

## Comprehensive review of telbivudine in pregnant women with chronic hepatitis B

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### Abstract

**AIM:** To achieve an evidence-based conclusion regarding the safety and efficacy of telbivudine during pregnancy.

**METHODS:** A pooled analysis of data from a literature search reported 1739 pregnancy outcomes (1673 live births) from 1725 non-overlapping pregnant women treated with telbivudine. The prevalence of live birth defects (3.6/1000) was similar to that of the non-antiviral controls (3.0/1000) and not increased as compared with overall prevalence (14.5 to 60/1000). No target organ toxicity was identified. The prevalence of spontaneous abortion in pregnant women treated with telbivudine (4.2/1000) was not increased compared with the overall prevalence (16/1000). The mother-to-child transmission rate was significantly reduced in pregnant women treated with telbivudine (0.70%) compared to those treated with the non-antiviral controls (11.9%;  $P < 0.0001$ ) or compared to the historical rates of hepatitis B virus (HBV)-infected population without antiviral treatment (10%-15%).

**RESULTS:** Cumulatively 489 pregnancy cases have been reported in the telbivudine pharmacovigilance database (with a cut-off date 31 August 2014), of those, 308 had known pregnancy outcomes with 249 cases of live births (239 cases of live birth without congenital anomaly and 10 cases of live birth with congenital anomaly). In the latest antiretroviral pregnancy registry report (1 January 1989 through 31 January 2015) of 27 patients exposed to telbivudine during pregnancy (18, 6 and 3 during first, second and third trimester, respectively) 19 live births were reported and there were no cases of birth defects reported.

**CONCLUSION:** Telbivudine treatment during pregnancy presents a favorable safety profile without increased rates of live birth defects, spontaneous abortion or elective termination, or fetal/neonatal toxicity. Exposure to telbivudine in the first, second and third trimester of pregnancy has been shown to significantly reduce the risk of HBV transmission from mother to child on the basis of standard immune prophylaxis procedure.

**Key words:** Telbivudine; Hepatitis B virus; Pregnancy; Mother-to-child transmission; Vertical transmission

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**Core tip:** The data from literatures, pharmacovigilance reports on telbivudine exposure and antiretroviral pregnancy registry during pregnancy in women with hepatitis B virus (HBV) infection showed no increased rates of live birth defects, spontaneous abortion or elective termination. No fetal/neonatal toxicity was reported during telbivudine treatment. Telbivudine exposure in the second and/or third trimesters of pregnancy has been shown to reduce the risk of HBV transmission from mother to child if administered in addition to hepatitis B immunoglobulin and HBV vaccination with a favorable safety profile.

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## INTRODUCTION

Chronic hepatitis B (CHB) infection is a major public health problem. Perinatal or childhood transmission of hepatitis B virus (HBV) commonly leads to chronic hepatitis which causes necroinflammation and progression of fibrosis resulting in higher risk of developing cirrhosis and hepatocellular carcinoma<sup>[1]</sup>. Over 50% of CHB carriers in endemic areas acquired their infection perinatally<sup>[2,3]</sup>. In the absence of prevention, infants born to hepatitis B e antigen (HBeAg) positive mothers have a 40%-90% risk of acquiring CHB *via* vertical

transmission<sup>[4]</sup>. In addition, 15%-90% of infected infants develop chronic infection (according to the HBeAg status of the mother), compared with < 5% of patients who acquire infection during adulthood<sup>[5-7]</sup>.

It was reported that 42.1% of infants born to HBsAg-positive mothers globally acquired HBV infection perinatally, because those infants did not receive any active or passive immunoprophylaxis for HBV. In contrast only 2.9% of infants who received immunoprophylaxis acquired HBV infection perinatally<sup>[8]</sup>. HBV perinatal transmission or mother-to-child transmission (MTCT) is considered to occur mainly at delivery. Therefore, standard immunoprophylaxis procedures to prevent perinatal transmission are recommended<sup>[9]</sup>. This standard procedure is based on the combination of passive and active immunization with hepatitis B immunoglobulin (HBIG) and HBV vaccination. However, immunoprophylaxis may not be effective in a proportion of newborns from highly viremic mothers (serum HBV DNA > 10<sup>6-7</sup> IU/mL) who are mostly HBeAg positive, who carry a > 10% risk of vertical HBV transmission despite efficient HBIG and vaccination<sup>[10]</sup>. The vaccine failure cases were reported in previous studies<sup>[11-13]</sup>. There was an earlier report from Mayotte, a French territory in Africa, that newborns who had received complete and timely sero-vaccination had a low immunoprophylaxis failure rate (3%)<sup>[14]</sup>.

