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Early First-Trimester Sibutramine Exposure

Pregnancy Outcome and Neonatal Follow-Up

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Abstract

Background: Sibutramine is a drug that is used in the treatment of obesity. There are currently no epidemiological studies relating to sibutramine exposure in pregnancy. The objective of our study was to determine whether sibutramine exposure during pregnancy constitutes a risk factor to the mother and developing fetus.

Methods: Fifty-two pregnant women who were exposed to sibutramine in the first trimester of pregnancy, when they were unaware of being pregnant, contacted our Teratology Information Service. We recorded the prospective outcomes of this case series between May 2001 and September 2004 with a complete neonatal follow-up up to 1 month after delivery.

Results: Seven cases of hypertensive complications were observed during pregnancies. No cases of congenital anomalies in neonates were observed.

Conclusion: Although many more cases are necessary to demonstrate that sibutramine is not teratogenic in pregnancy, our experience improves the counseling of pregnancies occurring involuntarily during sibutramine therapy.

Background

Sibutramine is a drug used in the treatment of obesity, in association with a strict diet and exercise regimen.[1] It is recommended for weight reduction or weight maintenance in obese patients with a body mass index (BMI) >30 kg/m^2 but without other risk factors, and also for patients with a BMI ≥27 kg/m^2 and who are affected by diabetes mellitus, hypertension or lipoprotein disorders.[2-4]

Sibutramine is administered orally and inhibits the reuptake of noradrenaline (norepinephrine), serotonin and dopamine.[5] During therapy, the main adverse effect is increased blood pressure, and monitoring of blood pressure is therefore recommended in patients who are exposed to sibutramine.[6] The daily dosage of this agent is 5–15mg.[7]

According to the US FDA, sibutramine belongs to pregnancy category C: the drug should be given only if the potential benefit justifies the potential risk to the fetus, but the manufacturer recommends the use of adequate contraception in childbearing women, and sibutramine should not be prescribed in pregnancy.[7] The avoidance of strict diets and appetite depressants is also suggested during pregnancy. Weight loss has been hypothesised as being a factor in embryo toxicity and teratogenic risk. It is also a negative contributor with regard to fetal-placental development.[8,9]

In the current literature, data about sibutramine exposure in pregnancy are very limited and there is no evidence of teratogenic effects.[10,11] In experimental animals sibutramine causes decreased food intake and increases body temperature.[12] Investigations have shown that the tissue distribution of sibutramine is no different in pregnancy, since very little of the drug crosses the placenta.[7] From studies in rats, there is no evidence of teratogenic effects at sibutramine dosages up to 10 mg/kg/day.[7] Rabbits exposed *in utero* to a toxic dose of sibutramine (15 mg/kg/day) developed a slightly shorter and broader snout, shorter rounded pinnae, a shorter tail, and shorter and more thickened long bones of the limbs compared with controls.[7] The rabbits also showed a slight increase in heart defects, although this was not confirmed in further investigations.[7]

The objective of our study was to determine whether sibutramine exposure during pregnancy constitutes a risk factor to the mother and developing fetus.

Methods

The Telefono Rosso – Teratology Information Service (TIS) is a specialised service that provides counseling concerning teratogenic risk during pregnancy in the preconceptional period and during lactation. It was principally set up because of the limited information existing in this field and the incorrect risk perception evident in a high proportion of patients. The information provided by the service concerning the teratogenic risks of drugs, chemicals and radiation depends on the available data. In addition to serving the community by preventing birth defects and some induced abortions due to fear of malformations, the Telefono Rosso represents a unique opportunity to add to the current body of knowledge, as it documents the outcomes of pregnancies exposed to a variety of agents. In this respect, the TIS may be considered an additional source of postmarketing surveillance data.

Between May 2001 and September 2004, all patients who had consulted the TIS about sibutramine exposure in early pregnancy were enrolled in our epidemiological study, after having obtained their oral consent for inclusion. We collected data regarding sibutramine dosage, adverse effects, treatment indications, period of exposure, weight loss during treatment, diet and other therapies. The following data were also collected: maternal age, obstetric history, smoking history, alcohol and illicit drug use, family and personal clinical and anamnestic information.

Gestational age was confirmed by an ultrasound scan in the first trimester. All patients were followed by phone interviews during pregnancy and up to 1 month after delivery. They were asked about pregnancy outcome, birth defects and neonatal complications.

