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Pregnancy outcome, thyroid dysfunction and fetal goitre after *in utero* exposure to propylthiouracil: a controlled cohort study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Human pregnancy experience with propylthiouracil has not shown an increased risk of major anomalies, but its use in pregnancy has been associated with fetal or neonatal thyroid dysfunction with or without goitre.
- The rate of these complications has not been prospectively evaluated.

WHAT THIS PAPER ADDS

- Based on prospective data from the Israeli Teratology Information Service, propylthiouracil was not associated with an increased teratogenic risk.
- Hypothyroidism was found in 9.5% (56.8% of whom with goitre) of fetuses or neonates, whereas hyperthyroidism was detected in 10.3%.
- In most cases neonatal thyroid functions normalized without treatment.

AIMS

Propylthiouracil (PTU) is presently considered to be the treatment of choice for hyperthyroidism in pregnancy. It is known to cross the human placenta, and therefore may affect the fetus. The major aims of this study were to evaluate the rate of major anomalies and to report the rate of fetal goitre, accompanied by hypothyroidism, in fetuses/newborns of mothers after *in utero* exposure to PTU.

METHODS

Prospective observational controlled cohort study of PTU-exposed pregnancies of women counselled by the Israeli Teratology Information Service between the years 1994 and 2004 compared with women exposed to nonteratogens.

RESULTS

We followed up 115 PTU-exposed pregnancies and 1141 controls. The rate of major anomalies was comparable between the groups [PTU 1/80 (1.3%), control 34/1066 (3.2%), $P = 0.507$]. Hypothyroidism was found in 9.5% of fetuses/neonates (56.8% of whom with goitre). Hyperthyroidism, possibly resulting from maternal disease, was found in 10.3%. Goitres prenatally diagnosed by ultrasound were successfully treated *in utero* by maternal dose adjustment. In most cases neonatal thyroid functions normalized during the first month of life without any treatment. Median neonatal birth weight was lower [PTU 3145 g (2655–3537) *vs.* control 3300 g (2968–3600), $P = 0.018$].

CONCLUSIONS

PTU does not seem to be a major human teratogen. However, it could cause fetal/neonatal hypothyroidism with or without goitre. Fetal thyroid size monitoring and neonatal thyroid function tests are important for appropriate prevention and treatment.

Introduction

Thyrotoxicosis occurs in approximately 0.2% of pregnancies and is caused most frequently by Graves' disease [1]. Graves' disease is an autoimmune disorder characterized by the production of autoantibodies of the IgG class, which binds to the thyroid stimulating hormone receptors, resulting in excess production of thyroid hormone [2]. Graves' disease is common in young women of childbearing age [2]. Poorly controlled disease during pregnancy can cause serious complications for both the mother (i.e. hypertension, heart failure and thyroid storm) and the fetus (fetal wastage, intrauterine growth restriction, low birth weight, preterm delivery, heart failure, hyperthyroidism, and thyroid dysfunction with or without goitre) [1, 3–5]. Antithyroid drugs are the treatment of choice for thyrotoxicosis in pregnancy. Propylthiouracil (PTU) and methimazole (MMI) have similar kinetics of transplacental transfer [6]. However, the use of PTU is preferred over the use of MMI during pregnancy, as the latter was associated with congenital cutis aplasia and with MMI embryopathy that includes choanal and oesophageal atresia as well at other anomalies [1, 7–10]. PTU can induce fetal goitre and lower neonatal birth weight in animal studies but did not have a classic teratogenic effect in animals [7]. In human studies, the prevalence of congenital anomalies after *in utero* exposure to PTU is well within the expected rate of anomalies [11, 12]. However, only few studies have been published and their sample size was relatively small ($n < 50$) [12–20]. Moreover, no recent studies have been published. PTU can suppress the fetal thyroid function after the 11th postconceptional week of pregnancy, when colloid begins to appear in the thyroid follicles and thyroxin can be demonstrated [21]. The effect is more prominent in the second half of pregnancy, due to increase in fetal thyroid hormone production [22]. Fetal thyroid suppression can occur in neonates whose mothers have been treated with PTU during pregnancy. Clinically, the hypothyroid state may be observed as goitre. Goitres from PTU exposure are usually small. However, large goitres that can cause respiratory compromise in the newborn have also been described [23, 24]. No prospective studies have been published to date to assess the exact rate of fetal or neonatal goitre accompanied by hypothyroidism after *in utero* exposure to PTU.