Antiviral therapy administered to HBV carrier mothers during pregnancy plus appropriate immunoprophylaxis to newborns have been suggested to effectively prevent MTCT by reducing maternal HBV DNA levels and developing passive immunization in newborns. The European Association for the Study of the Liver (EASL) guidelines recommend the use of a nucleos(t)ide analogue to reduce viral loads in pregnant women who are hepatitis B surface antigen (HBsAg) positive and have high HBV DNA levels (> 10<sup>6-7</sup> IU/mL) to enhance the effectiveness of HBIG and vaccination<sup>[15,16]</sup>. Pregnant women with cirrhosis have an increased risk of developing maternal complications, significant perinatal complications, and poor pregnancy outcomes<sup>[9]</sup>. Therefore, it is often recommended that woman of child-bearing age with advanced fibrosis or cirrhosis should be treated with nucleos(t)ide analogues and that their treatment regimen must be maintained during a future pregnancy<sup>[13]</sup>.

No anti-HBV therapies are currently approved for the prevention of MTCT in pregnancy. Each antiviral has been assigned by the Food and Drug Administration (FDA) to one pregnancy drug class based on preclinical evaluation of the potential teratogenicity. Of the seven antiviral drugs for CHB currently available, alpha interferons and pegylated alpha interferons have anti-proliferative actions and are contraindicated during pregnancy<sup>[15]</sup>. Of the currently approved five oral nucleos(t)ide analogues, tenofovir and telbivudine belong to pregnancy category B (animal reproduction studies have failed to demonstrate a risk to the fetus and studies in pregnant women failed to demonstrate a risk to the fetus), while the other three

**Table 1 Food and drug administration pregnancy categories for hepatitis B virus antiviral therapy<sup>[15]</sup>**

Pregnancy category	definition	HBV therapy categorization
A	Adequate and well controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)	None
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women or animal studies that have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester	Telbivudine; Tenofovir
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well controlled studies in humans, but potential benefits might warrant use of the drug in pregnant women despite potential risks	Lamivudine; Entecavir; Adefovir
D	There is positive evidence of human fetus risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits might warrant use of the drug in pregnant women despite potential risks	None
X	Studies in animals or humans have demonstrated fetus abnormalities, and/or there is positive evidence of human fetus risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits	Interferon

drugs, lamivudine, adefovir and entecavir, belong to pregnancy category C (animal reproduction studies have shown an adverse effect on the fetus and no adequate or well controlled studies in humans)<sup>[15]</sup> (Table 1). Of the aforementioned drugs, there are limited data on treating HBV infection during pregnancy. A prospective randomized controlled trial of tenofovir in HBV infected mothers have been reported<sup>[17]</sup>. Treatment with lamivudine in late pregnancy has shown reduced mother-to-infant transmission but drug resistance is a potential concern<sup>[15]</sup>.

Telbivudine has shown no carcinogenicity, teratogenicity, mutagenicity or mitochondrial toxicity in pre-clinical studies. Telbivudine has demonstrated greater antiviral and clinical efficacy than lamivudine in CHB patients<sup>[18-20]</sup>. In a prospective cohort study, telbivudine showed better preventive effect in reducing perinatal transmission when used in early trimesters of pregnancy than latter in pregnancy. There were no complications or severe adverse events observed in telbivudine-treated mothers or infants<sup>[21]</sup>. Another study showed that telbivudine treatment in chronic HBV-infected mothers was effective in blocking the MTCT of HBV and growth and development of the children were normal<sup>[22]</sup>. As recommended by EASL and the Asian-Pacific Association for the Study of the Liver guidelines, telbivudine is listed as one of the preferred drugs to be used for the prevention of MTCT in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA > 10<sup>6-7</sup> IU/mL)<sup>[15,23]</sup>.

Here we present a summary of the information available on the safety and efficacy of telbivudine when used during pregnancy. This analysis was based on scientific literature, and analysis of a Novartis pharmacovigilance database and a public Antiretroviral Pregnancy Registry. The objective of this analysis was to achieve an evidence-based conclusion regarding the safety and efficacy of telbivudine use in HBV infected pregnant mothers and to confirm the observations from telbivudine preclinical studies.

