Appetite suppressants in pregnancy

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Abstract

OBJECTIVES: Both, obesity as well as anorexia may be associated with infertility and other complications of pregnancy. Weight loss during pregnancy is therefore considered a risk factor. Weight loss and appetite suppressant are contraindicated during pregnancy, but the unintended exposure is probably not associated with higher risk. Our work was focused on trends in the appetite suppressants use in the Czech Republic and their embryotoxicity.
METHODS: The pregnancies exposed to various appetite suppressants were followed prospectively in the years 1997–2012. The study group was compared to the comparison group which enrolled pregnant women exposed to non-teratogenic drugs. Drugs used as appetite suppressants were sibutramine and phentermine.
RESULTS: Number of calls for this type of exposure was rare till 2005. Their number started to increase until 2009. Later, number of calls decreased because both drugs were withdrawn from the market. This finding reflects increasing tendency for the weight control in the group of fertile women in the Czech Republic. In our study, we did not reveal differences in pregnancy outcomes between study and comparison groups.
CONCLUSIONS: However, we should be aware of the increasing food supplements exposure, that could be used as alternative to the appetite suppressants. Their potential risk results from the limited or completely absent control of their origin. Some of them have probably only placebo effect, but some of them could represent the risk.

INTRODUCTION

Both, obesity as well as anorexia may be associated with infertility and other complications of pregnancy. Risk associated with obesity could be assigned to unknown diabetes mellitus or hypertension. However, weight loss during pregnancy represents a risk factor as well. Low intake of proteins, vitamins, and essential elements, or activation of toxins from adipose tissue may be the reason. Weight loss and appetite suppressants are therefore contraindicated during pregnancy. However, unintended exposure is probably not associated with higher risk. Although the obesity is considered a risk factor during pregnancy, the only rational indication for pharmacological intervence is BMI >30, or BMI >27 in patients with other risk factors as diabetes mellitus type II or dyslipidemia (Garcia-Bournissen *et al.* 2007). Sibutramine, phentermine, and orlistat were the observed appetite suppressants during defined period in the Czech Republic. There is only limited information about their embryotoxicity. The diet and control of food intake by the appetite sup-

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pressants are popular especially among young women in their reproductive period. In fact, the unintended exposure to appetite suppressant may appear during early pregnancy, because almost 50% of pregnancies are unintended. There are only few epidemiological studies relating to appetite suppressant in pregnancy (De Santis *et al.* 2006; Jones *et al.* 2002). The objective of our study was to map the trends in appetite suppressant use in the Czech Republic and determine whether appetite suppressant exposure during pregnancy constitutes a risk factor to the mother and developing fetus.

METHODS

The thirty-eight pregnant women, who were exposed to appetite suppressant in the first trimester, contacted Czech Teratology Information Service (CZTIS) between January 1997 and December 2012. Time of the first contact was till 16 week of pregnancy. At the first contact with the CZTIS, participants were asked to enrol in the study and were interviewed (by phone or by written questionnaire) for demographic background parameters, general medication and obstetric histories, details of the present pregnancy and details of the exposure to drugs, as well as any other exposures or risk factors (such smoking, alcohol use ect.). Maternal variables included age at conception, number of previous pregnancies, time of contact. After delivery, the women were contacted to ascertain pregnancy outcome parameters. The main outcome was the prevalence of major congenital malformation; secondary outcomes were rate of abortions (spontaneous or elective), rate of preterm deliveries (birth at week <38) and birth weight.

Student´s T-test was applied to normally distributed, continuous variables and categorical variables were analysed with Chi-squared and Fisher´s exact tests where appropriate. Results were expressed as mean and standard deviation.

Patients characteristics

Calls for the appetite suppressant exposure were rare in our database as we registered only 38 calls. Seventeen cases with known pregnancy outcome were included in our study: eight pregnancies were exposed to phentermine and nine pregnancies were exposed to sibutramine. No pregnancy was exposed to orlistat for the obesity treatment. Orlistat was used strictly for the hyperlipidemia treatment and therefore the pregnancies were not included in our study. Remaining 21 pregnancies exposed to appetite suppressant were excluded because follow up was not obtained or mothers did not want to participate in the study. The mean age of women included in the study was 32.3. It was mainly their first pregnancy.

