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Article

Hyperthyroidism in Pregnancy: the Delicate Balance between too Much or too Little Antithyroid Drug

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Abstract: Overt hyperthyroidism during pregnancy is associated with risk of maternal-fetal complications. The antithyroid drugs (ATD) have a potential risk for teratogenic effects and fetal–neonatal hypothyroidism. This study evaluated ATD treatment and thyroid function control during pregnancy, and pregnancy outcome in women with hyperthyroidism. ***Patients and methods:*** retrospective analysis of 36 single fetus pregnancies in 29 consecutive women (median age 30.3 ± 4.7 years) with hyperthyroidism diagnosed before or during pregnancy; a control group of 39 healthy euthyroid pregnant women was used. ***Results:*** 26 women had Graves' disease (GD, 33 pregnancies), 1 had a hyperfunctioning autonomous nodule, 2 had gestational transient thyrotoxicosis (GTT). Methimazole (MMI) was administered in 22 pregnancies (78.5%), Propylthiouracil (PTU) in 2 (7.1%), switch from MMI to PTU in 4 (14.2%), no treatment in 8 pregnancies (3 with subclinical hyperthyroidism, 5 euthyroid with previous GD remission before conception). One spontaneous abortion at 5 weeks (3.4% of pregnancies) and 1 premature delivery at 32 weeks with perinatal death in 24h (3.4%) were recorded in 2 of the 8 pregnancies of GD patients diagnosed shortly before (< 6 weeks) or during gestation. In women treated more than 6 months until conception (20 pregnancies): a) median ATD doses were lower than those in women diagnosed shortly before or during pregnancy; b) ATD was withdrawn in 40% of pregnancies in trimester (T) I, all on MMI < 10 mg/day (relapse in 14.2%), and in up to 55% in TIII; c) TSH level was below normal in 37%, 35% and 22% of pregnancies in T I, II and III respectively; FT4 was increased in 5.8% (T I) and subnormal in 11.75% in TII and III; d) one fetal death due to a true umbilical cord knot was recorded. Hyperthyroidism relapsed postpartum in 83% of GD patients (at median 3 ± 2.6 months). One child had neonatal hyperthyroidism (3.3% of live children in GD women) and a small atrial sept defect (4% of live children in ATD treated women). Mean birth weight did not differ from that of the control group. ***Conclusion.*** In hyperthyroid women with long-term ATD control before conception, drugs could be withdrawn in TI in a third of them, and fetal complications were rare. Frequent serum TSH and FT4 monitoring is needed in order to maintain optimal thyroid function during pregnancy.

Keywords: hyperthyroidism; Graves' disease; pregnancy; antithyroid drug; drug withdrawal; postpartum recurrence; birth defects

1. Introduction

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Hyperthyroidism occurs due to an inappropriately high synthesis and secretion of thyroid hormone by the thyroid gland. In women, hyperthyroidism is related to menstrual cycle disorders (oligomenorrhea, amenorrhea) and infertility [1]. As a result, the diagnosis of hyperthyroidism during pregnancy is relatively uncommon. The prevalence of overt hyperthyroidism in pregnant women ranges from 0.1 to 0.9 %, while subclinical thyrotoxicosis occurs in about 2% [2,3]. Most of these cases are due to Graves' disease (GD) (90 – 95%), or the human chorionic gonadotropin (HCG) mediated hyperthyroidism in the first trimester, named gestational transient thyrotoxicosis (GTT, 1 – 11%) [3,4]. Other causes of thyrotoxicosis (toxic nodular goiters, thyroiditis) are less frequent during pregnancy.

Untreated hyperthyroidism is associated with an increased risk for fetal loss, preterm labor, intrauterine growth restriction, hydrops, congenital malformations in the neonate, and neurobehavioral disorders later in children, as well as maternal complications such as pregnancy-induced hypertension and maternal congestive heart failure [5-6].

The treatment of hyperthyroidism must consider the etiology, the hormonal changes that take place during pregnancy and influence the course of the disease, and the potential teratogenic effect of the antithyroid drugs. While treatment is typically not necessary in GTT, it is recommended in GD for overt hyperthyroidism [7,8]. The treatment of choice consists of antithyroid drugs (ATD): Methimazole (MMI), Carbimazole (CMZ), and Propylthiouracil (PTU), which have similar efficacy [7,8]. ATD has been associated with several side effects, either in the mother (the most severe being liver failure and agranulocytosis [9,10]) or in the fetus (birth defects associated with the use of the drugs in early pregnancy – teratogenesis [10-11] or fetal–neonatal hypothyroidism, ATD being able to cross the placenta and affect the fetal thyroid function [12].

Therefore, the current guidelines recommend the use of the lowest doses of thionamides that control thyroid function, targeting a maternal serum-free thyroxine (FT4) level at or just above the upper reference limit [7,8]. Whenever possible, notably in women treated and controlled for several months before pregnancy, ATD may be withdrawn in the first trimester [7,8]. Maintaining the delicate balance between too much or too little ATD during pregnancy and breastfeeding is further complicated by the evolution of GD, which may present aggravation in the first trimester, remission during late pregnancy, and relapse during the postpartum period [13,14]. Frequent monitoring of serum thyroid-stimulating hormone (TSH) and FT4 is recommended during pregnancy in order to maintain optimal thyroid function [7].

The aim of this study was to evaluate the antithyroid treatment dosage and thyroid function control during and after pregnancy, and pregnancy outcome in a series of women with hyperthyroidism, in a real-life setting.

2. Patients and Methods

Twenty-nine women diagnosed with current or previous hyperthyroidism and pregnancy, evaluated consecutively by the authors between 2000 – 2020 in a tertiary care center of Endocrinology and/or a tertiary care center of Obstetrics and Gynecology, were included in a retrospective analysis. A control group of 39

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pregnant women with normal thyroid function (evaluated before delivery) was compared for the pregnancy outcome.

1.1. *Study design*

Inclusion criteria. The patients were included if they have been diagnosed with hyperthyroidism (current or cured after ATD treatment), had data regarding the ATD use during pregnancy (dosage, timing), at least 2 evaluations for serum TSH and FT4 during pregnancy and data regarding the pregnancy outcome. In these 29 patients with a mean age (± standard deviation) of 30.3 ± 4.7 years (22 – 41) at the diagnosis of pregnancy, 36 singleton pregnancies have been followed-up (5 women had 2 pregnancies and 1 woman 3 pregnancies).