## MATERIALS AND METHODS

### Preclinical studies

Several preclinical studies of reproductive and developmental toxicity have been conducted with telbivudine to assess its potential adverse effects on fertility, general reproductive performance, development of the conceptus, gestation, birth and post-natal performance (Novartis; data on file). An overview of these studies conducted is summarized in Table 2.

### Clinical studies

Programmed searches were conducted in literature databases for an extensive literature review. The cut-off periods were set as no starting limit till May 2015. Databases included BIOSIS Previews, EBM Reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database), Embase, International Pharmaceutical Abstracts, MEDLINE (including in-process and other non-indexed citations, MEDLINE Daily Update, and OLDMEDLINE). The search strategy included the following keywords in all fields using different combinations with the Boolean operators OR and AND: "telbivudine" or equivalent names ("2' deoxy beta thymidine", "beta thymidine", "epavudine", "LdT 600", "NV 02B", "NV02B", "Sebivo" or "Tyzeka"); pregnant or pregnancy; hepatitis. Another search was conducted in Chinese databases to review Chinese literatures in the following Chinese databases: Wanfang Med Online (med.wanfangdata.com) and China Knowledge Resource Integrated Database (www.cnki.net). Keywords for search in Chinese databases included "telbivudine", "gestation", "pregnancy", "intrauterine infection", "mother-to-child transmission" and "vertical transmission".

A consistent methodology was used when reviewing each paper. The main criterion for selecting a publication

**Table 2** Reproductive and developmental toxicity with telbivudine

Study type	Route of administration	Species	No. of animals	Doses (mg/kg per day)	Treatment	Reference
Rat studies						
Fertility, reproduction, developmental	Oral gavage	Sprague Dawley rats	25 males 25 females	0, 100, 500, 1000	Males: -28 AC to DG 17 Females: -15 AC to DG 17	Study 1314-001
Fertility	Oral gavage	Sprague Dawley rats	25 males 25 females	0, 1000, 2000	Males: -28 AC to DG 13	Study 1314-005
Fertility	Oral gavage	Sprague Dawley rats	25 males 25 females	0, 2000	Females: -15 AC to DG 7	Study 1314-006
Peri/postnatal	Oral gavage	Sprague Dawley rats	25 females	0, 100, 250, 1000	Females: DG 7 to DL 20	Study 1314-003
Rabbit study						
Developmental	Oral gavage	New Zealand White rabbits	20 females	0, 50, 250, 1000	Females: DG 6-18	Study 1314-002

AC: Ante coitum; DG: Gestation day; DL: Lactation day.

was completeness of safety data ("adequate safety information" was defined as including both pregnancy and pregnancy/infant outcome to address the safety profile of telbivudine use in pregnancy) and non-overlapping cases. For articles reported more than once by the same author, the corresponding author was contacted for clarification of the case details. Systemic reviews or meta-analysis were not included in this analysis. Studies with non-overlapping data and safety information were selected and analyzed. All pregnant women who were treated with telbivudine during the period of pregnancy and were reported with a pregnancy outcome were included in the analysis of this review. All those pregnancies without a pregnancy outcome reported or lost to follow up were excluded from this review.

### Pharmacovigilance database

Pregnancy cases from Novartis pharmacovigilance database were collected with a cut-off date of 31 August 2014. Data collected prospectively (acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination (e.g., fetal ultrasound or serum markers) were separated from data collected retrospectively (acquired after the outcome of the pregnancy was known or after the detection of a congenital malformation on prenatal test). Only safety data were collected from the cases; data on perinatal and intrauterine information was not adequately collected.

### Antiretroviral pregnancy registry

The Antiretroviral Pregnancy Registry (APR; [www.APRRegistry.com](http://www.APRRegistry.com)) is designed to collect and evaluate data on the outcomes of pregnancies exposed to antiretroviral products. It has been actively collecting relevant data since January 2003 and telbivudine has been included in the list of evaluated drugs. An interim analysis report is issued online semi-annually including data from 1 January 1989 through the latest period. The interim report contains analyses of voluntary prospective reports (i.e., reports made to the Registry prior to the outcome of pregnancy being known) of prenatal exposures. Additionally, data from retrospective reports are collected,

but the outcomes are reviewed and evaluated separately. The present analysis was based on the latest available APR Interim Report<sup>[24]</sup> (1 January 1989 through 31 January 2015)

### Endpoints assessment and variables of analysis

The following endpoints were selected in pregnant women with HBV infection: Pregnancy outcome and efficacy of preventing MTCT.