Comparison group

The comparison group comprises the women who inquired for drugs, which are considered non-teratogenic (as penicillins, macrolides, analgesic ect.), vaccination with inactive bacteria as tetanus, and food supplements. The comparison group enrolled 85 pregnant women. The mean age of women in comparison group was 31.6 years. Number of previous pregnancies was higher in that group. It was mainly their second pregnancy (mean 1.8).

Tab. 1. There was no statistically significant difference between exposed and comparison groups in the frequency of malformations, spontaneous and elective abortions.

	Appetite suppressant	Comparison group	Chi-square
Malformations	0	2	p=0.5461
Spontaneous abortions	1	2	p=0.4038
Elective abortions	2	5	p=0.3616

Tab. 2. We did not record differences in newborns weight and length and duration of pregnancy between exposed and comparison groups.

	Appetite suppressant	Comparison group	t	*p*-value
Weight (mean)	3450 g	3415 g	0.205318	0.837759
Length (mean)	50.21 cm	48.72 cm	0.357586	0.721472
Duration of pregnancy in weeks	39.57	39.9	0.8528	0.3958

RESULTS

Exposures to the appetite suppressant were rare in our database being one or two cases per year till 2007. Then, the number of calls increased up to nine cases in 2009. Later, inquiries for those drugs decreased, because they were withdrawn from the market. However, the calls for food supplement exposure appeared at the same time. Trends in exposure to appetite suppressants are demonstrated on Figure 1.

We did not reveal statistically important differences in demographic parameters (age, parity, time of call) between study and comparison groups. Moreover, majority of the women exposed to appetite suppressants were not obese and drug was used for the weight control, only (with or without recorded weight reduction).

There were also no differences in the risk of malformation being in both groups within expected range (Table 1). Results for both groups of appetite reducers did not vary. Spontaneous abortion appeared during week 7 of pregnancy in 27 years old woman. It was her