The objectives of the present study were to evaluate prospectively whether *in utero* exposure to PTU increases the rate of major anomalies above the rate in a control group of pregnant women, who consulted with the Israeli Teratology Information Service (TIS) about nonteratogenic exposure, and to assess the rate of fetal or neonatal goitre accompanied by abnormal thyroid functions in the neonate. Additional objectives were to compare pregnancy outcome, birth weight and gestational age at delivery between the two groups.

Methods

The study was conducted at the Israeli TIS. All women who contacted (directly or through their healthcare providers) the service between the years 1994 and 2004 for information about gestational exposure to PTU were prospectively enrolled in the study. Details of exposure were collected during pregnancy using a structured questionnaire. Standardized data collection forms were used to record the following information by telephone: maternal demographics, medical and obstetrical histories, exposure details (dose, duration and timing of pregnancy), and concurrent exposures. Verbal consent to participate in the study was given by the woman at initial contact. Since the study was observational it was exempt from Institutional Review Board approval. After the expected date of delivery, follow-up was conducted by a telephone interview with the woman, using a structured questionnaire to obtain details on the pregnancy outcome, gestational age at delivery, birth weight, major or minor birth defects and fetal or neonatal thyroid status. When the mother reported an anomaly, she was asked to send medical documents verifying the diagnosis. A certified paediatrician contacted the mother again for further details. Alternatively, an attempt was made to contact the child's physician for verification. Our offspring follow-up in the index and control groups was preformed between the neonatal period and 6 years of age. However, in 65% of the PTU cases, it was carried out within the first 2 years of life. The control women consulted with the TIS regarding exposures not known to be teratogenic, such as: antibiotics (e.g. penicillins, cephalosporins, erythromycin), paracetamol, topical preparations not containing retinoids, oral contraceptives, taken before pregnancy and no later than the first 4–5 weeks of gestation, hair dye and house-cleaning agents, low-dose diagnostic irradiation, vitamin supplementation, analgesics, antacids and thyroxin replacement.

The Israeli TIS had 234 calls regarding PTU exposure during pregnancy, 18 of which were repeated calls regarding the same pregnancy. Follow-up was obtained on 115 women (115/216 = 53.3%) who were exposed to PTU during pregnancy and gave birth to 106 neonates. Of these, 101 could not be reached due to change of address or telephone disconnection. In addition, follow-up was obtained on 1141 control women who gave birth to 1057 neonates. Part of the present control group has been used previously [25].

The primary outcome of interest was the rate of major anomalies (those having a structural abnormality that has serious medical, surgical or cosmetic consequences) [26] in women who were exposed to PTU during pregnancy. The analysis of major anomalies was performed on women who were exposed to PTU between weeks 4 and 13 to exclude those exposed only during the 'all or none' period or those exposed beyond the period of organogenesis. In the case of multiple births, each live-born was included in

the analysis. Children with minor anomalies or functional problems without any morphological changes (e.g. systolic heart murmur with normal echocardiography, slight developmental delay) or complications of preterm delivery were not considered as having major anomalies. However, abnormalities detected by prenatal ultrasonography (if verified postnatally or by autopsy) are included in our study, since antenatal screening for major anomalies is routinely preformed in Israel. The analysis of major congenital anomalies was performed out of live-born infants and elective terminations of pregnancy due to prenatally diagnosed anomalies. Exclusion of the latter cases would cause underreporting of anomalies. Another major outcome of interest was to assess the rate of fetal and neonatal thyroid dysfunction with or without goitre. In this group we included only women who were exposed to PTU beyond the 13th gestational week after the last menstrual period, since the fetal thyroid begins to function only then. Gestational age in the present study applies to weeks post last menstrual period. Secondary end-points were pregnancy outcome (i.e. live birth, miscarriage, pregnancy termination, stillbirth and ectopic pregnancy), the rate of preterm delivery (<37 weeks gestational age), gestational age at delivery and birth weight.