Exclusion criteria. Pregnant women with a history of hyperthyroidism who had no record on serum TSH and FT4 during pregnancy, no data regarding the ATD use during pregnancy (dosage, timing), or did not consent to register the medical data.

A control group of 39 pregnant women with normal thyroid function and 39 single fetus pregnancies, who delivered at term, was randomly recruited from the Filantropia Hospital; mean age was 27 ± 4.1 years (19 – 37); mean serum TSH before delivery was 1.85 ± 0.88 mIU/L (range 0.36 – 3.95 mIU/L), normal range 0.35 – 4.5 mIU/L.

1.2. *Data collection*

1.2.1. *Evaluation of the thyroid function and treatment*

The thyroid function has been evaluated with various commercial assays. Serum TSH was considered low if below 0.1 mIU/L and high if > 2.5 mIU/L in trimester I or > 3.5 mIU/L in trimester II and III; FT4 was compared with the non-pregnant normal values. No local references for pregnancy were available either for TSH, FT4, or total triiodothyronine (T3). Data regarding treatment with ATD, type of treatment, dose, duration, drug switch, drug withdrawal, side effects were retrieved from medical files.

1.2.2. *Evaluation of the pregnancy outcome*

Data regarding pregnancy duration, outcome, complications of mother and fetus, type of delivery, children's sex, weight, APGAR score, birth defects, or other complications in the neonates were collected from the files. The trimesters of pregnancy are abbreviated as T I, T II, T III. The patients have signed an informed consent for the use of their medical data for scientific research, approved by the institutional ethics committee.

1.3. *Statistics*

Normally distributed data are presented as mean ± standard deviation (SD) and compared using t- test. Data with non-normal distribution are presented as median ± standard deviation (range) and compared with ANOVA test. Statistical processing was performed using SPSS 22.0 software package.

3. Results

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3.1. Demographics

The main characteristics of the 29 patients (36 pregnancies) are described in Tables 1 and 2.

Table 1. General characteristics of pregnant women with hyperthyroidism

Patients	N = 29 women and 36 single fetus pregnancies
Age at pregnancy, years, mean ± SD	30.3 ± 4.7 (range 22 – 41)
Etiology of hyperthyroidism	Graves' disease (GD): N = 26 (33 pregnancies) Hyperfunctioning autonomous nodule: N = 1 Transient gestational thyrotoxicosis: N = 2
Graves ophthalmopathy	N = 7 (6 mild, 1 moderate) (7/22 evaluable GD women, 31.8%)
Treatment with antithyroid drugs (ATD) during pregnancy	Treatment: 28 pregnancies Methimazole (M): 22 pregnancies (78.5% of treated women) Propylthiouracil (P): 2 pregnancies (7.1%) Switch from M to P: 4 pregnancies (14.2%) No treatment: 8 pregnancies (2 with GTT, 1 subclinical GD, 5 euthyroid in previous GD remission before conception)
Treatment withdrawal during pregnancy	16 out of 28 treated pregnancies (57.1%), maintained until delivery in 14 out of 28 pregnancies (50%) At pregnancy diagnosis (<6 weeks): n = 8 (resumed in 1 – 14.2%) During 2nd trimester: n = 5 During 3rd trimester: n = 3
Recurrence or aggravation of thyrotoxicosis after delivery	20 out of 24 pregnancies in ATD treated women (83.3%, all with GD); 3 out of 5 women with GD remission and no treatment before & after conception (60%) Median interval ± SD until recurrence/aggravation (range): 3 ± 2.6 months (range 1 – 10 months)

Legend: GTT – gestational transient HCG-mediated thyrotoxicosis; GD – Graves' disease

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Table 2. Synopsis of women with hyperthyroidism, monitored during pregnancy

		Before pregnancy Dose / thyroid status	TRAb (IU/mL)	First trimester 4-9w	First trimester 10-14w	Second trimester 15-19w	Second trimester 20-23w	Second trimester 24-27w	Third trimester 28-31w	Third trimester 32-35w	Third trimester 36-39w	Pregnancy outcome/ delivery	Postpartum H. recurrence/ aggravation (months)
		I. Hyperthyroid women treated with ATD more than 6 months until pregnancy											
1.1.	27y	M 2.5/ 2d	**8.5** ->- <0.3	-	-	-	-	-	-	-	-	girl 3300g, A8	4m
		N		**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	C-section 39w	
1.2.	30y	M 2.5	**5.15**	M 2.5/ 2d	M 2.5	M 2.5	-	-	-	-	-	girl, 3300g, A9	3m
		N		**N**	**SH**	**SH**	**hT**	**N**	**N**	**N**	**N**	C-section 39w	
2*.	36y	M 2.5 /2d	N/A	M 2.5/ 2d	M 2.5/ 2d	M 2.5/ 2d	M 2.5/ 3d	-	-	-	-	girl, 2950g	2m
		N		**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	C-section 37w	
3.	30y	M 2.5	N/A	M 2.5	M 2.5	M 2.5	M 2.5	M 2.5	M 2.5	M 2.5	M 2.5	girl, 2950g, A7	No on M 10
		N		**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	C-section 38w	
4.	37y	M 5	1.66	-	-	-	-	-	-	-	-	boy, 3500g,	4m
		N		**N**		**N**	**N**	**N**	**N**	**N**	**N**	C-section 36w	
5.1.	25y	M 5	N/A	-	-	-	-	-	-	-	-	Intrauterine death&,	7m
		N		**N**		**N**		**N**		**N**		C-section 40 w	
5.2.	26y	M 5	N/A	-	-	-	-	-	-	-	-	girl, 2800g, A9	7-8m
		N		**N**		**N**		**N**		**N**		C-section 38w	
5.3.	29y	M 5	6.72	-	-	-	-	-	-	-	-	boy, 3750g, A10	7m
		N		**N**		**N**		**N**		**N**		C-section 39w	
6.	31y	M 5	1.37	-	-	-	-	-	-	-	-	girl, 3150g, A9/10	N/A
		N		**N**			**N**			**hT**	**N**	Vaginal 39w	
7.2.	31y	M 5	N/A	M 5	M 2.5	-	-	-	-	-	-	boy 3500g, A10	1m
		N			**N**	**N**	**N**			**N**		C-section 39w	
8.1.	27y	M 5	N/A	P 50	P 50	P 37.5	P 25	-	P 12.5	P 12.5	P 12.5/ 2d	boy	3m
		N		**SH**	**N**	**N**	**N**	**N**	**N#**	**N**	**N**	Vaginal at term	
9.	26y	M 10	**2.07**	-	-	-	-	-	-	-	-	girl, 2750g, A10	3m (SH)
		N		**N**						**N**		C-section 39w	
10.	34y	M 10	0.31	-	M 10	M 10	M 10	M 7.5	M 5	M 2.5	M 2.5	girl, 3000g, A10	No on M 5
		N		**N**	**H**	**SH**		**N**	**N**	**N**		Vaginal 28w	
11.	31y	M 10	N/A	M 10	M 10	M 10	M 10	M 10	M 10	M 10	M 10	boy, 3700g, A9-10	**N**/A
		H		**N**				**N**				C- section	
12.	29y	M 10	N/A	M 10	M 10	M 7.5	M 6.25	M 6.25	M 6.25	M 5	M 5	boy, 2250g, A9	No on M 5
		N; "hot" nodule		**N**			**hT/N**	**N**	**hT**	**N**		C-section 40w	
13.	23y	M 10	N/A	P 250-200	P 150	P 150	P 150	P 150	P 150	P 150	P 150	girl, 2700g, A10	3 m (no treatment 2m be-
				SH	**SH**	**SH**	**SH**	**SH**	**SH**	**SH**	**SH**	C-section 39w	fore)
14.	31y	M 10	**3.69^**	M 10	M 10	P 100	P 50	P 50	P 50	P 50	P 50	girl, 4250g, A9-10	**N**/A