According to the Committee for Medicinal Products for Human Use (CHMP) 2005 guidelines on the exposure to medicinal products during pregnancy, "pregnancy outcome" is defined as the end products of pregnancy, which include three main categories: (1) fetal death; (2) termination of pregnancy; and (3) live birth<sup>[25]</sup>.

Fetal death (intrauterine death or *in utero* death) is defined as death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not show any evidence of life [World Health Organization (WHO) International Classification of Diseases (ICD) 10]. There are 2 types of fetal death: (1) early fetal death (before 22 completed weeks of gestation) comprises ectopic pregnancy (extra-uterine pregnancy or early fetal death most often in the Fallopian tube) and miscarriage (spontaneous abortion or molar pregnancy); and (2) late fetal death (after 22 completed weeks of gestation) is known as stillbirth.

Termination of pregnancy (induced abortion or elective abortion) is artificial interruption of pregnancy.

Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which breathes or shows any evidence of life after separation (WHO ICD 10).

The same guidelines also defined the variables used to measure prevalence of birth defects<sup>[25]</sup>: (1) live birth prevalence rate = (number of cases among live born infants/total number of live born infants) × 1000; (2) birth prevalence rate = [number of cases among live and stillborn infants/total number of (live + still) born infants] × 1000; and (3) Total prevalence rate = (number of cases among live births, stillborn and terminated pregnancies)/(number of live births, stillbirths and



**Table 3** Non-overlapping literature references of telbivudine exposure during pregnancy

Ref.	Original language	Study design	LdT starting trimester during pregnancy	No. of pregnancy with exposure to LdT	Maternal HBV DNA (at inclusion)
Chen <i>et al</i> <sup>[46]</sup>	Chinese	Prospective	1 <sup>st</sup> trimester	43	$\geq 1 \times 10^7$ copies/mL
Han <i>et al</i> <sup>[47]</sup>	English	Prospective	2 <sup>nd</sup> and 3 <sup>rd</sup> trimesters	362	$> 1.0 \times 10^6$ copies/mL
Jiang <i>et al</i> <sup>[53]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimesters	28	$> 10^3$ copies/mL (at inclusion)
Liu <i>et al</i> <sup>[38]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	5	$\geq 1 \times 10^7$ copies/mL (before treatment)
Liu <i>et al</i> <sup>[28]</sup>	English	Prospective	1 <sup>st</sup> trimester	89	$> 1 \times 10^5$ copies/mL
Liu <i>et al</i> <sup>[21]</sup>	English	Prospective	1 <sup>st</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> trimesters	82	$\geq 10^6$ IU/mL
Mohan <i>et al</i> <sup>[54]</sup>	English	Prospective	1 <sup>st</sup> trimester	1	$4.0433 \times 10^4$ copies/mL
Peng <i>et al</i> <sup>[39]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	40	$\geq 1 \times 10^6$ copies/mL
Wu <i>et al</i> <sup>[27]</sup>	English	Prospective	2 <sup>nd</sup> or 3 <sup>rd</sup> trimester	279	$> 10^6$ IU/mL
Yu <i>et al</i> <sup>[44]</sup>	English	Prospective	1 <sup>st</sup> , 2 <sup>nd</sup> or 3 <sup>rd</sup> trimester	233	$> 1.0 \times 10^6$ copies/mL
Zeng <i>et al</i> <sup>[40]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	22	$\geq 10^5$ copies/mL
Zeng <i>et al</i> <sup>[22]</sup>	English	Prospective	1 <sup>st</sup> or 3 <sup>rd</sup> trimester	54	Not reported
Zhao <i>et al</i> <sup>[55]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	30	Not reported
Zhang <i>et al</i> <sup>[41]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	31	$> 1 \times 10^7$ copies/mL
Zhang <i>et al</i> <sup>[42]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	60	$\geq 1 \times 10^6$ copies/mL
Zhang <i>et al</i> <sup>[26]</sup>	English	Prospective	3 <sup>rd</sup> trimester	257	$> 6 \log_{10}$ copies/mL
Zhou <i>et al</i> <sup>[43]</sup>	Chinese	Prospective	3 <sup>rd</sup> trimester	36	$\geq 1 \times 10^7$ copies/mL
Zhou <i>et al</i> <sup>[45]</sup>	Chinese	Prospective	1 <sup>st</sup> trimester	73	$\geq 1 \times 10^7$ copies/mL

terminated pregnancies)  $\times 1000$ .