Statistical analysis

The statistical calculations were done using SPSS (SPSS Inc., Chicago, IL, USA) or Epi Info 2000 software (for relative risk and power calculations). Dichotomous data were compared by χ^2 or Fisher's exact tests, when appropriate, and were expressed as ratios or percentage. Continuous data that were not normally distributed were compared using Mann–Whitney signed test, and were expressed as median with interquartile range (IQR). Linear and logistic regressions were performed post hoc to analyse the relative contribution of various nondependent predictors to differences in dependent variables. Linear regression analysis was used to evaluate the relative contribution of various predictors to the difference in gestational age at delivery and birth weight. A positive β coefficient indicates a positive relationship, whereas a negative β coefficient implies a negative relationship. Logistic regression analysis was used to evaluate the relative contribution of various predictors to the development of fetal/neonatal hyperthyroidism.

Results

We prospectively collected information on 115 women exposed to PTU during pregnancy, and followed up their pregnancy outcome after their expected date of delivery. More than half of the women (55.6%) had started treatment with PTU prior to their pregnancy, whereas in 44.4% the disease was diagnosed during pregnancy, mostly in the first trimester. In 9.6% of the women who had been treated with MMI prior to pregnancy, the treatment was replaced with PTU during the first trimester. In the majority of women in our cohort, exposure to PTU began in the first trimester (85.4%) of pregnancy, whereas 12.6% began the treatment with PTU during the second trimester and 1.9% were exposed to PTU only during the third trimester. In all the women in our cohort the indication for the treatment with PTU was hyperthyroidism. However, only few women knew the precise aetiology of their disease, which in most cases was Graves' disease.

The median daily dose of PTU was 150 mg (IQR = 100–200 mg) for a median duration of exposure of 231 days (IQR = 147–273 days). In half of the women the dose of PTU was constant throughout pregnancy, while in 5.9% of the women the dose was increased during pregnancy and in 44.1% it was decreased during pregnancy. The median gestational age at initial call was 10 weeks in the PTU group (IQR = 7–15) and 10 weeks in the control group (IQR = 7–17) ($P = 0.507$).

Table 1

Maternal characteristics (age and obstetrical history)

	PTU	Control	*P*-value
Median age, years (IQR)	31 (28–35)	30 (27–33)	0.029
Pregnancy order	*n* = 109	*n* = 1100	0.662
PO1 (%)	27 (24.8)	255 (23.2)	
PO 2–4 (%)	62 (56.9)	672 (61.1)	
≥PO 5 (%)	20 (18.3)	173 (15.7)	
Parity	*n* = 111	*n* = 1099	0.949
P0 (%)	33 (29.7)	315 (28.7)	
P1 (%)	69 (62.2)	700 (63.7)	
≥P2 (%)	9 (8.1)	84 (7.6)	
Miscarriages	*n* = 111	*n* = 1091	0.025
None (%)	78 (70.9)	873 (80.0)	
One or more (%)	32 (29.1)	218 (20.0)	
ETOP	*n* = 110	*n* = 1091	0.656
None (%)	97 (88.2)	977 (89.6)	
One or more (%)	13 (11.8)	114 (10.4)	
Stillbirths	*n* = 109	*n* = 1090	1.000
None (%)	108 (99.1)	1077 (98.8)	
One or more (%)	1 (0.9)	13 (1.2)	

ETOP, elective termination of pregnancy; IQR, interquartile range; PO, pregnancy order; PTU, propylthiouracil.

Maternal characteristics

A comparison of maternal characteristics between the PTU and control groups is presented in Table 1. The women in the PTU group were significantly older (31 years, IQR = 28–35) compared with those in the control group (30 years, IQR = 27–33) ($P = 0.029$), and there was a higher proportion of past miscarriages in the PTU group (29.1%) compared with the control group (20.0%) ($P = 0.025$). No significant differences were detected between the PTU and control groups in pregnancy order, parity or history of therapeutic abortions or stillbirth.

