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Pregnancy outcomes after maternal varenicline use; analysis of surveillance data collected by the European Network of Teratology Information Services

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ABSTRACT

Varenicline is a smoking cessation aid for which limited data exist concerning safety during human pregnancy. This multicentre prospective observational comparative cohort study was undertaken using surveillance data collected by the European Network of Teratology Information Services. The study sample consisted of 89 varenicline exposed pregnancies and two matched comparator groups; 267 non-teratogen exposed (NTE) controls and 78 exposed to nicotine replacement therapy or bupropion (NRT/B) for smoking cessation. For all exposed pregnancies, varenicline use only occurred in the first trimester, with a considerable proportion discontinuing use in the very early stages of pregnancy. The major congenital malformation rate (n = 2/89, 2.25%) was in keeping with the expected background rate (2–4%), and was not significantly increased for first trimester varenicline-exposed infants in comparison with non-exposed controls (vs. NTE: OR 2.02, 95%CI 0.166 to 17.9, vs. NRT/B: OR 0.874, 95%CI 0.0620 to 12.3). However, the small sample size produced very imprecise risk estimates.

1. Introduction

Smoking tobacco during pregnancy is associated with a higher risk of several adverse obstetric, fetal and infant outcomes including spontaneous abortion, stillbirth, premature delivery, intrauterine growth restriction, placental abruption, congenital malformation, sudden infant death syndrome, childhood cancer, behavioural and neurodevelopmental disorders, asthma, obesity and diabetes [1–12]. Healthcare professionals therefore encourage smoking cessation among patients who have failed to discontinue smoking prior to pregnancy.

For the general non-pregnant population the most effective tobacco smoking cessation strategies involve a combination of behavioural support therapy with pharmacological smoking cessation aids[13] such as nicotine replacement therapy (NRT), bupropion or varenicline. However, there is limited evidence regarding efficacy and safety for these pharmacotherapeutic options during pregnancy [14].

Varenicline (Champix®/Chantix®; Pfizer Limited, Anatomical Therapeutic Chemical (ATC) code: N07BA03) is a partial agonist of the α4β2 neuronal nicotinic acetylcholine receptor (nAChR), and a full agonist of the α7 nAChR[15] licensed for use as a smoking cessa-

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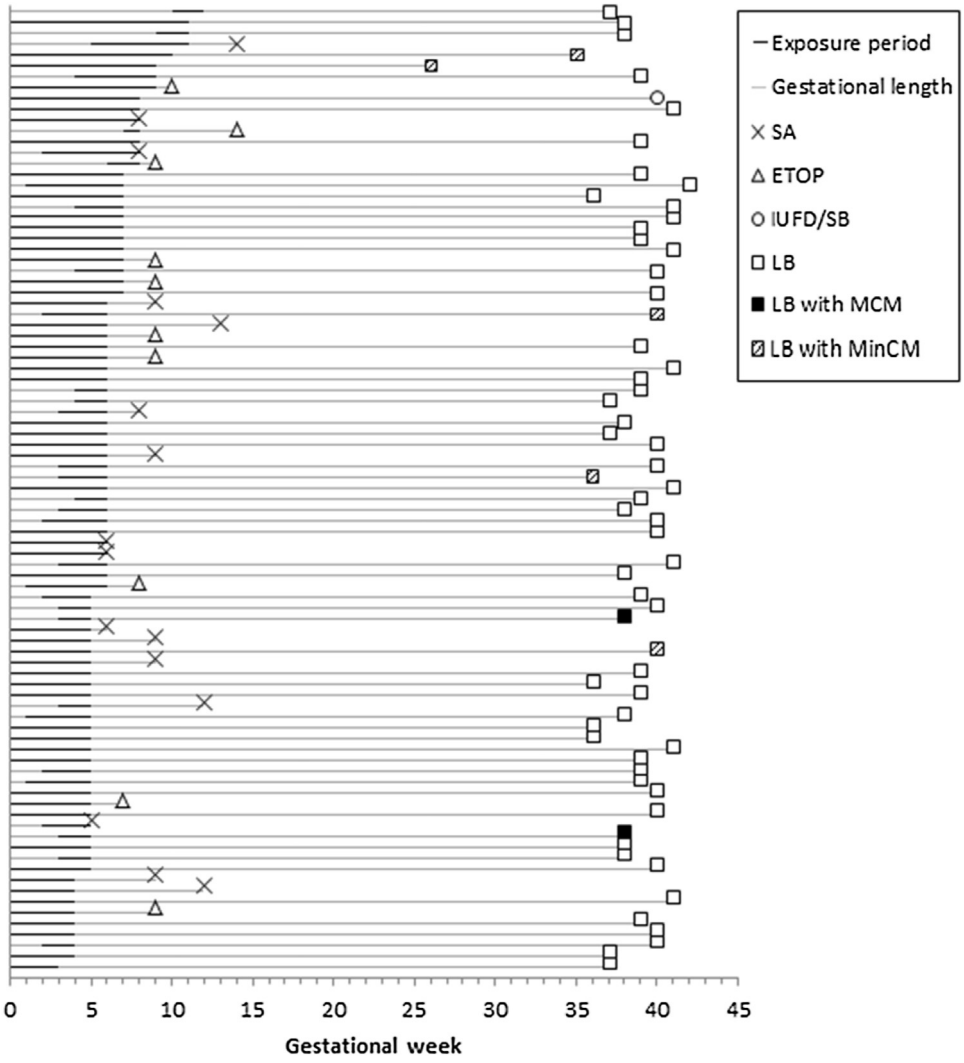