The efficacy variable is the rate of MTCT, which is conservatively defined as evidence of HBV infection (detectable HBV DNA or detectable HBsAg) at the age of 6-12 mo or older in the source literature references.

## RESULTS

### Preclinical studies

Studies in pregnant rats (Study 7245-112) and rabbits (Study GVA00010) showed that telbivudine crosses the placenta. Developmental toxicity studies in rats (Study 1314-001) and rabbits (Study 1314-002) at doses up to 1000 mg/kg per day and with exposure levels 6- to 37-times higher indicated that telbivudine was not a developmental toxin in either species (Table 2). Similarly, the high doses (1000 mg/kg per day) given to rats during the peri- and post-natal developmental periods showed no evidence of post-natal developmental toxicity or change in behavior (Study 1314-003). Based on these findings, it is concluded that telbivudine is not teratogenic and has shown no adverse effects in developing embryos and fetuses, as well as in pre- and postnatal development. Telbivudine use is considered to pose a negligible risk to fetus during pregnancy.

### Clinical studies from literature search

**Characteristics of the selected cases:** A total of 18 publications with non-overlapping data and safety information were identified through the literature search, in which 1725 mothers were treated with telbivudine during pregnancy period. These 1725 non-overlapping pregnancy cases were all prospective cases where mothers were exposed to telbivudine during different trimester of pregnancy. The 18 selected publications are listed in Table 3.

**MTCT rate:** Based on the literature review, MTCT rate of telbivudine treatment during pregnancy with the

standard immunoprophylaxis procedure was reported to be 0.70% (11/1572; Table 4). Of the 11 infants with MTCT, 8 mothers started telbivudine treatment from 3<sup>rd</sup> trimester and 3 mothers started from 1<sup>st</sup> trimester. Of the 11 infants with MTCT, 6 mothers had  $> 6 \log$  copies/mL HBV DNA prior to telbivudine treatment, 2 mothers had  $> 5 \log$  copies/mL and 2 mothers had  $> 3 \log$  copies/mL HBV DNA. There was no report on HBV DNA level for 1 mother.

Of the 18 selected literature references, 14 had a non-antiviral control group. The MTCT rate in the non-antiviral treatment group was 11.9% (124/1041; Table 4). The MTCT rate calculated in telbivudine treated patients (0.70%) was significantly lower vs MTCT rate calculated in patients from non-antiviral control group (11.9%) ( $P < 0.0001$ , Fisher's exact test).

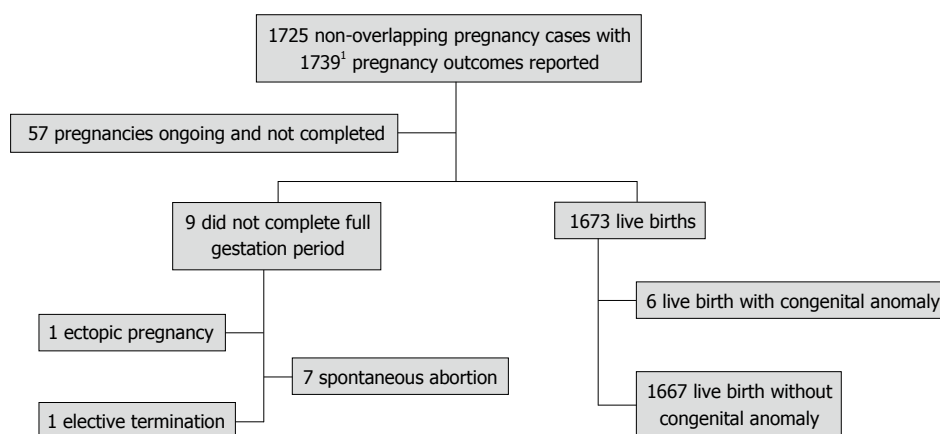
**Rates of birth defects:** A total of 1739 pregnancy outcomes were reported from 1725 pregnancies (Figure 1). The safety outcomes of infants in terms of rates of birth defects were calculated according to the three definitions of the CHMP guidelines<sup>[25]</sup>.