Pregnancy outcome

A comparison of pregnancy outcome between the PTU and control groups is presented in Table 2. There was no

Table 2
Pregnancy outcome

	PTU	Control	p value
Pregnancy outcome	*n* = 115	*n* = 1141	
Deliveries (%)	102 (88.7)	1030 (90.3)	0.589
Miscarriages (%)	9 (7.8)	72 (6.3)	0.528
ETOP (%)	4 (3.5)	35 (3.1)	0.776
Stillbirth (%)	0	3 (0.3)	1.000
Ectopic pregnancies (%)	0	1 (0.1)	1.000
Number of live-born infants	*n* = 106 (2 sets of twins, 1 set of triplets)	*n* = 1057 (23 sets of twins, 2 sets of triplets)	
Major birth defects (%)	1 (1.3) *n* = 80+	34 (3.2) *n* = 1066+	0.507
Median gestational age (IQR)	40 (38–40) *n* = 100	40 (39–41) *n* = 1018	0.018
Preterm delivery (<37 weeks) (%)	10 (10.0) *n* = 100	58 (5.7) *n* = 1018	0.086
Median birth weight (g) (IQR)	3145 (2655–3537) *n* = 104	3300 (2968–3600) *n* = 1038	0.018

ETOP, elective termination of pregnancy; IQR, interquartile range; PTU, propylthiouracil. +–including multiple gestations.

increase in the rate of major anomalies among live births and elective terminations of pregnancy due to prenatally diagnosed anomalies between the PTU and control women, whose exposure was during the organogenetic period (4–13 weeks) [1/80 (1.8%) *vs.* 34/1066 (3.2%), respectively; relative risk 0.39 with 95% confidence interval (CI) 0.05, 2.83]. There was only one infant (first born girl) born to a woman treated with 225–300 mg day^{-1} of PTU throughout pregnancy who had developmental dysplasia of the hip and was treated with braces. In both groups, cases with umbilical hernia without surgical intervention and cases with suspected hydronephrosis detected by prenatal sonography followed by a normal postnatal kidney ultrasound were not considered major anomalies. No significant differences were detected between the PTU and control groups in pregnancy outcome (i.e. number of live births, miscarriages, elective terminations of pregnancy, stillbirths and ectopic pregnancies) or in the rate of preterm deliveries.

The IQR of gestational age at delivery was significantly lower in the PTU group (38–40) compared with the control group (39–41) ($P = 0.018$). The median birth weight was 150 g lower in the PTU group (3145 g, IQR = 2655–3537) compared with the control group (3300 g, IQR = 2968–3600) ($P = 0.018$). In order to evaluate the relative contribution of various predictors to the difference in the gestational age at delivery and neonatal birth weight, linear regression analysis was performed. The following predictors were entered into the model of gestational age at delivery: cigarette smoking (<10 cigarettes day^{-1} and ≥10 cigarettes day^{-1} relative to nonsmokers), maternal age, PTU dose at initial contact, pregnancy order and multiple pregnancies. The model explained 16.1% of the variance. The only significant predictors were multiple pregnancies ($\beta = -3.793$, 95% CI −4.335, −3.250, $P < 0.001$) and PTU dose at initial contact ($\beta = -3.718$, 95% CI −0.005, −0.001, $P = 0.004$). The previous predictors in addition to the gender of the newborn, concomitant use of β-blockers and gestational age at delivery were entered into the model of neonatal birth weight. The model explained 39.7% of the variance. The significant predictors were gestational age at delivery ($\beta = 136.649$, 95% CI 123.622, 149.676, $P < 0.001$), multiple pregnancies ($\beta = -404.014$, 95% CI −532.079, −275.949, $P < 0.001$), gender ($\beta = -129.153$, 95% CI −181.083, −77.222, $P < 0.001$, i.e. women associated with a lower birth weight), pregnancy order ($\beta = 17.374$, 95% CI 0.900, 33.848, $P = 0.039$), smoking ≥10 cigarettes day^{-1} ($\beta = -133.654$, 95% CI −264.220, −3.088, $P = 0.045$) (smoking <10 cigarettes day^{-1} did not significantly contribute to the variance in birth weight) and maternal age ($\beta = 6.478$, 95% CI 0.107, 12.849, $P = 0.046$).

