50] Denominator is all pregnancies with known outcomes.

b From CDC pregnancy outcome statistics (range of values between 1994 and 2004).[19] Denominator is all pregnancies with known outcomes.

c Total of spontaneous abortions and stillbirths.

d Denominator is 94 live births.

e From CDC pregnancy outcome statistics (range of values between 1996 and 2006).[21]

CDC = US Centers for Disease Control and Prevention.

sensitive period for these birth defects; the indication for oseltamivir was influenza treatment in two mothers, and was not reported for the third (one of the VSD cases). The possible significance of these two defects is discussed further in section 4. In the remaining birth defect cases, exposure to oseltamivir did not occur during the sensitive period for development of the defect or there was insufficient information for medical assessment. Six of the nine pregnancies in question resulted in delivery, and the other three resulted in therapeutic abortion. For two of the three therapeutic abortions, karyotyping revealed chromosomal abnormalities (one case with an unknown chromosomal anomaly and hydrops fetalis, the other with trisomy 21) that arose before oseltamivir exposure.

3.3 Reports of Maternal Exposures to Oseltamivir in the Published Literature

A literature search of PubMed and DataStar (MEDLINE 1993 onwards) conducted in January 2009 using different combinations of the search terms ('oseltamivir' OR 'Tamiflu' AND 'birth defect', 'malformation', 'anomaly', 'parturition', 'prematurity', 'low birth weight', 'IUGR' [intrauterine growth retardation], 'abortion', 'pregnancy complications') yielded no published articles.

Two articles published after the cut-off date of our literature search reported case series of Japanese women who were exposed to oseltamivir or zanamivir during pregnancy;[55,56] however, the more recent of the two articles (Tanaka et al.[56]) duplicates the oseltamivir data from the earlier article (Hayashi et al.[55]), and the single case of VSD reported in this case series was already recorded in the Roche safety database and is summarized in the previous section.

Hayashi et al.[55] reported on a series of 79 women who took oseltamivir during the first trimester of pregnancy for at least 1 day between 2002 and 2006. Pregnancy outcomes were known for 66 of these women, of whom 43 took the drug in the most critical period for teratogenic risk to the fetus. The authors considered day 28 to day 50 from the last menstrual period as the most critical period for birth defects in general. A birth defect (VSD, already summarized in the previous section) was reported in one of 43 women who were exposed during the most critical period.[55] Of the other 42 women who took oseltamivir during the critical period, 41 gave birth to healthy infants and one woman had a missed abortion.

4. Discussion

Inadvertent exposure of pregnant women to drugs during pregnancy is likely, whether for the treatment of a pre-existing condition or newly diagnosed condition, and often happens before a

Table III. Case descriptions for nine pregnancies resulting in birth defects recorded in the Roche oseltamivir safety database, as of 14 December 2008

Adverse event (preferred term)	Age of mother (y)	Indication for oseltamivir use	Time of oseltamivir exposure (date of first dose if known)/trimester	Sensitive period for birth defect[a]	Exposure to oseltamivir during sensitive period	Other observations	Pregnancy outcome
Anencephaly	25	Influenza	In 2nd or 3rd month (estimated)/first	Before the 26th day of gestation[41]	No		Therapeutic abortion
Anophthalmos	Unknown	Influenza	Between 5th and 6th week/first	Between the 4th and 8th week of gestation[51]	Yes		Delivery
Cleft lip and palate	30	Influenza	Day 200/third	Between the 6th and 10th week of gestation[51]	No		Delivery
Chromosome abnormality and hydrops fetalis	25	Influenza	Day 43/first	NA	No	Chromosomal abnormality; no preconception exposure to drug; chromosomal abnormalities are most common cause of non-immune, non-anaemic hydrops fetalis before 24th week of gestation[52]	Therapeutic abortion
Hydrocele	Unknown	Unknown	Unknown	NA	Insufficient information for evaluation	Insufficient information for evaluation	Delivery (premature)
Melanocytic nevus	23	Influenza	Day 20/first	Between the 5th and 25th week of gestation[53]	No		Delivery
Trisomy 21	33	Influenza-like illness	Day 32/first	NA	No	Chromosomal abnormality; no preconception exposure to drug. Down's syndrome occurs because of meiotic non-disjunction of chromosome 21, either during gametogenesis or in the immediate post-fertilization state[54]	Therapeutic abortion
Ventricular septal defect	36	Influenza	Day 34/first	Before the 6th week of gestation[51]	Yes		Delivery
Ventricular septal defect	Unknown	Unknown	Between day 28 and day 50/first	Before the 6th week of gestation[51]	Yes		Delivery

a In all cases, gestation is measured from time of conception, not the last menstrual period.