Of the 1673 live births, a total of 6 infants had birth defects (3 infants with ankyloglossia, cutaneous hemangioma, and vaginal canal leak<sup>[22]</sup>; 1 infant with unilateral cleft palate<sup>[26]</sup>; 2 infants with a congenital cleft lip, palate and ear accessories<sup>[27,28]</sup>). Of the 6 infants with birth defects, 4 were born to mothers starting telbivudine treatment in 1<sup>st</sup> trimester and 2 were born to a mother starting telbivudine treatment in 2<sup>nd</sup> or 3<sup>rd</sup> trimester. The "live birth prevalence rate" was  $6/1673 = 3.6/1000$  which was not significantly different from the non-antiviral control ( $3.0/1000$ ) ( $P = 1.0000$ ) (Table 4). Since no stillbirth was reported, the "birth prevalence rate" was same as the "live birth prevalence rate"  $6/1673 = 3.6/1000$ , which was not significantly different from the non-antiviral control ( $3.0/1000$ ) ( $P = 1.0000$ ). The "total prevalence rate" of birth defects with telbivudine exposure was  $7/1674 = 4.2/1000$  (Table

**Table 4** Summary of prevalence rates of birth defects, abortion and perinatal transmission rates with telbivudine exposure during pregnancy in literature studies

	Events (n)	Population (N)	Rate in telbivudine treated patients (n/N)	Non-antiviral treatment control in literature studies	Background rates in overall population (prevalence based on surveillance reports)
Birth defects: Live birth prevalence	6	1673	3.6/1000 <sup>a</sup>	3.0/1000	14.5-60/1000 <sup>1</sup>
Birth defects: Birth prevalence	6	1673	3.6/1000 <sup>a</sup>	3.0/1000	NA
Birth defects: Total prevalence	7	1674	4.2/1000 <sup>b</sup>	3.0/1000	NA
Spontaneous abortion	7	1682	4.2/1000	NA	16/1000 <sup>2</sup>
Elective termination	1	1682	0.6/1000	NA	230/1000 <sup>3</sup>
MTCT	11	1572	0.70% (11/1572) <sup>d</sup>	11.9% (124/1041)	10%-15% <sup>4</sup>

<sup>1</sup>EUROCAT data<sup>[48]</sup>; MACDP data<sup>[49]</sup>; Christianson *et al*<sup>[50]</sup> (2006); Dai *et al*<sup>[54]</sup> (2011); <sup>2</sup>US CDC data<sup>[51]</sup>; <sup>3</sup>WHO data<sup>[52]</sup>; <sup>4</sup>Historical data from HBV-infected population without antiviral treatment<sup>[10-12]</sup>. <sup>a</sup> $P = 1.0000$  vs non-antiviral treatment control in the same literature studies (Fisher's exact test); <sup>b</sup> $P = 0.7502$  vs non-antiviral treatment control in the same literature studies (Fisher's exact test); <sup>d</sup> $P < 0.0001$  vs non-antiviral treatment control in the same literature studies (Fisher's exact test). NA: Not available; MTCT: Mother-to-child transmission.



**Figure 1** Analysis of the pregnancy outcomes from non-overlapping literature references. <sup>1</sup>1734 pregnancy outcomes from 1721 pregnancy mothers due to multiple births.

4), which was not significantly different from the non-antiviral control (3.0/1000) ( $P = 0.7502$ ).

**Pharmacovigilance database:** A total of 489 cumulative pregnancy cases have been reported in the telbivudine pharmacovigilance database (with a cut-off date 31 August 2014). Of the 489 cases, 308 had known pregnancy outcomes with 249 cases of live births (239 cases of live birth without congenital anomaly and 10 cases of live birth with "congenital anomaly" including medical conditions that were not birth defects). Of these 10 cases, 6 cases were considered with congenital birth defects (one case each of hypertrophic pyloric stenosis, cryptorchism, atrial septal defect, syndactyly, hemangioma, and congenital heart disease). Of these 6 cases, 3 had telbivudine exposure during the first trimester.