Fetal/neonatal thyroid status

Data on neonatal thyroid function were available on 87 infants. Data on ultrasound directed to fetal thyroid were available on 89 fetuses. Ultrasound directed to the fetal thyroid gland was performed in 51/89 (57.3%) and found positive in 5/51 (9.8%). In 16 cases a disturbance in the fetal/neonatal thyroid status was detected. Hypothyroidism was detected in 7/74 (9.5%) pregnancies exposed after week 13 to PTU, which resulted in delivery of a live-born infant. Hyperthyroidism was detected in 9/87 (10.3%) pregnancies with data on neonatal thyroid function. Two neonates who had fetal hypothyroidism accompanied by goitre eventually developed neonatal hyperthyroidism after treatment. The exact details of the cases are presented in Table 3.

Fetal/neonatal hypothyroidism All women whose fetus/infant developed hypothyroidism used PTU throughout

Table 3

Details of antithyroid drug exposure, pregnancy and neonatal management in cases with thyroid dysfunction with or without goitre

Antithyroid drug dose	Duration of exposure	Prenatal diagnosis and treatment	Birth weight and gender	Postnatal diagnosis and treatment
Hypothyroidism without goitre				
MMI until week 7, then 300 mg day^{-1} of PTU	Throughout pregnancy	Normal US	4400 g male (GD)	Neonatal hypothyroidism on screening tests, received L-thyroxine until 3–4 months, since then – normal thyroid functions
300 mg day^{-1} of PTU	Throughout pregnancy	Not performed	3700 g female	Neonatal hypothyroidism on screening tests, spontaneously resolved after 1 month
N/A	Until week 32	Normal US, hypothyroidism diagnosed on cordocentesis week 32, on repeated cordocentesis a month before delivery – normal thyroid functions	2750 g male	Normal thyroid functions without goitre after delivery
Hypothyroidism accompanied by goitre				
200 mg day^{-1} of PTU, then decreased to 50 mg day^{-1} on week 30	Throughout pregnancy	Goitre detected on US since week 20, hypothyroidism detected on cordocentesis week 34	3500 g male	Neonatal hyperthyroidism accompanied by goitre detected at delivery, received PTU for 1 month after which thyroid status was normal
150 mg day^{-1} of PTU gradually increased towards week 28	Throughout pregnancy	Not performed	2800 g female	Neonatal hypothyroidism accompanied by goitre was detected at delivery, received L-thyroxine for a few months, the goitre resolved after a few days and thyroid status returned to normal after $^{1}/_{2}$ year
150 mg day^{-1} of PTU	Between weeks 13 and 22	Goitre was detected on US on week 22 (thyroid gland on 95 percentile), on repeated US on week 31 the goitre decreased dramatically (thyroid gland was on 55 percentile)	4000 g female	Normal thyroid functions without goitre after delivery
200 mg day^{-1} of PTU gradually decreased to 100 mg day^{-1} during pregnancy	Between weeks 7 and 30	Goitre was detected on US, responded to PTU dose decrease, completely resolved by week 30 after discontinuation of PTU	4365 g female	Neonatal hyperthyroidism detected at delivery, spontaneously resolved after 2 months
Hyperthyroidism without goitre				
MMI until week 4, then 25 mg day^{-1} of PTU	Throughout pregnancy	Not performed	3600 g male	Neonatal hyperthyroidism on screening tests, spontaneously resolved
150 mg day^{-1} of PTU gradually decreased to 50 mg day^{-1}	Till 2 weeks before delivery	Normal US	3250 g female	Neonatal hyperthyroidism on screening tests, spontaneously resolved after 10 days
300 mg day^{-1} of PTU which was gradually decreased to 100 mg week^{-1}	Between weeks 2 and 24	Not performed	2625 g female	Neonatal hyperthyroidism on screening tests and 2 weeks later, spontaneously resolved after 2.5 months
100 mg day^{-1} of PTU	Throughout pregnancy	Normal US	3300 g male	Neonatal hyperthyroidism on screening tests, spontaneously resolved
200 mg day^{-1} of PTU which was gradually decreased to 150 mg day^{-1}	From week 8 till the end of pregnancy	Normal US	2910 g female	Neonatal hyperthyroidism until 3 months, spontaneously resolved
50 mg day^{-1} of PTU	Throughout pregnancy	Normal US; SVT on fetal echocardiography – from 29 weeks, the mother was treated with digoxin and sotalol	3100 g male	Neonatal hyperthyroidism on the first week after delivery, spontaneously resolved, after a week he developed SVT with normal thyroid functions, and was treated with flecainide until 7 months
200 mg day^{-1} of PTU	Throughout pregnancy	Normal US	3110 g female	Lost 35% of her weight during the first 11 days after delivery, was hospitalized and diagnosed with hyperthyroidism, received MMI until 4 months, since then – normal thyroid functions
Hyperthyroidism accompanied by goitre				
150 mg day^{-1} of PTU gradually decreased during pregnancy	From week 21 till the end of pregnancy	Goitre detected on US week 21, resolved after the beginning of PTU treatment	4340 g male	Normal thyroid functions without goitre after delivery
100–150 mg day^{-1} of PTU	Throughout pregnancy	Goitre detected on US since week 24 until delivery	2715 g male	Hyperthyroidism accompanied by goitre was detected at delivery, spontaneously resolved after 1 month