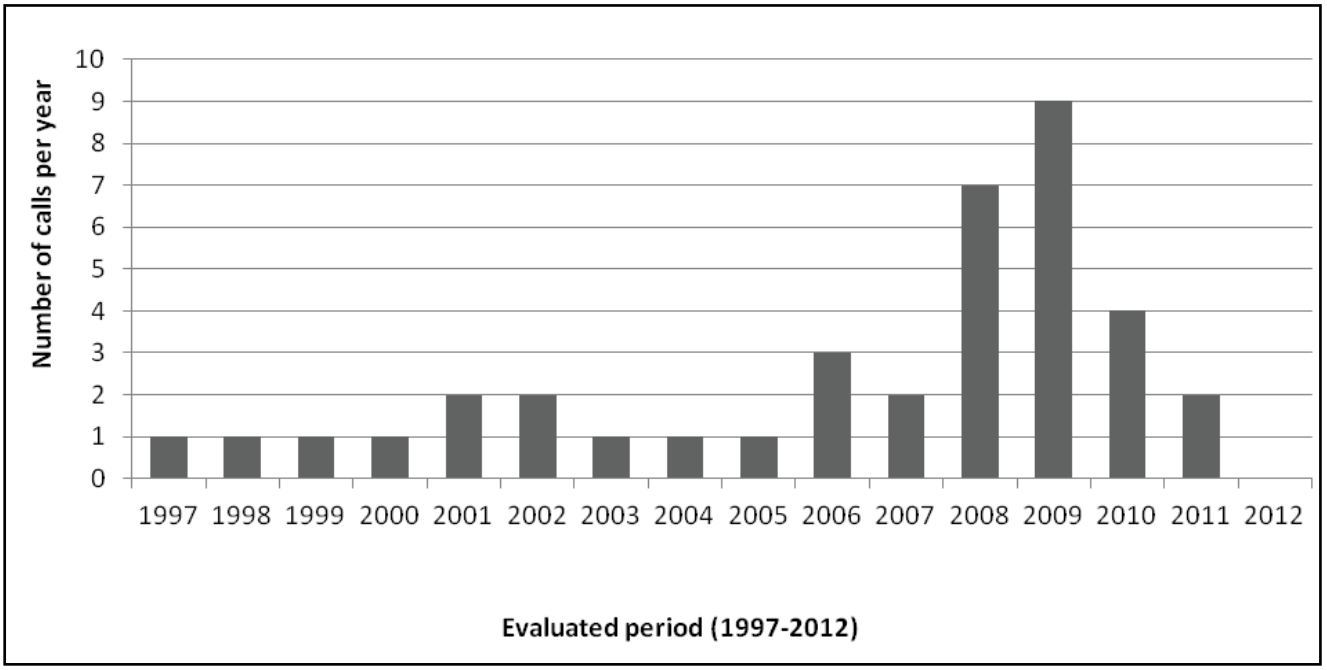

Fig. 1. Diagram demonstrates calls for appetite suppressants in particular years. Number of exposures increases up to year 2009. Later number of exposed pregnancies decreased to no cases in 2012. Last and this year (2011 and 2012) we obtained also calls on food supplements used as anti-obesity treatment (they are not included in diagram).

forth pregnancy. Elective abortions were in 36 and 35 years old women. One of those fetuses was diagnosed with Down syndrome. Exposure during the first trimester was not associated with reduction of newborns weight, length of pregnancy and frequency of negative pregnancy outcomes (Table 2).

DISCUSSION

The appetite suppressant are drugs used in the treatment of obesity, in association with a strict diet and exercise. However, the avoidance of strict diets and appetite suppressants is suggested during pregnancy.

Sibutramine is appetite suppressant, which inhibits the re-uptake of noradrenaline (nor-epinephrine), serotonin and dopamine. It was originally developed as an antidepressant in the 1980s, but was found to induce marked weight loss, affecting both food intake and energy expenditure. It also enhances the physiological process of satiety and stimulates thermogenesis. It was marketed in the US as a weight loss medication in 1997 (Einarson *et al.* 2004). Teratology testing on laboratory animals demonstrated negative pregnancy outcomes (abortion, malformation) only in doses toxic for mother (Francia-Farje *et al.* 2010, Reprorisk 2012). There were only few reports about exposure to sibutramine during pregnancy, but they did not reveal higher risk of malformations. Moreover, weight of newborns was in normal range (De Santis *et al.* 2006; Garcia-Bournissen *et al.* 2007;Kadioglu *et al.* 2004; McElhatton & Stephen 2006; Ramzi *et al.* 2005). Drug was withdrawn from the market in 2010 because of clinical data suggesting it may increase the risk of heart attack and stroke (Reprorisk 2012).

Phentermine is a sympathomimetic amine used as an appetite suppressant. Drug is related to amphetamines. Until 1997, this drug was also sold in combination with dexfenfluramine. A combination of phentermine and topiramate is being evaluated for the treatment of obesity. Testing on laboratory animal did not reveal higher risk of adverse effect (Thoma-Laurie *et al.* 1982; Bratter *et al.* 1999). In data from the California Teratology Information Service, no significant increase in the frequency of major congenital anomalies was found in 84 infants of women who used the combination phentermine/fenfluramine during the first trimester of pregnancy (Jones *et al.* 2002).

Our study is in agreement with other previous studies. Drugs were withdrawn not for their teratogenicity, but for cardiovascular complication (sibutramine) or potency to induce addiction (phentermine). In present time, there is no registered appetite suppressant on the market in the Czech Republic except for orlistat which is registered for the hyperlipidemia treatment anyway.

The recent exposure to the appetite suppressant was not to the above mentioned drugs but to the food supplements, that could be used as an alternative to the drugs. The potential risk results from the limited or completely absent control of the origin. However, the risk for the population may be probably higher, because women who want to control their weight are searching for the help on internet drug-stores or they use food supplements, that could be used as an alternative. They may be the fakes without any effective substance

but they may contain dangerous components as heavy metals etc. Some of the food supplements have probably only placebo effect, but they could represent the potential risk as *XLS Medical Fatbinder* containing Litramine, a patented fibre complex that is clinically proven to bind fat (as fibrates which are contraindicated during pregnancy) and vitamins: Vitamin A – acetate (retinol), vitamin D3 (cholecalciferol) and vitamin E – acetate (alpha-tocopherol) with unknown (not declared) dose of retinol. Compare to drugs, the food supplement production is not controlled properly. They may contain heavy metals (lead, mercury, cadmium) and pollutants. Content of effective substances is not controlled as in the case of the drugs and it is not declared. They can be without any effect (only placebo) or they may be dangerous, because tests demonstrating efficacy and safety are not needed. In fact, we changed the drug with known risk for food supplement or the fake with unknown threat.

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Potential Conflicts of Interest: *None disclosed.*

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