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						SH	**SH**		**SH**	**SH**		C-section	
15.1.	36y	M 10 **N**	N/A	P 100	P 150 **H**	P 150 **N**	P 100	P 100 **N**	P 100	P 100 **N**	P 100	boy, 3700g, A10 C-section 38w	3m
15.2.	38y	P 200 **SH**	N/A	P 150-100 **SH**	P50	P 50 **SH**	P 50	-	-	- **SH**	-	girl, 3600g, A10 C-section 38w	1m
16.	22y	P 300 **SH**	**13.73**	P 300	P 300	P 150 **SH**	P 150	P 150	P 150	P 150	P 150 **SH**	girl, 3140g, A9 C-section 39w	3m (no treatment since delivery)
		II. Hyperthyroid women diagnosed shortly before or during pregnancy											
		IIa. Women treated with ATD less than 6 weeks until pregnancy											
17.	26y	M 20 1m **H**	**4.19**	M 30 **H**	M 30	M 10 **SH**	M 10	M 10 **N**	- **N**	-	-	girl, 4250g, A9 Vaginal 40w	1.5m
18.1.	25y	M 40-20 1m **H**	N/A	M 15 **SH, SA**								Spontaneous abor-tion at 5w	10 m (no treatment 5 m before)
		IIb. Women who started ATD during pregnancy											
7.1.	29y	-	**5.44^**	-	-	- **H**	M 10 **H**	M 5 **SH**	M 5 **SH**	M 5 **SH**	M 5	girl, 3100g, A9 C-section 39w	3m
18.2.	26y	M 7m, stop 5m	**1.56^**	-	- **H**	M 5 **H**	M 5	M 5	M 5	M 5	M 5	boy, 4000g, A9 Vaginal 40w	4m
19.	26y	M 6m, stop 3.5y	N/A	-	-	-	-	M 45 **H**	M 30 **H**	M 30 **PD**		boy; neonate death in 24h; Vaginal **32w**	N/A
20.	29y	-	**24.5^**	-	-	M 30 **H**	M 15 **N**	M 2.5	M2.5/2d **hT**	-	-	girl, 3100g C-section	10m (not tested before)
21.	30y	-	**1.89** 1.57 postP	-	M 10-7.5 **H**	M 5 **H**	M 2.5 **SH**	M 2.5/2d **SH**	- **SH**	- **SH**	-	girl, 2490g, Vaginal 39w	2m borderline SH, then normal
22.	40y	-	**36**	-	-	-	-	-	M 15 **H**	M 15 **H**	M 20 **H**	girl, 3170, A9 C-section 38w	Stable mild H at 3w
		III. Women with hyperthyroidism not treated with ATD during pregnancy											
		IIIa. Transient gestational thyrotoxicosis											
23.	33y	- **N**	0.41	-	- **SH**	- **N**	-	-	-	-	-	girl, Vaginal 39w	No at 2m; short term-H at 17m
24.	30y	- **N**	0.28^	-	- **H/SH**	- **N**	-	-	-	-	-	N/A	N/A
		IIIb. GD with subclinical hyperthyroidism											
25.	33y	M 4m, stop 2.5y; **SH**	**5.55**	- **SH**	- **SH**	-	- **N**	-	- **N**	-	- **N**	girl**, N/A	N/A
		IV. Women with hyperthyroidism in remission after previous ATD treatment (euthyroid, not treated during pregnancy)											
8.2.	31y	M 4y, stop 1y; **N**	**1.5**	-	- **N**	LT4-12.5 **Sh**	LT4-37.5 **Sh**	LT4-37.5 **N**	LT4-50 **Sh**	LT4-50	LT4-50	child Vaginal at term	No

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26.	35y	M 1y, stop 3y, M 9m, stop 4y; **N**	**13.2** postP	- **N**	- **N**	- **N**	- **N**	- **N**	- **N**	- **N**	- **N**	girl 3150g, A9/9 Vaginal	3m
27.	32y	M 4y, stop 3y **N**	**10.3** postP	-	- **N**	-	- **N**	-	-	- **N**	-	boy, 3150g, A10, C-section 39w	4m
28.	26y	M 9m, stop 3m; **N**	**2.41**	- **N**	- **N**	-	- **N**	-	-	- **N**	-	boy, 3260g, A8 C-section at term	No
29.	41y	M 1y, stop 1.3y; **N**	**3.88** →0.3 **1.94** postP	-	-	- **N**	LT4-25 **hT**	LT4-37.5 **hT**	LT4-50 **hT**	LT4-62.5 **hT**	LT4-62.5	child, C-section at term	6.5m