Fig. 1. Period of varenicline use, length of gestation and pregnancy outcome among the 89 exposed pregnancies.
Key: SA = spontaneous abortion, ETOP = elective termination of pregnancy, IUFD/SB = intrauterine fetal death/stillbirth, LB = live birth, MCM = major congenital malformation, MinCM = minor congenital malformation.

tion aid [16]. Varenicline is formulated as the tartrate salt and has a molecular weight of 361.35 Da; it is readily absorbed following oral exposure which provides a high systemic availability, with maximal plasma concentrations usually observed within four hours [17]. It appears to be minimally metabolised with around 92% excreted unchanged in urine, and has an elimination half-life of approximately 24 h [17]. Preclinical safety studies of varenicline did not identify adverse effects at doses similar to those used in human therapy [16]. Although post-marketing pharmacovigilance surveillance has included reports of neuropsychiatric symptoms, seizures, hypersensitivity and cutaneous reactions in some patients, a randomised, double-blind, active and placebo controlled clinical trial indicated that smoking cessation may have contributed to many of the neuropsychiatric symptoms which have previously been reported [16].

Based on evidence provided from a Cochrane review of randomised controlled studies, varenicline has greater efficacy than placebo, nicotine replacement therapy or bupropion for smoking cessation among non-pregnant patients [18]. However, studies concerning the safety of varenicline use during pregnancy are extremely limited.

Preclinical reproductive toxicity studies performed by the manufacturer exposed pregnant rats and rabbits to doses approximating 36 and 50 times respectively the maximum recommended human daily exposure (based on AUC at 1 mg administered twice daily (BID)), and did not suggest an increased risk of teratogenicity [17,19]. However, administration of doses approximating 50 times the maximum recommended human daily exposure (based on AUC at 1 mg administered BID) to pregnant rabbits resulted in reduced fetal weights which were not apparent at 23 times the maximum recommended human daily exposure (based on AUC following 1 mg BID), while the offspring of pregnant rats treated with doses of varenicline equivalent to 36 times the maximum recommended human daily exposure (based on AUC at 1 mg administered BID) experienced decreased fertility rates and increases in auditory startle response [17].

Although placental passage of varenicline has been documented in both rats and rabbits[19] no such studies have been performed in humans. However, based on molecular weight and pharmacoki-