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ORIGINAL ARTICLE

Antiobesity drugs in early pregnancy and congenital malformations in the offspring

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Summary Little information exists on the possible teratogenic effect of modern antiobesity drugs. The present study refers to orlistat, sibutramine, and rimonabant. Data in the Swedish Medical Birth Register were utilised. During the years 1998—2011, among 392,126 infants born, 509 had been exposed to antiobesity drugs in early pregnancy: 248 to orlistat, 242 to sibutramine, 12 to rimonabant, 13 to unspecified antiobesity drugs. Simultaneous use of orlistat and sibutramine occurred in six cases. No increase in major malformation risk was seen after orlistat (relative risk = 0.42, 95% confidence interval 0.11—1.07) but a significantly high risk was seen after sibutramine (relative risk = 1.81, 95% confidence interval 1.02—2.99). The latter effect, which seemed to be mainly due to an increased risk for a cardiovascular defects, may be related to the capacity of the drug to prolong QT-time. Sibutramine has been withdrawn in Europe but is still available on the Internet and is a component in some slimming preparations. Among the 12 infants exposed to rimonabant, two which were in a twin pair were malformed.

Introduction

In many parts of the world an obesity epidemic has occurred during the last few decades. A marked increase in the rate of obese pregnant women has been noticed and among them also numerous ill effects on pregnancy outcome, including an increased risk for congenital malformations in the offspring [1]. One way to achieve a weight loss is by use of antiobesity drugs of different nature. Previously these were mainly based on sympaticomimetic drugs related to amphetamine, e.g., dexamphetamine or phenmetrazine. Some discussion of a teratogenic effect of these drugs existed. Heinonen et al. [2] found no evidence for a teratogenic effect but other researches did [3,4]. More recently phenermine (related to amphetamine) together with fenfluramine has been used in some countries. No certain teratogenic activity was found in a limited study on 98 women [5].

In Sweden three drugs have been sold as antiobesity drugs during the last 15 years: sibutramine, orlistat, and rimonabant. For all three

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warnings about use during pregnancy have existed but exposure may well occur in unplanned pregnancies. Only a few relatively small studies have been published on maternal use of sibutramine and infant congenital malformations, mainly obtained from teratology information services [6—11]. No malformations were reported. A meeting abstract described 15 infants born after exposure to orlistat, none was malformed [10]. No study of rimonabant during pregnancy has been found.

The present study reports data on pregnancy outcome after maternal use in early pregnancy of antiobesity drugs: orlistat, sibutramine, and rimonabant.

Materials and methods

The study is based on the Swedish Medical Birth Register [12] which contains medical information on nearly all (1—2% missing) deliveries in Sweden. Information on the use of drugs in early pregnancy was obtained from midwife interviews at the first prenatal visit, usually in weeks 10—12. At this visit, the woman was asked what drugs she had taken since she became pregnant and the midwife wrote down the drug name in clear text in the medical form which is used in all prenatal centres in Sweden. Copies of these records, records from the delivery, and from the paediatric examination of the newborn were sent to the National Board of Health and Welfare and were computerised. The drug names were centrally transformed into ATC (Anatomical, Therapeutic, Chemical) codes. Antiobesity drugs are there listed under A08A. The first exposure to an antiobesity drug (orlistat) was recorded in 1998. Therefore the analysis was restricted to 1998—2011.

The Medical Birth Register among other things contains information on date of delivery, maternal age, parity, smoking in early pregnancy and prepregnancy weight and height from which body mass index (BMI) is calculated. Presence of congenital malformations in the offspring is ascertained from three sources: information in the Medical Birth Register based on the neonatal examination of a paediatrician, congenital malformations reported to the Register of Birth Defects (previous Register of Congenital Malformations), and discharge diagnoses from inpatient treatments in all hospitals in Sweden (Patient Register, previously Hospital Discharge Register) [13]. Data from these three sources were linked using the unique personal identification number which everyone living in Sweden has. Malformations were coded according to the International Classification of Diseases (ICD), 10th edition.

In order to reduce variability in the registration of malformations, so-called ''relatively severe malformations'' were studied. Then infants with only one or more of the following conditions were excluded: preauricular appendix, tongue tie, patent ductus arteriosus in preterm infants, single umbilical artery, undescended testis, hip (sub)luxation, and nevus.

Risk estimates as odds ratios (OR) were obtained with Mantel—Haenszel procedure and approximate 95% confidence intervals (95% CI) with Miettinen's method. Adjustment was made for year of birth, maternal age (5-year classes, <20, 20—24 etc.), parity (1 to ≥4 where 1 means first baby born), smoking in early pregnancy (unknown, none, <10 cigarettes/day, ≥10 cigarettes/day), and BMI (unknown, <18.5, 18.5—24.9, 25—29.9, 30—34.9, ≥35). When the expected number of outcomes (adjusted as above) was <10, a risk ratio (RR) was instead calculated as the observed over expected number with 95% CI from Poisson distributions.

Ethics: The study was performed within the responsibilities of the National Board of Health and Welfare and therefore no ethical approval from outside ethical committees was needed.

Results

Antiobesity drug use in early pregnancy was reported by 505 women with 509 infants (four twin pairs). The distribution of drug use is seen in Table 1. The total number of women in the register these years was 1,371,506 with 1,392,126 infants. Thus only about 4 per 10,000 had used these drugs when becoming pregnant. Fig. 1 shows the number of users in each year 1998—2011.

The characteristics of the women who gave birth after early use of antiobesity drugs are shown in Table 2. The use appears to increase with maternal age and with parity >2. There is a nearly significant association with maternal smoking and as expected

Table 1 Specification of antiobesity drugs used in early pregnancy. Note that six women used both sibutramine and orlistat.

Drug	No. of women	No. of infants
Sibutramine	242	242
Orlistat	245	248
Rimonobant	11	12
Unspecified	13	13
Total	505	509