GD, gestational diabetes; MMI, methimazole; N/A, not available; PTU, propylthiouracil; SVT, supraventricular tachycardia; US, ultrasound directed to fetal thyroid.

pregnancy or until goitre was detected (see Table 3). The range of the PTU dose was 150–300 mg day^{-1}. None of the women took low doses. The dose was constant throughout pregnancy except for the cases in which goitre was detected, and thus the dose was decreased. Only in one case was the dose increased due to development of tachycardia in both the mother and fetus.

In order to evaluate the relative contribution of various predictors on the development of fetal/neonatal hypothyroidism, logistic regression analysis was performed. Duration of exposure (as a marker of the severity of the disease) and dose of PTU were entered into the model. No significant correlation was found between the above predictors and the development of fetal/neonatal hypothyroidism.

In 42.8% (3/7) of the neonates who developed hypothyroidism the neonatal weight was $\geq$4000 g. Hypothyroidism without goitre was detected in 4.1% (3/74) of the neonates. Two of the three were diagnosed on neonatal screening tests after delivery. One of them did not need medical care, and the other neonate was treated with L-thyroxine for 3–4 months. In one case, the hypothyroidism was detected by cordocentesis, which was performed in the 32nd week of pregnancy, and fetal thyroid status returned to normal 1 month prior to delivery, after the mother stopped using PTU. In 5.4% (4/74) of the neonates the hypothyroidism was clinically observed as goitre. In 3/4 the goitre was diagnosed on prenatal ultrasound directed to the fetal thyroid, and resolved after the mother stopped using PTU. In one case prenatal ultrasound directed to fetal thyroid was not performed and the goitre and abnormal thyroid function were detected only after delivery. The neonate was treated with L-thyroxine for half a year. In two of the four neonates, whose goitre resolved after the mother stopped using PTU, hyperthyroidism was diagnosed on screening tests after delivery. One of them did not need medical care, and the other was treated with PTU. In both cases fetal thyroid status returned to normal after 2 months.

Fetal/neonatal hyperthyroidism: The range of the PTU dose in the women whose fetus/infant developed hyperthyroidism was 25–200 mg day^{-1} (see Table 3). In half of the women there was no change in the dose throughout pregnancy and in the other half the dose was decreased. Two women were diagnosed with hyperthyroidism during pregnancy on weeks 8 and 21 and were treated until delivery, and one woman used PTU between 2 and 22 weeks of pregnancy.