Fifty-nine cases were reported with the following situations: Ectopic pregnancy ( $n = 2$ ), spontaneous abortion ( $n = 11$ ), intrauterine death ( $n = 3$ ), neonatal death ( $n = 1$ ), elective termination with fetal defects ( $n = 5$ ) and elective termination without fetal defects or unknown ( $n = 37$ ).

**Antiretroviral pregnancy registry:** Based on the cumulative current APR report (1 January 1989 through 31 January 2015), a total of 17332 evaluable prospective cases treated with anti-retroviral drugs during pregnancy period [most with human immunodeficiency virus (HIV) infection] were included in the primary analysis. Of the 8602 birth outcomes with a 1<sup>st</sup> trimester exposure to an antiretroviral drug, there were 219 reports of birth defects. Of the 9026 birth outcomes in the combined second and/or third trimester exposure to antiretroviral drugs, 249 were reported birth defects. Of 27 patients who were exposed to telbivudine during pregnancy (18, 6 and 3 during first, second and third trimester, respectively), 19 live births were reported and there were no cases of birth defects reported.

## DISCUSSION

The prevention of vertical transmission of HBV from mothers to their infants, while limiting toxicity is the key for treating pregnant women with HBV infection and is a significant unmet medical need. Telbivudine, classified as a FDA pregnancy category B drug, is listed

as one of the preferred drugs and may be used for the prevention of MTCT in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA  $> 10^{6-7}$  IU/mL)<sup>[15,23]</sup>. Preclinical studies have demonstrated that telbivudine is not teratogenic and has not shown any adverse effects in developing embryos and fetuses, as well as in pre- and postnatal development. However, certain other antiviral drugs are associated with some potential teratogenic risks during fetal development. A French long-term perinatal cohort study in HIV-infected mothers reported the risks of lamivudine exposure during pregnancies as it causes birth defects in children<sup>[29]</sup>. In the present analysis, based on a systematic literature review of clinical studies, the total prevalence rate of live birth defects in telbivudine-treated pregnancies was not significantly different as compared to the non-antiviral controls in the same literature studies or did not increase as compared to overall prevalence. In the six cases that were reported with congenital anomalies, no particular organ toxicity emerged. Three infants were reported with ankyloglossia, cutaneous hemangioma, and vaginal canal leak; 1 infant with unilateral cleft palate; 2 infants with a congenital cleft lip, palate and ear accessories. The reported prevalence of accessory auricle (0.06%) in this study was not higher than in studies from China (0.3%)<sup>[30]</sup>, Taiwan (0.2%)<sup>[31]</sup>, or Turkey (0.47%-0.7%)<sup>[32,33]</sup>. The reported prevalence of cleft lip and palate (0.12%) in this study was similar to those rates reported in studies performed in China (0.13%)<sup>[34]</sup>, in United States (cleftlip with or without palate 0.114% or cleft palate without cleft lip 0.109%)<sup>[35]</sup>.

The present analysis provides evidence that telbivudine usage in pregnant women in all pregnancy trimesters is generally safe and efficacious, which is in accordance with the EASL guidelines<sup>[15]</sup>. Moreover, at least 297 mothers with telbivudine exposure during 1<sup>st</sup> trimester were included in our study. Of note, 4/6 infants with birth defects were born to mothers who were exposed to telbivudine in the 1<sup>st</sup> trimester; and 8/11 infants with MTCT were born to mothers who were exposed to telbivudine in the 3<sup>rd</sup> trimester of pregnancy. Accordingly, the starting trimester of telbivudine treatment should be a balanced decision considering the maternal HBV DNA load and the need of minimizing risk of birth defects to achieve a best efficacy and safety outcome.

The pharmacovigilance database setting is different from clinical trials in terms of nature, objective or data completeness. In a clinical trial setting, all pregnancy cases treated with telbivudine are required to be collected either prospectively or retrospectively according to a predefined protocol. In contrast, pharmacovigilance database is an observational setting which is targeted to collect adverse event cases reported from all sources and physicians (or consumers) are trained to report cases when any "adverse" event occurs. However, pregnancy is usually not regarded by physicians and consumer as an "adverse" event. As a result, a majority of pregnancy cases with normal outcomes are not reported to the pharmacovigilance database, but those with unfavorable

pregnancy or infants' outcome are more likely to be regarded as "adverse" events and reported. In other words, pregnancy cases with normal outcomes are either under-reported by physicians or cannot be sufficiently collected in the current safety database settings. Therefore, in this review, data from the pharmacovigilance database was cited as another source of data, and it was not pooled with data from literature studies to calculate the prevalence rates of birth defects.