Legend. All women have been diagnosed with Graves' disease (GD), except patient MO who had an autonomous hyperfunctioning nodule and 2 patients with transient gestational hyperthyroidism in the first trimester; TRAb = thyrotropin receptor antibodies; normal value < 1 IU/mL, positive > 1.5 – 1.75 IU/mL, in bold = increased levels; ^ TRAb levels were measured during 2nd or 3rd trimester of pregnancy; postP = postpartum; ATD = antithyroid drugs; M = methymazole (mg/day); P = propylthyouracil (mg/day), - = no treatment, LT4 = levothyroxine (mcg/day); the recommended treatment dose is noted at each time frame; N = normal thyroid function, H = overt hyperthyroidism, SH = subclinical hyperthyroidism (TSH < 0.1 mIU/L, normal FT4 or/and FT3), hT = hypothyroxinemia (normal TSH, low FT4); Sh = subclinical hypothyroidism (TSH > 2.5 mIU/L, normal FT4); w = weeks of pregnancy, m = months; y = years; PD = premature delivery, SA = spontaneous abortion; * Pregnancy after IVF with donated oocyte; & Intrauterine death at 40 weeks due to a true umbilical cord knot; ** this child had normal weight and fetal morphometric ultrasound evaluation at 35 weeks (last known data); # P was reintroduced for new ocular symptoms; N/A = data not available.

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3.2 Type of hyperthyroidism

The etiology of hyperthyroidism was Graves' disease (GD) in 26 out of 29, 89.6% pregnant women (33 out of 36 pregnancies, 91.6%), hyperfunctioning autonomous nodule in 1 pregnancy (3.4% of women, 2.7% of pregnancies), and transient gestational thyro-toxicosis (GTT) in 2 women (6.8% of women, 5.5% of pregnancies).

The diagnosis of GD was based on suppressed TSH, high total thyroxine (T4)/FT4 or/and T3, and increased TSH receptor antibodies-TRAb (>1.5 – 1.75 IU/L, depending on the assay) or antithyroid peroxidase antibodies (TPOAb) when TRAb was not available; a goiter was palpable in 20 GD patients (no data in the other 6); Graves' ophthalmopathy was recorded in 7 out of 22 GD patients (31.8%): mild in 6 women, moderate in one, no data in 4 patients.

The patient with autonomous nodule had a multinodular goiter with a dominant, scintigraphycally „hot" 2.5 cm left lobe nodule, negative for TRAb and TPOAb. The two patients with GTT had normal values of TSH and FT4 before pregnancy, suppressed TSH, normal or borderline high FT4 in the first trimester, normal TRAb, and again normal TSH and FT4 after 4-6 weeks (in the 2nd trimester). One had a small diffuse goiter.

3.3 Treatment with ATD

Sixteen of 29 women (20 pregnancies) had been treated with ATD for more than 6 months until pregnancy (up to 5 years). At the diagnosis of pregnancy 1 woman had overt hyperthyroidism, 2 had subclinical hyperthyroidism, the others had normal thyroid function.

In other 8 pregnancies, the treatment was either started less than 6 weeks before the diagnosis of pregnancy (n = 2), or during pregnancy, in week 12 – 25, median week 16. All were hyperthyroid in pregnancy (Tables 2 and 3).

Table 3. Serum TSH, FT4 and the dosage of antithyroid drugs in women with hyperthyroidism treated during pregnancy

	Serum TSH (mIU/L)			**Serum FT4 (ng/dL)**		
Women treated more than 6 months before pregnancy (n= 20 pregnancies, 16 women)						
	1st trimester	**2nd trimester**	**3rd trimester**	**1st trimester**	**2nd trimester**	**3rd trimester**
Mean value (range)	0.40 (nd-1.06)	0.61 (nd-2.12)	0.57 (nd -1.9)	1.09 (0.82–1.12)	1.03 (0.71–2.04)	0.92 (0.63–1.44)
At least once below normal	7/19 (37%)	6/17 (35%)	4/18 (22%)	0/17 (0%)	2/17 (11.7%)	2/17 (11.7%)
At least once above normal	0/19 (0%)	0/17 (0%)	0/19 (0%)	1/17(5.8%)	0/17 (0%)	0/17 (0%)
Methimazole mg/day (median, range)	5 (2.5 at 2d–10) N = 18	4.37 (2.5 at 2d–10) N = 6	3.75 (2.5 – 10) N = 4			

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Propylthiouracil mg/day (median, range)	150 (50 – 300) N= 5	75 (25 – 150) N = 6	75 (12.5–150) N = 5			
No treatment by the end of trimester	7/20 (35%)	12/20 (60%)	11/20 (55%)			
Women who started treatment shortly before (< 6 weeks) or during pregnancy (n = 8 pregnancies, 7 women)						
Mean value (range)	nd	nd	0.24 (nd – 1.2)	1.96 (1.3–2.63)	2.43 (1.18– 5)	1.07 (0.59–1.73)
At least once below normal	3/3 (100%)	6/6 (100%)	4/6 (80%)	0/3	0/6	1/5 (20%)
At least once above normal	0/3 (0%) P = 0.032	0/6 (0%) P = 0.013	0/6 (0%) P = 0.12	2/3 (66%) P=0.045	5/6 (83%) P< 0.001	1/5 (20%) P = 0.22
Methimazole mg/day (median, range)	20 (10 – 30) N = 3	10 (5–45) N = 6	5 (2.5/2 d–30) N = 5			
Propylthiouracil mg/day (median, range)	-	-	-			
No treatment by the end of trimester	0/3 (0%) P = 0.52	0/6 (0%) P = 0.017	3/7* (42.8%) P = 1			

Legend: Below normal: TSH <0.1 mIU/L, FT4 below the lower normal range of the assay; above normal: TSH >2.5–3.5–3.5 mIU/l (in trimester 1, 2 and 3, respectively), FT4 above the upper limit of the normal range of the assay; nd = not detectable (below the lower detection limit of the assay); d = days; *1 patient, treated for only 1 month before pregnancy, had a spontaneous abortion at 5 weeks; 1 patient had a premature delivery at 32 weeks; p were calculated for comparison of the 2 groups of women.