Results

A total of 52 patients, who had become pregnant while undergoing treatment with sibutramine, were enrolled in the study. All pregnancies were singleton, apart from one twin pregnancy. There were eight miscarriages, five elective abortions, three preterm deliveries and 36 deliveries at term, with a total of 40 livebirths (table I).

Only eight women met the criteria for treatment with sibutramine since they had no risk factors and their BMI was >30. On the other hand, 43 of 52 patients had a BMI <30, with no risk factors. The mean maternal dose of sibutramine was 10.90 mg/day (range 5–20) [table II]. The duration of sibutramine therapy ranged from 5 days to 360 days. Thirty-nine patients began sibutramine therapy before conception. However, all patients were exposed to sibutramine in the first trimester of pregnancy from conception to 54 days after conception (16.07 ± 11.14) and not beyond this point, with all women discontinuing sibutramine upon detection of pregnancy.

Table I. Maternal features of study group (n = 52)

Maternal feature	Mean ± SD
Maternal age (y)	33.63 ± 4.46
Gravidity	1.67 ± 0.94
Parity	0.52 ± 0.7
Previous miscarriage	0.12 ± 0.43
Body mass index (kg/m^2)	26.71 ± 4.99

Table II. Features of patients exposed to sibutramine (n = 52)

Parameter	Mean ± SD
Total exposure period (d)	68.62 ± 79.26
Exposure period from conception (d)	16.07 ± 11.14
Sibutramine dose (mg/day)	10.90 ± 3.10
Maternal weight loss (kg)	5.5 ± 5.06
Weight loss period (d)	70.34 ± 75.28
Weight loss per wk (g)	623.34 ± 596.62

The maternal weight loss during treatment ranged from 0kg to 25kg, and the weekly weight loss was up to 2778g (table II).

Four of nine patients who lost >1000g/week had miscarriages and one who had a prenatal diagnosis of trisomy 18 decided to terminate her pregnancy.

Twenty-one of 52 patients were treated with sibutramine in combination with other drugs, of which eleven were receiving only weight-loss therapies. Two of these eleven patients had a miscarriage; the first was taking tiratricol (triiodothyroacetic acid), synephrine, fluoxetine, thiazide diurectics, deanol and benfluorex until the sixth week of gestation, and the second was taking fluoxetine, metformin, bupropion, synephrine and buspirone until the fifth week of gestation.

The remaining nine patients, who had normal pregnancies, were being treated with metformin and tiratricol (four cases), clorazepate and fluoxetine (two cases), fluoxetine and benfluorex (two cases) and orlistat (one case).

Ten of twenty-one patients were also exposed to other drugs for different indications. Four patients affected by hypothyroidism were undergoing therapy with levothyroxine. One patient was being treated with flutamide for hirsutism; one patient was taking clorazepate for anxiety; one allergy patient treated with oxatomide was also administered levonorgestrel to induce abortion, though unsuccessfully; one patient received a high dose of vitamin A (60 000 IU daily) for acne; and one required propranolol therapy for essential hand tremors. Finally, one patient who had undergone abdominal surgery was exposed to low molecular weight heparin and cephalosporins.

It is notable that sibutramine was being used in association with fluoxetine in six cases, even though it is recommended that it should not be administered with other serotonergic agents.

All the women were on strict hypocaloric diets and had taken neither fortified food nor vitamins.

No cardiovascular complications described in the literature (tachycardia, arrhythmia, sudden death) occurred in our cases.[13-15]

Four pregnancies were complicated by hypertension and these women were treated with methyldopa from the 11th, 31st, 36th and 37th week of gestation, respectively. The BMI values of these women were 28, 34.7, 35.6 and 27.3 kg/m^2, respectively. The birth weights of their neonates were 3550, 2400, 3530 and 3250g, respectively.

Three pregnancies were complicated by pre-eclampsia and the babies were delivered by Caesarean section at 28, 32 and 37 weeks. The birth weights were 970, 2890 and 3010g, respectively. The maternal BMI values were 34.9, 28 and 26 kg/m^2, respectively.

The mean delivery week was 38.92 ± 2.61 among the 39 women who delivered, and the birth weight ranged from 970g to 4100g. There were three cases of preterm delivery, two of which were the pre-eclamptic patients, who delivered at 28 and 32 weeks, respectively, and the third was a woman with a twin pregnancy who delivered at 35 weeks. Twenty of the 39 pregnancies were delivered vaginally.