Several recent reviews on telbivudine use in pregnancy have reported results of pregnancy outcomes and prevention of HBV transmission, which were consistent with our results. A meta-analysis of telbivudine use in pregnancy (two randomized controlled trials and four non-randomized controlled trials) analyzed 306 mothers who received telbivudine treatment (vs no treatment,  $n = 270$ ). After a follow-up of 6-12 mo after delivery, HBV DNA positive rates were 0.9% in the telbivudine group vs 14.6% in the control group<sup>[36]</sup>.

In another review of 8 studies, a total of 663 infants born to telbivudine-treated mothers had significantly lower rates of HBsAg positivity and HBV DNA positivity measured post-partum at 6 mo (OR = 0.06,  $P < 0.00001$ ; OR = 0.05,  $P = 0.0003$ ) and 12 mo (OR = 0.13,  $P = 0.007$ ; OR = 0.08,  $P = 0.001$ ) vs the non-treatment control<sup>[37]</sup>.

Although the mechanism of MTCT of HBV is not yet fully elucidated, there are three proposed mechanisms (intrauterine transmission, transmission during delivery and post-partum transmission)<sup>[9]</sup>. Maternal serum HBV DNA level has been identified as the most important independent risk factor for MTCT<sup>[15]</sup>.

A majority of patients in our analysis had HBeAg-positive CHB and high HBV DNA levels prior to treatment with HBV DNA levels and HBeAg status being evenly matched between the telbivudine-treated patient and control groups. Telbivudine use during pregnancy resulted in a low rate of MTCT at 0.70% despite high HBV DNA levels at baseline. The MTCT rate in the non-antiviral control groups of the 14 literature references was 11.9%, which was similar to the rates reported in previous literature references (10%-15%)<sup>[10,11]</sup>. These results from 18 different studies with 1725 pregnancies indicate that the overall blocking of vertical transmission is 99.3% (MTCT 0.70%). Of the 18 literature studies, 15 studies did not report antiviral resistance associated with telbivudine treatment; 3 studies had reported a resistance rate of 1.2%, 2.3% or 6.5%.

A limitation of the analysis is the follow-up period in literature references which was a maximum of 12 mo for most of infants; therefore, long-term effects on such infants remain to be assessed.

In conclusion, the data from literatures, post-marketing pharmacovigilance reports on telbivudine exposure and APR during pregnancy in women with HBV infection showed no increased rates of live birth defects, spontaneous abortion or elective termination. No fetal/neonatal toxicity was reported during telbivudine treatment. The favorable safety profile observed from telbivudine reproductive and developmental preclinical

studies have been confirmed in various clinical settings. Importantly, based on the evidences from more than 1700 of HBV infected mothers reported from literature, telbivudine exposure in pregnancy has been shown to reduce the risk of HBV transmission from mother to child if administered in addition to HBIG and HBV vaccination with a favorable safety profile.

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## COMMENTS

### Background

Currently, no anti-hepatitis B virus (HBV) therapies are approved for the prevention of mother-to-child transmission (MTCT) of HBV during pregnancy. In this comprehensive review, data were collected from the published literature, a pharmacovigilance database and an ongoing public registry antiretroviral pregnancy registry (APR).

### Research frontiers

Here the authors present a summary of the information available on the safety and efficacy of telbivudine when used during pregnancy. This analysis was based on scientific literature, and analysis of a Novartis pharmacovigilance database and a public APR.

### Innovations and breakthroughs

The favorable safety profile observed from telbivudine reproductive and developmental preclinical studies have been confirmed in various clinical settings. Importantly, based on the evidences from more than 1700 of HBV infected mothers reported from literature, telbivudine exposure in pregnancy has been shown to reduce the risk of HBV transmission from mother to child if administered in addition to hepatitis B immunoglobulin and HBV vaccination with a favorable safety profile.

### Peer-review

This is a very interesting study on the safety of telbivudine administration in pregnancy and its efficacy in preventing MTCT of HBV infection. The data are well analysed and written and the conclusions are useful particularly for the hepatitis B e antigen positive mothers with high viral loads.

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