ATD type (Tables 1 and 3). Most of the treated patients received Methimazole (MMI) - in 22 out of 28 treated pregnancies (78.5%), Propylthiouracil (PTU) in 2 (7.1%), switch from MMI to PTU in 4 pregnancies (14.2%); no treatment was administered in 8 pregnancies (2 with GTT, 1 with a chronic subclinical GD, 5 in previous GD remission, with euthyroidism maintained without ATD before conception); of note, in Romania PTU is not commercially available.

ATD dosage (Tables 2 and 3). Pooled data using a 20:1 equivalence ratio for PTU to MMI showed that in women with previous long-term ATD treatment, the median doses at the diagnosis of pregnancy, i.e 5 mg/day (range: 2.5 mg every other day – 15 mg/day) were lower than those administered in women diagnosed de novo or shortly before pregnancy: 17.5 mg/day (range 5 - 45 mg/day), $p<0.05$. However, the difference between groups was no longer significant in the 3rd trimester, showing the potential for rapidly decreasing doses even in women diagnosed during pregnancy.

ATD withdrawal was recorded in T I in 8 (40%) of the pregnancies of long-term treated women (all on MMI doses ranging from <2.5 mg up to 10 mg/day) and in up to 55% of pregnancies in T III (11/20 pregnancies). The withdrawal was possible during T III also in 3 of 7 (42.8%) of patients diagnosed shortly before or during pregnancy. In 2 patients who withdrew ATD, treatment was restarted due to hyperthyroidism relapse: in 1 of 8 patients after withdrawal in T I (14.2%) and in 1 patient after withdrawal in T II (out of 5, 20%).

3.4 Control of thyroid function during pregnancy

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In patients treated before pregnancy, maternal TSH level was below normal in 37% of pregnancies in T I, in 35% in T II and in 22% in T III; high FT4 was recorded in 5.8% of pregnancies (in T I only) and subnormal FT4 was noted in 11.7% of pregnancies in T II and in T III (Tables 2 and 3). However, in more than 80% of cases, FT4 levels were below the upper 1/3 of the normal non-pregnant range. In patients who started ATD shortly before or during pregnancy (n = 8), hyperthyroidism persisted in 2, subclinical hyperthyroidism in 4, euthyroidism was followed by low FT4 in one, no data after ATD was started is available for the last patient.

Two patients diagnosed with GTT did not receive ATD treatment and normalized their thyroid function at the beginning of T II. The untreated subclinical GD spontaneously normalized in TII.

Evolution in the 5 patients considered in GD clinical remission, without treatment before and during pregnancy: a tendency towards subclinical hypothyroidism/hypothyroxinemia developed during pregnancy and LT4 was started in 2 patients, the others remained euthyroid during gestation.

3.5 Postpartum recurrence/ relapse /aggravation of hyperthyroidism

Postpartum recurrence/aggravation of hyperthyroidism was noted in 20 out of 24 (83.3%) pregnancies of treated women, all recorded in patients with GD (at median 3 ± 2.6 months, range 1-10 months); recurrence was also noted in 3 of 5 (60%) patients with previous remission of the hyperthyroidism before pregnancy (all having elevated TRAb levels postpartum (Tables 1 and 2).

3.6 Pregnancy outcome

Details are shown in Table 4.

Table 4. Pregnancy outcome

	Women with hyperthyroidism (previous or current) N = 29 women, 36 single fetus pregnancies	**Control normal women** N = 39 women, 39 single fetus pregnancies	**P value**
Age at pregnancy, years, mean ± SD	30.3 ± 4.7 29.6 ± 4.5 in ATD treated women	27.0 ± 4.1	<0.01
Pregnancy outcome	31 live children (91.1% of 34 evaluated; 2 unknown*) **Women treated for more than 6 months before pregnancy (20 pregnancies):** 1 fetal death at 40 weeks due to true umbilical cord knot **Women who started ATD shortly before or during pregnancy (8 pregnancies):** 1 spontaneous abortion at 5 weeks 1 premature delivery at 32 weeks, with neonate death within 24 hours (respiratory distress) **Women in GD remission before pregnancy (5 pregnancies):** 5 live children (1 unknown)	39 live children	

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	Untreated hyperthyroidism (3 pregnancies): 1 live child (2 unknown*)		
Delivery type	Vaginal: 10 (28.5%) C-section: 23 (65.7%); 85% in women treated > 6 m; 57% in women diagnosed shortly before or during pregnancy, p=0.049 Unknown: 2 (5.7%)	Vaginal: 17 (43.5%) C-section: 22 (56.5%)	0.32
Mean gestational age (weeks)	38.4 ± 1.7 38.5 in women treated > 6 m, 38.0 in women treated shortly before or during pregnancy (p = NS)	39.05 ± 1.2	0.11
Children Sex F: M Congenital anomalies Follow-up >2 years Fetal/neonatal hyper-thyroidism Fetal/neonatal goiter or congenital hypothy-roidism	N = 35* 20 F:11 M (4 unknown) 1 small atrial sept defect – ostium secundum (in 25 live children of ATD treated women, 4%) 13 of 25 children of ATD treated women (52%) 1 child (in 30 live children from GD women, 3.3%) 0 cases	N = 39 15 F: 24 M None N/A 0 cases 0 cases	0.053
Children's birth weight, mean ± SD, grams	a) All women treated during pregnancy (n = 24 children): 3267 ± 515 b) Women treated more than 6 months before, and during pregnancy (n = 18 children): 3238 ± 480 c) Women who stopped ATD before week 10 (n = 6 children): 3208 ± 391 d) Women diagnosed and treated shortly before (n=1) or only during pregnancy (n = 5): 3352 ± 652 [p = NS between groups b), c) d)]	3342 ± 469	0.56 0.45 0.47 0.97

Legend. GD = Graves' disease; TRAB = Thyrotropin receptor antibodies; F = female; M = male, N/A = not available; m = months; *1 child had female sex, normal weight and normal fetal morphometric ultrasound evaluation at 35 weeks (last known data);

There were 31 live children out of 34 (91.1%, 2 patients were lost to follow-up); one spontaneous abortion at 5 weeks (3.4% of pregnancies in women with hyperthyroidism), and one premature delivery (3.4%) at 32 weeks, with perinatal death within a few hours (respiratory distress) (3.4%). These were recorded in 2 of the 8 patients with GD diagnosed shortly before or during pregnancy. One fetal death at 40 weeks due to a true umbilical cord knot (3.4%) was recorded in 1 of the 20 patients with long-term ATD before pregnancy.