There was not a high incidence of spontaneous abortion (15.9%). Four of eight spontaneous abortions occurred in women who had weight losses of >1000 g/week; three were for unidentified causes and the last was as a result of amnionitis at 18 weeks.

Hypertensive disorders were the only complication during pregnancy and the neonatal complications observed were two tracheal intubations carried out in babies whose mothers had undergone a Caesarean section because of hypertension at 28 and 41 weeks of gestation (table III). A prenatal diagnosis of trisomy 18 was made in a woman exposed to sibutramine who subsequently decided to terminate her pregnancy. We have no data about congenital anomalies in pregnancies complicated by miscarriage or terminated by legal abortion. One fetal

Table III. Pregnancy and neonatal outcomes in study group (n = 52)

Pregnancy outcomes [numbers (%)]	
Live births	40/53[a] (75.47)
Elective abortions	5/53[a] (9.4)[b]
Miscarriages	8/53[a](15.09)
Stillbirths	0/53[a](0)
Preterm deliveries (<37wk)	3/52 (5.7)
Vaginal deliveries	20/39 (52.63)[c]
Pregnancy complications (total)	7/52 (9.6)
Pregnancy complications (hypertensive disorders)	7/52 (9.6)
Neonatal outcomes	
Congenital anomalies [numbers (%)]	0/40[c] (0)
Neonatal complications[d] [numbers (%)]	2/40[c] (5)
Gestational age at birth in weeks (mean ± SD)	38.92 ± 2.61
Birth weight in grams (mean ± SD)	3266.10 ± 530.34
Birth weight ≥4000g [numbers (%)]	1/40[c] (2.5)
Birth weight ≤2500g [numbers (%)]	2/40[c] (5)

a Fifty-one singleton and one twin pregnancies.

b One trisomy 18.

c Of all live births.

d Two orotracheal intubations.

autopsy, performed after a second trimester spontaneous abortion leading to amnionitis, was normal.

Discussion and Conclusions

Our data represent the prospective outcomes of a case series concerning the effects of sibutramine after involuntary exposure in early pregnancy. We recorded 52 cases of pregnant women exposed to sibutramine over a period of 40 months, in spite of the manufacturer's warnings to avoid pregnancy during treatment.

Seven of our 52 patients met the present criteria for treatment with sibutramine, highlighting the improper prescription of sibutramine in many cases. In some cases (6/52 cases), sibutramine was prescribed together with other drugs, such as fluoxetine (a serotonergic agent), even though the association with sibutramine is not recommended.

In our investigation, hypertensive disorders were the only complication observed in pregnancies exposed to sibutramine. Although increasing blood pressure is a proven sibutramine adverse effect, gestational hypertension or pre-eclampsia developed several weeks after the end of therapy in all of our cases. Any linkage with sibutramine exposure seems, therefore, unlikely. On the other hand, a relationship with overweight and metabolic disorders (common in obese women) should be considered, as the pregnant women affected by gestational hypertension or pre-eclampsia had a mean BMI value of 30.6 kg/m^2.

We documented no increase in congenital anomalies or adverse pregnancy outcomes after first-trimester exposure to sibutramine.

At present our data are too limited to exclude a minimal teratogenic risk related to sibutramine therapy in early pregnancy. In addition our follow-up was carried out when the neonate was 1 month old, but some birth defects, especially cardiac defects, can manifest later in infancy. Our figures, therefore, may underestimate the number of birth defects. We also have not included a comparative control group and the outcomes were obtained from a telephone interview of the mother without any confirmatory medical record review. There could, therefore, be recall bias, especially regarding maternal medical conditions and/or complications during pregnancy and/or delivery. However, our case study is the largest and most comprehensive to date and, therefore, in our opinion, we can exclude a high teratogenic risk. Nevertheless, we feel that as many cases as possible should continue to be collected in order to improve the counseling of pregnant women exposed to sibutramine.

In conclusion, we wish to clearly state that sibutramine treatment and strict dieting are not suitable in pregnancy. Increased thermogenesis or ketosis and acidosis connected to food deprivation or ketogenic diets could be responsible for toxic damage to the embryo and/or congenital malformations, especially central nervous system disease.[8,9] Periconceptional weight loss and severe diet regimens, moreso than sibutramine exposure, are therefore important indications for performing second level fetal ultrasound.

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