In order to evaluate the relative contribution of various predictors on the development of fetal/neonatal hyperthyroidism, multiple linear regression analysis was performed. First week of exposure (as a marker of late diagnosis of the mothers' disease), duration of exposure and dose of PTU (as markers of the severity of the disease) were entered into the model. The model was not significant. Thus, no correlation was found between the above predictors and the development of fetal/neonatal hyperthyroidism.

Nine fetuses or neonates had hyperthyroidism, seven without and two with goitre. In 8% (7/87) of the neonates, hyperthyroidism was detected without goitre. As shown in Table 3, in the majority of these neonates the hyperthyroidism was asymptomatic, and 6/7 did not require antithyroid medications. In one case the hyperthyroidism was symptomatic and the neonate was treated with MMI for 4 months. In 2.3% (2/87) of the neonates the hyperthyroidism was clinically observed as goitre on prenatal ultrasound directed to the fetal thyroid gland. In one case the goitre resolved after the beginning of PTU treatment during pregnancy, and in the second case the neonate was born with a goitre despite increasing the dose of PTU during pregnancy, and resolved spontaneously after 1 month. One girl who was diagnosed with hyperthyroidism was excluded, since the disease appeared when she was 4 years old, after a normal pregnancy, delivery and infancy. The child was born to a mother who was exposed to PTU in an increasing dose throughout pregnancy. Both prenatal ultrasound directed to the fetal thyroid and neonatal thyroid functions were normal. At 4 years of age the girl dramatically lost weight (from the 90th to the 50th percentile), goitre was detected on physical examination, and hyperthyroidism with thyroid-stimulating immunoglobulins (TSI) was detected on laboratory tests. The girl received medical treatment and was under observation for a year, after which she started to gain weight (75%ile) and her thyroid functions were normal.

Discussion

The present study, which is the largest prospective controlled cohort on PTU exposure during pregnancy, followed up 115 pregnancies to examine the rate of major anomalies. Both the PTU-exposed group and their controls had anomaly rates within the expected baseline risk for the general population. The incidence of major anomalies recognized at birth among live-born infants is 1–3% [17]. The incidence is as high as 5% if one includes anomalies detected later in childhood, including mental retardation [27]. It is also consistent with most previous reports not associating PTU exposure during pregnancy with a teratogenic risk in humans [10–18]. This study has confirmed that PTU does not represent a major teratogenic risk when used in clinically recommended doses in humans.

The follow-up rate in the PTU group was 53.3%. However, it is important to note that the losses to follow-up were due to technical reasons, e.g. telephone disconnection, recording wrong number at initial call, or change of address, and not due to refusal to participate in the follow-up interview; in fact, all women who were reached agreed to be interviewed for this study. We therefore believe that it does not introduce a significant selection bias.

A sample size of 80 live births in the PTU group exposed in the first trimester of pregnancy with a ratio of 1 : 13 to the control group, power of 80%, assuming a baseline risk of 3% for major anomalies, enables detection of a 3.6-fold increase in the overall rate of major anomalies (with 95% CI).

The rate of miscarriages in our study is lower than the rate of 10–12% described in the literature [28, 29]. This could be a result of the relatively late time in pregnancy at which women initially contacted the TIS, as most spontaneous abortions occur during the first 3 months of pregnancy. In the present study, the median gestational age at call was 10 weeks in both groups. Low miscarriage rate is often reported in other TIS studies.

The IQR of gestational age at delivery was lower in the PTU group compared with the control group, although no significant difference was found between the two groups in the rate of preterm deliveries. The high rate of multiple pregnancies in the PTU group and relatively high dose of PTU at initial contact could explain approximately 16.1% of the difference. However, we lacked data on three important risk factors for preterm delivery – history of preterm delivery, premature rupture of membranes and maternal control of hyperthyroidism – which could probably explain the rest.

The median neonatal birth weight was 150 g lower in the PTU group compared with the control group. The early gestational age at delivery, the high rate of multiple pregnancies, female gender of the newborn, low pregnancy order, smoking (≥10 cigarettes) and younger maternal age could explain approximately 39.7% of the difference. However, we lacked data on maternal thyroid status during the third trimester, in which the fetus gains most of its weight. Poorly controlled disease during this period was shown to increase the rate of lower neonatal birth weight by four- to ninefold [1].