No goiter was recorded in the fetuses or live neonates; only 1 case of neonatal hyperthyroidism (3.3% of 30 live children from GD women) and 1 birth defect (4% of children of ATD treated women), i.e., a small atrial sept defect – ostium secundum, with mild systolic murmur (II/VI), were noted in a child born to a GD patient diagnosed and treated with MMI from the beginning of TIII onward. The follow-up was longer than 2 years in 13 out of 25 children (52%) from women with ATD treatment during pregnancy.

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No neonatal hypothyroidism was declared by the patients (however, data on this subject were missing in most of the patient's files).

The gestational age and birth weight of children born to ATD treated women were not significantly different from those of children born to normal control women, either for the whole group (Table 4, figure 1 and 2) or separated by sex (data not shown). No differences were recorded in women with long term ATD treatment, compared to those who started treatment shortly before or during pregnancy. No difference was noted in the percent of C-sections in treated versus control women (most of those being performed for obstetrical reasons not related to hyperthyroidism, except moderate exophthalmos).

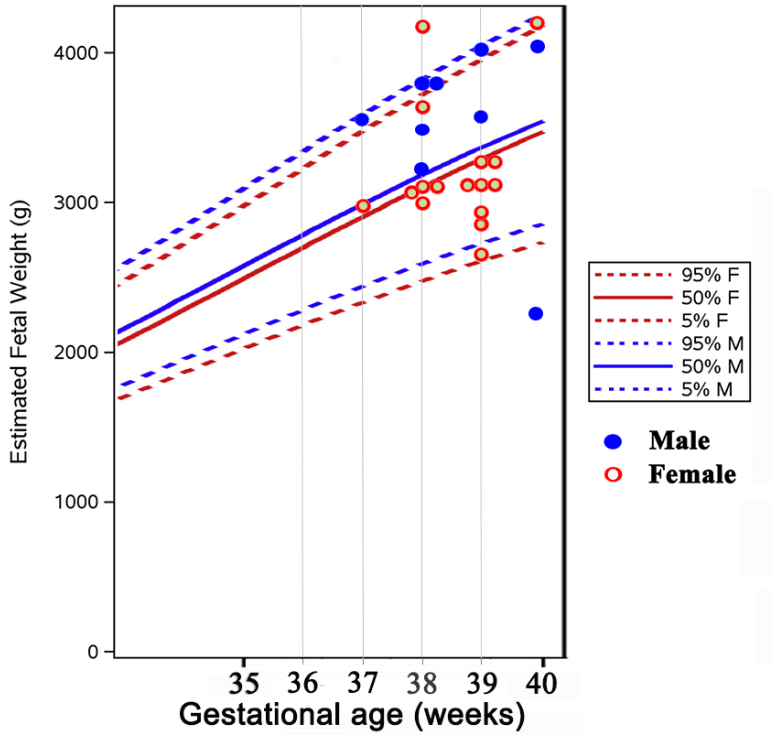

Figure 1. Distribution of birth weight in newborns from mothers with hyperthyroidism

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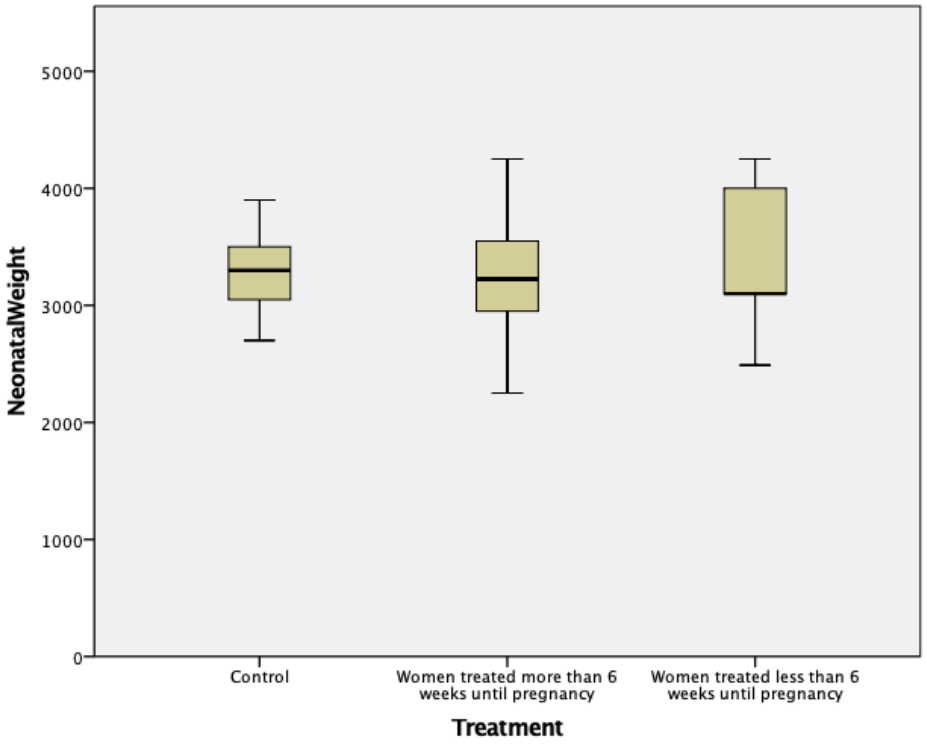

Figure 2. Newborn's weight, in mothers treated with ATD compared to healthy controls

4. Discussion

Hyperthyroidism is due to excessive production of thyroid hormones and is characterized by a low/suppressed serum level of thyroid-stimulating hormone TSH, associated with an increased level of peripheral hormones (total and free thyroxine-FT4 and/or total and free triiodothyronine-T3) in the biochemically overt form of the disease, or with normal FT4 and FT3 levels in subclinical hyperthyroidism [11].

