Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

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Evidence of the risk of birth defects with efavirenz use is limited. We updated a meta-analysis of birth defects in infants with first trimester efavirenz exposure up to July 2011. In 21 studies, there were 39 defects among live births in 1437 women receiving first trimester efavirenz [2.0%, 95% confidence interval (CI) 0.82–3.18]. The relative risk of defects comparing women on efavirenz-based (1290 live births) and non-efavirenz-based regimens (8122 live births) was 0.85 (95% CI 0.61–1.20). One neural tube defect was observed (myelomeningocele), giving an incidence of 0.07% (95% CI 0.002–0.39).

Current antiretroviral treatment guidelines in resource-limited settings recommend efavirenz or nevirapine as first-line drugs [1]. Efavirenz is widely used because it is well tolerated, easy to monitor, conveniently coformulated as a once-daily pill and shows similar virologic suppression to nevirapine. However, efavirenz use during the first trimester of pregnancy is contraindicated due to animal data and case reports indicating a potential association with neural tube defects [2]. We previously published a systematic review and meta-analysis that found no increase in overall birth defects comparing first trimester receipt of efavirenz-based and non-efavirenz-based regimens, although the limited number of reports prevented a definitive conclusion regarding the risk of rare outcomes such as neural tube defects [3]. We updated our systematic review to include data up to July 2011.

Using a predefined protocol (http://tinyurl.com/3hzz5wo), we combined terms for efavirenz, pregnancy and birth outcomes and searched the following databases up to 1 July 2011 without language restrictions: MEDLINE via PubMed; EMBASE; CINAHL and PsychInfo; Cochrane CENTRAL; LILACS; Current Controlled Trials; BioMedCentral and Public Library of Science; and websites of major HIV conferences such as International AIDS Society conferences up to July 2011 and Conferences on Retroviruses and Opportunistic Infections up to February 2011. Data were abstracted from the latest Antiretroviral Pregnancy Registry (http://www.apregistry.com), and the following treatment cohorts were contacted: the MTCT Plus Initiative; Médecins Sans Frontières; the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDA-SA); and the Reproductive Health Research Unit (RHRU).

The primary endpoint was birth defects of any kind. Unsystematic observations (case series or case reports) were excluded. Point estimates and 95% confidence intervals (CIs) were calculated for birth defects reported among live births for each study (spontaneous and induced abortions and stillbirths were excluded). Proportions were summarized using random effects meta-analysis using a Freeman–Tukey arcsine transformation of the raw proportions. The $\chi^2$-statistic was calculated to assess between-study heterogeneity. For cohorts reporting birth outcomes of infants exposed to efavirenz vs. other antiretrovirals during the first trimester, relative risks (RRs) and CIs were calculated and data pooled using random effects method. Subgroup analyses assessed potential effects on the pooled estimates of study design, location, exposure duration and publication status. All analyses were conducted using Stata, version 11 (StataCorp LP, College Station, Texas, USA).

The initial search yielded 798 publications and 885 conference abstracts, from which 32 studies were reviewed as full text. Twenty-one studies were included for analysis (among which 19 reported our primary outcome), including 13 prospective studies. This updated review found 181 additional live births with first trimester efavirenz exposure and birth defect data from five additional cohorts [4–8], one updated study [9] of a previous report [10], and the updated Antiretroviral Pregnancy Registry [11].

Across the 19 studies reporting birth defects among 1437 live-born infants born to women receiving efavirenz in the first trimester, birth defect prevalence ranged from 0% [12] to 22.6% [13], with a 2.0% pooled prevalence (CI 0.82–3.18); heterogeneity between studies was low ($\chi^2 = 1.89$). One neural tube defect was observed (myelomeningocele) [11], giving an incidence proportion of 0.07% (CI 0.002–0.39) (Table 1) [4–9, 11–23]. In a subgroup analysis, there was no difference according to publication status ($P = 0.58$), study design ($P = 0.19$) or exposure duration ($P = 0.96$); prevalence appeared higher in developed countries compared with developing countries ($P = 0.015$).

Eleven studies reported birth defects among infants born to women receiving first trimester efavirenz-containing regimens (38 defects among 1290 live births) and
nonefavirenz-containing regimens (316 defects among 8122 live births), giving a nonsignificant RR of 0.85 (CI 0.61–1.20); heterogeneity was low ($I^2 = 0$) (Fig. 1). The pooled estimate was not affected by subgroup analyses that compared study setting ($P = 0.47$), duration of efavirenz exposure ($P = 0.78$) or publication status ($P = 0.50$).

The reporting of secondary outcomes varied across studies. Eight studies reported spontaneous abortions, with prevalence ranging from 0% [6] to 16.05% [14]. The prevalence of stillbirths, reported by eight studies, ranged from 0% [19] to 13.3% (MTCT-Plus). The prevalence for termination of pregnancy, reported by 10 studies ranged from 0% [6] to 33.7% [24]. Three studies reported data on termination of pregnancy (none based on prenatal screening) for women exposed to efavirenz-containing and nonefavirenz-containing regimens [9,19,24], giving a RR of 2.81 (95% CI 0.94–8.36) for efavirenz-exposed women. Finally, five studies reported on preterm delivery, with prevalence ranging from 9.1% [19] to 18.2% [20].

The methodological quality of included studies was judged to be moderate. The vast majority of reports were from prospective cohorts (1364 live births), and only four studies were composed of less than 10 patients with first trimester efavirenz use. Ascertainment of birth defects among stillborn/terminated births was only reported by two studies (the prevalence of birth defects was consistent with data reported for live births).

This expanded review confirms the previous meta-analysis findings of no increased risk of overall birth
defects among women receiving first trimester efavirenz. The pooled prevalence of birth defects for women exposed to first trimester efavirenz (2.0%) is similar to that for women exposed to nonefavirenz-based regimens in the antiretroviral pregnancy registry (2.9%) [11], and in the general population (6%) [25]. Incidence of neural tube defects remains low (0.07%), but this estimate is derived from a small sample.

Strengths of this review include a broad search strategy that identified data from the grey literature and unpublished cohorts, and the inclusion of updated data for several cohorts. Limitations include the inconsistent reporting of secondary outcomes and the potential for bias associated with selective abortion as a result of prenatal screening that could result in a reduction of birth prevalence. We consider such bias unlikely, given that none of the studies reporting rates of termination of pregnancy among women exposed to efavirenz used prenatal screening to guide termination decisions and note that in the Antiretroviral Pregnancy Registry the reported prevalence of birth defects among induced abortuses of women exposed to antiretroviral therapy in the first-trimester (2.5%) is consistent with the background prevalence [11]. The main limitation of this review is the small sample size. It is notable that more than 80% of data come from just four studies in which prospective reporting of birth outcomes has been established [9,11,15,16]. The lack of systematic recording of birth outcomes from women receiving antiretroviral drugs during pregnancy persists, with reports of birth outcome data for only 181 live births found by this review in the last 18 months. Prospective surveillance systems particularly in developing countries are needed to improve data reporting and inform the assessment of risk of rare defects.

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Conflicts of interest

There are no conflicts of interest.

Fig. 1. Relative risk of birth defects on efavirenz vs. nonefavirenz regimens. CI, confidence interval; EFV, efavirenz.
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