In two neonates, who were diagnosed with hyperthyroidism on screening tests, thyroid status returned to normal after 7–10 days rather than after 2–3 months, after which the maternal TSI disappear from neonatal blood. This could be a result of neonatal thyroid-stimulating hormone surge followed by a rise in T3/T4 levels, which normally occur during the first 3 days after delivery. Measuring thyroid hormones too early will detect neonatal physiological hyperthyroidism, which has no connection to maternal hyperthyroidism [30]. One girl, who was diagnosed with hyperthyroidism when she was 4 years old, was excluded since the aetiology for her hyperthyroidism was probably Graves' disease, not related to the maternal hyperthyroidism during pregnancy. Graves' disease is a very rare condition in childhood that appears mainly in females, and its presenting symptoms are diarrhoea and weight loss, as in our case. In 25% complete remission occurs after a few months of medical treatment [27].

No correlation was found in our study between neonatal hyperthyroidism and first week of exposure (as a marker of late diagnosis of the mothers' disease), duration of exposure (as a marker of the severity of the disease) or dose of PTU. This is not surprising since, as described in the literature, the most accurate predictor of neonatal hyperthyroidism is TSI level >500% during the second trimester of pregnancy [31]. There is wide variability between patients in the severity of hyperthyroidism and in their response to PTU. Therefore, the dose of PTU is not an optimal predictor for the severity of the disease [32].

The neonatal birth weight was ≥4000 g in 42.8% of the neonates who were diagnosed with hypothyroidism. This finding is consistent with the literature, which describes high birth weight as one of the presenting characters of neonatal hypothyroidism. However, the exact mechanism is unknown [27]. In our study 5.4% of neonates developed goitre accompanied by hypothyroidism; this differs from 12% goitres with hypothyroidism, which was described by Briggs [11] from the reported cases in the literature. Reporting and publication biases can explain the discrepancy. All the cases in which the goitre was detected by prenatal ultrasound were successfully treated *in utero* by dose modification, and the neonates suffered from neither goitre nor hypothyroidism. This emphasizes the significance of performing prenatal ultrasound directed to fetal thyroid in pregnancies at risk. Half of the neonates who were diagnosed with goitre accompanied by hypothyroidism and were successfully treated *in utero* developed hyperthyroidism after delivery. This probably results from the dominant effect of maternal TSI on the neonatal thyroid gland after the gradual decrease in the dose of PTU during pregnancy [30]. Our study found no correlation between the dose of PTU and the duration of exposure, and the risk of developing hypothyroidism. According to the literature, it is difficult to predict the risk of neonatal hypothyroidism. Many studies have found correlation between maternal and fetal thyroid status. Therefore, one should use the minimal dose of PTU in order to keep the FT4 in the upper third of normal values for the prevention of neonatal hypothyroidism [1].

The main conclusion of our study, which is in line with previous publications, is that PTU exposure does not seem to increase the rate of major anomalies when given in clinically used dosage. In addition, PTU exposure beyond the 13th week after the last menstrual period caused hypothyroidism in 9.5% of fetuses/neonates and hyperthyroidism in 10.3%. In less than half of the cases it was accompanied by goitre. Fetal goitre by itself is not necessarily a sign of hypothyroidism, and whenever fetal goitre is observed it may be advisable also to evaluate fetal thyroid function. We should remember, however, that in most cases neonatal thyroid functions returned to normal even without treatment. As PTU is known to pass through the placenta [6], it may have direct effects on the fetus; alternatively, the effects on the fetus may be attributable to the maternal antibodies or thyroid status.

This is the first prospective study to evaluate the rate of neonatal goitre in pregnant women treated with PTU. Our study also emphasizes the significance of performing prenatal ultrasound directed to the fetal thyroid gland. The latter enables prenatal diagnosis and treatment by dose modification in order to prevent the development of neonatal goitre [33, 34].

Competing interests

None declared.

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