4.1 Causes of hyperthyroidism during pregnancy

It is essential to understand the underlying etiology for thyrotoxicosis in order to recommend appropriate treatment in pregnancy. Graves' disease (GD) and human chorionic gonadotropin (HCG) mediated hyperthyroidism (GTT) are the most common [2,3]. Approximately 90-95% of hyperthyroid pregnant women have GD [3]. When the diagnosis of hyperthyroidism is made during the first trimester of pregnancy, the HCG-mediated hyperthyroidism, named gestational transient thyrotoxicosis (GTT), must be taken into account. In most cases, this is a subclinical hyperthyroidism, which appears after the 6th week of pregnancy due to the physiological rise in HCG secretion; HCG shares a structural homology with TSH and stimulates maternal thyroid function[15]. A serum HCG concentration of 10000 UI/L is associated with a 0.1 mUI/L decrease of TSH serum concentration [16]. Between weeks 7 and 11 of gestation, a TSH <0.1 mIU/L occurs in about 5% of women, with levels being completely suppressed in 0.5 to 1% [17]. GTT has a spontaneous resolution by 14-18 weeks of gestation as the values of HCG decrease [18]. Levels of HCG correlate with the degree of nausea, and the thyrotoxic

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symptoms are usually mild. GTT has a good prognosis, is associated with a favorable outcome of the pregnancy, the thyroid gland is not enlarged, and usually does not require antithyroid treatment [4,18] (which was not prescribed in our 2 women with subclinical GTT).

HCG mediated hyperthyroidism can also be diagnosed in other circumstances associated with high serum concentrations of HCG, such as multiple pregnancy, hyperemesis gravidarum (loss of 5% body weight, dehydration, and ketonuria), gestational trophoblastic disease [4,7] or mutations in the TSH receptor [19].

GD consists of hyperthyroidism, goiter, eye disease, and occasionally a dermopathy referred to as pretibial myxedema. It is caused by the presence of autoantibodies to TSH receptors (TRAb) that activate the receptor and promote the synthesis of thyroid hormones as well as the diffuse enlargement of the thyroid gland [20]. The evidence of TRAb in serum, increased T3 or T3/T4 ratio and the signs of orbitopathy on clinical examination differentiate Graves` disease from GTT [7,8,18]. GD typically requires treatment. Other less frequent causes of thyrotoxicosis during pregnancy include toxic multinodular goiter and toxic adenoma (in <5% of cases, as in our series) and subacute thyroiditis (more frequent in the postpartum period); other causes are exceedingly rare [2,3].

4.2 Difficulties in the diagnosis of hyperthyroidism during pregnancy

In pregnant women, the diagnosis of hyperthyroidism meets specific challenges. The *signs and symptoms of hyperthyroidism* may be confounded with physiological changes of pregnancy: tachycardia, heat intolerance, anxiety, emotional lability, diaphoresis, gastrointestinal symptoms such as nausea, vomiting, and diarrhea (which may be confounded with pregnancy disgravidia), fatigue. More specific are hand tremor, weight loss despite a normal or increased appetite [20], exophthalmos, suggesting the diagnosis of GD, signs and symptoms of congestive heart failure [8,20]. The thyroid gland volume may be increased, as in all of the GD women in our series.

Several *physiological adaptative changes* occur since early pregnancy, affecting maternal thyroid function and the hormonal tests. Apart from the early decrease in serum TSH, there is an increase in the synthesis of TBG (thyroxine-binding globulin) caused by the high serum levels of estrogen, leading to an increase in total T4 and T3 levels, but not in the free T4 and T3 [15] [21].

The *measurement of free T4* by indirect analog immunoassays may be influenced by the increased TBG values and hemodilution [22]. In pregnancy weeks 9-12, the FT4 upper reference limit may be slightly higher (~ 5%) than the non-pregnancy reference limit, while in the second, and especially in the third trimester is lower than non-pregnancy values [21,17] . These changes should be taken into account when assessing the diagnosis and the ATD control of the thyroid function. The use of local trimester-specific and assay-specific reference ranges for TSH, and free T4 is recommended [7,8], but they were not available for the patients in our series.

Changes in iodine requirements during pregnancy and the influence of iodine deficiency. Iodine clearance is two times higher during pregnancy as a consequence of the increased renal blood flow and glomerular filtration rate [15]. As a result,

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iodine intake must be higher in pregnant than in nonpregnant women, and the World Health Organization recommends an intake of 250 mcg of iodine daily during pregnancy and lactation [7]. Both iodine excess and deficiency are harmful and impair fetal development [23]. In our country, in which iodine deficiency is present on 2/3 of the territory, we have previously shown higher cord blood levels of TSH and lower levels of T4 in newborns from iodine-deficient areas compared to those from iodine sufficient regions [24]. After the introduction of the universal salt iodization in 2002, median urinary iodine concentration normalized in schoolchildren and improved in pregnant women from iodine-deficient areas [25,26]. Of note, pregnant women from rural areas or eating daily less than 5 slices of bread (containing iodized salt) may still be at risk for iodine deficiency [26]. The presence of an endemic, sometimes nodular, goiter in a pregnant woman could produce difficulties in identifying the cause of concomitant hyperthyroidism (as it was the case in 1 GD patient with a thyroid nodule and in a GTT patient with goiter, in our study).

4.3 Pregnancy complications in women with hyperthyroidism

The diagnosis of maternal hyperthyroidism is mandatory as the poorly controlled disease leads to pregnancy complications. Maternal hyperthyroidism is associated with miscarriage (in 3.4% of women with hyperthyroidism in our series), premature labor and preterm birth (3.4% in our study), low birth weight, stillbirth, preeclampsia, and heart failure [5,27,28,29]. Preterm delivery was reported in 4-11% of mothers treated for hyperthyroidism during pregnancy and 53% of untreated mothers [30,31].