NA = not applicable.

woman knows that she is pregnant.[24] The potential for a drug to cause harm to mother and/or fetus is therefore an important element in benefit-risk analysis, but this information can take time to accumulate. Pregnant women are normally excluded from clinical trials conducted during a drug's development programme,[24,57] although some pregnant women may accidentally receive an investigational drug during a trial. When a drug is first marketed, the only available data on fetal effects come from animal reproductive toxicology studies.[24] Postmarketing surveillance entailing close monitoring of all pregnancy and fetal outcomes in women exposed to the drug during pregnancy is therefore vital.

Based on reports from the oseltamivir safety database over a 9-year period, comprising 115 known pregnancy outcomes in women exposed to oseltamivir during pregnancy, the rates of three adverse pregnancy outcomes – fetal loss (spontaneous abortions and stillbirths), therapeutic abortion and pre-term delivery – were not higher than background rates reported in published literature. Comparison with background rates is the best way to assess the adverse effects of drugs on these three outcomes because of their relatively high frequencies in the general population.[24]

As the background rate of individual birth defects is low, comparison of this rate with the combined rate of all reported defects following exposure to a given drug is not informative. The US FDA therefore recommends single-case analysis for each birth defect, including a report of whether exposure to the drug occurred during the sensitive period for development of the defect in question.[24] Of the 100 maternal exposures in the oseltamivir database for which information on fetal outcome was available, nine cases of birth defects were reported. In five of these cases, exposure to oseltamivir did not occur during the sensitive period for the development of the defect in question, and in one other case, there was insufficient information for assessment. In the remaining three cases – two of VSD and one of anophthalmos – exposure to oseltamivir occurred during the sensitive period for the defect (the first trimester), but for all three defects, the possibility exists that they would have arisen without oseltamivir exposure. In the general population, VSD occurs at a rate of 42 per 10 000 live births, whereas anophthalmos has an incidence rate of 0.3 per 10 000 live births.[58,59] The article by Hayashi et al.,[55] which reported one of the two VSD cases mentioned above, found no other birth defects in a series of 79 Japanese women who took oseltamivir during the first trimester (one stillbirth was reported).

Data from animal studies and toxicology reports indicate that oseltamivir has a very low propensity to produce adverse effects on pregnancy or fetal outcomes.[45] Because the metabolic fate of oseltamivir in animals is similar to that in humans, these pre-clinical data can be expected to be relevant to humans. In addition, human placental model data show that oseltamivir and oseltamivir carboxylate are not readily transferred from mother to fetus at normal therapeutic doses.[46] Another potential cause of birth defects in oseltamivir-treated mothers is exposure to the influenza virus itself or, more probably, the fever associated with influenza. Microphthalmos, a defect that is closely related to anophthalmos, is among a range of birth defects reported to be induced by hyperthermia.[41] The association between influenza infection and adverse pregnancy outcomes is still not well understood.[28] There is some evidence for an increased risk of adverse fetal outcomes (birth defects) on exposure to influenza or fever during the first trimester.[36,42]

There are limitations to the use of data from spontaneous reporting and comparisons with background rates. Spontaneous reporting is likely to result in under-reporting of the true rate of maternal drug exposures. In addition, individuals who experience adverse pregnancy outcomes are more likely to report them than those who experience a normal outcome, and this reporting bias means that the reported rate of adverse pregnancy outcomes is likely to be higher in a retrospective analysis than in a prospective study.[60]

5. Conclusions

On the basis of the information and analysis presented in this article (data up to December 2008), maternal exposure to oseltamivir does not

appear to be causally related to adverse pregnancy or fetal outcomes. Although no controlled clinical trials have been conducted on the use of oseltamivir in pregnant women, limited data from postmarketing and retrospective observational surveillance reports in conjunction with animal study data do not indicate direct or indirect harmful effects with respect to pregnancy, or embryonic or fetal development. One study has been published since our literature search was conducted;[61] this retrospective cohort investigation found no difference in rates of stillbirth and major and minor malformations between fetuses exposed to oseltamivir and unexposed controls, which supports our conclusions. Pregnant women may receive oseltamivir after the clinician has considered the available safety information, the pathogenicity of the circulating influenza virus strain and the general health of the pregnant woman. Given the established efficacy of oseltamivir and the high-risk status of pregnant women with influenza, clinicians should decide on a case-by-case basis whether the benefits of using oseltamivir to treat or prevent influenza in pregnant women might outweigh any potential risks from influenza or oseltamivir. Additionally, they should consider recent guidance published by health authorities on this topic,[16-18] and emerging evidence of the benefits of early antiviral therapy in pregnant women hospitalized with pandemic (H1N1) 2009.[62] The dataset on pregnancy outcomes after exposure to oseltamivir contained in this article is the first to be reported. The uncertainty of the estimates derived from the data warrants follow-up, and a larger dataset on exposures is now being collected. Roche will continue to closely monitor all reports of oseltamivir use during pregnancy, including all information received during the influenza A (H1N1) 2009 pandemic.

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