In our series, one woman diagnosed with severe GD hyperthyroidism and hypertension in the second trimester had a premature delivery at 32 weeks, after 7 weeks of high-dose MMI treatment (45 - 30 mg/day). She had been first diagnosed after a previous pregnancy, and had a 3.5 year - history of uncontrolled hyperthyroidism due to noncompliance to treatment. The neonate died within a few hours due to respiratory failure; no malformations were noted, but data were anamnestic, and the patient was lost to follow-up. Either hyperthyroidism *per se* or the high dose of ATD treatment could have contributed to this unfavorable outcome. In other patient, who was treated only 4 weeks before pregnancy and was incompletely controlled, an early miscarriage occurred at 5 weeks. A third child died at 40 gestational weeks due to a true umbilical cord knot, probably not related to ATD, which had been withdrawn in early pregnancy.

Intrauterine growth restriction was reported in women with hyperthyroidism, caused by direct effects of the excess thyroid hormones and by the associated preeclampsia [32]. In our study, only 1 child had a birth weight below the 5th percentile of normal children (4.1% of the treated pregnancies); he was born to a mother treated with MMI during the whole pregnancy (10 to 5 mg/day). Mean birth weight did not differ significantly in children born to women diagnosed *de novo* during pregnancy, in those from women treated with ATD since before pregnancy and in those from normal control women (table 4, figure 2).

4.4 Treatment in pregnant women with hyperthyroidism

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The goal of the treatment in pregnant women with hyperthyroidism is to provide an excellent fetal and maternal outcome by preventing the complications induced by uncontrolled maternal hyperthyroidism, as well as the development of maternal or fetal hypothyroidism [7,18].

Therapeutic strategies depend on the cause and severity of the disease, timing of the diagnosis in relation to pregnancy (before or during early or advanced pregnancy) and should take into account the risk of side-effects [7,18,33].

Women with symptomatic, overt hyperthyroidism require treatment, while in subclinical hyperthyroidism or GTT, treatment with ATD is not recommended [7,8]. Women with subclinical hyperthyroidism who were not treated have been monitored with measurements of TSH, free T4, and/or total T4 at four to six weeks, as recommended by the guidelines [7,8], until normalization occurred in the second trimester,

Women with overt hyperthyroidism during pregnancy usually need treatment with antithyroid drugs (ATD): Methimazole (MM^{34}I), Carbimazole (CMZ), or Propylthiouracil (PTU) [7,18,33], which are considered equally effective. Thionamides inhibit the iodination of thyroglobulin and thyroglobulin synthesis. PTU can also inhibit the conversion of T4 to T3 [7,35]. Alternatively, surgery may be indicated in the second trimester if allergy or intolerance to treatment occurs, but the risk of miscarriage and preterm birth is increased [7,8].

ATD has been associated with several side effects. In pregnant and nonpregnant women, rash, urticaria, and arthralgia are more common (1-5%), while the most severe side effects are rare (0.1-1%): liver toxicity, including fulminant hepatic failure mostly developed on PTU, a lupus-like syndrome, agranulocytosis and, more recently described, a few cases of acute pancreatitis on MMI [8,9,10,35]. Both MMI and PTU can cross the placenta and, when used in early pregnancy, may have teratogenic effects in the fetus [10,34,36,11] (they are pregnancy category D drugs, i.e., they may be used if the potential benefits outweigh the potential risks for the mother and fetus).

4.5 Fetal and neonatal outcomes

Birth defects were recorded in approximately 4-9% of pregnancies with MMI exposure and in 1.9-8% of pregnancies with PTU exposure in several, but not all studies [34,36,11,35,37]. A recent meta-analysis including 6212322 pregnancies and 388976 birth defects from 7 cohort studies and 1 case-control study has calculated even lower adjusted risks of having congenital anomalies related to ATD, compared to the unexposed population [38]. The excess risk for *any* and *major* birth defects per 1000, respectively, was 10.2 and 1.3 for PTU, 17.8 and 2.3 for MMI/CMZ, 32.5 and 4.1 for both MMI/CMZ and PTU, 9.6 and 1.2 for untreated hyperthyroidism [38].

MMI and CMZ -associated defects include aplasia cutis, facial dysmorphism, or more severe, albeit rare, defects in the so-called MMI/CBZ embryopathy: choanal or esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and other abdominal wall defects, ventricular septal defects [34,36,11].

Congenital defects associated with PTU use are milder and include face and neck cysts and urinary tract defects in males, and may be revealed later, after 1-2

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years from birth [34]. There is not a clear association between the PTU dose and the occurrence of birth defects, although this seems more convincing for MMI [11]. The most sensitive period for teratogenesis is between 6 and 10 weeks of pregnancy [39]. Therefore PTU is preferred over MMI during the pre-pregnancy period and through the first trimester, while the use of "block and replace" treatment with high doses of ATD and L-thyroxine is not recommended during pregnancy [7,8].

In our series, in which about half of the children have been followed–up for more than 2 years, there were no serious birth defects described in the 25 live neonates from women treated with ATD during pregnancy, only 1 small atrial sept defect (4% of live children in ATD treated women). The median dose of MMI during early pregnancy was usually low, 5 mg/day in women treated for at least 6 months before pregnancy, and higher, around 20 mg/day in women treated less than 6 weeks before conception.

ATD-induced fetal hypothyroidism is another risk which should be avoided. Maternal thyroid hormones are essential for the fetal central nervous system development during the first trimester when the fetal thyroid is not functional [40]. The fetal thyroid begins to secrete thyroid hormones from about week 16 of gestation and is more sensitive to ATD than the maternal thyroid [41]. Low thyroid function after birth is encountered in one-half of neonates whose mothers were treated with PTU or MMI during pregnancy and who had normal serum T4 concentrations [41].

High, as well as low, maternal free T4 levels have been associated with adverse effects on child IQ at 6 years of age [6], and maternal hyperthyroidism may be associated with higher risks for seizures and for attention deficit hyperactivity symptoms later in children [42].

Consequently, if antithyroid drugs are required in pregnancy, the current guidelines recommend using the lowest possible dose to keep the maternal serum-free T4 at or just above the upper limit of normal [7,8,18,33].

In our series, there were no cases with neonatal hypothyroidism recorded. The data are limited by the fact that in Romania the neonatal TSH screening program for congenital hypothyroidism has been generalized since 2011, and only children with dry-spot TSH ≥ 17 mIU/L are recalled [43].

Fetal and neonatal hyperthyroidism

GD with high maternal TRAb titers (> 3 times the upper limit of normal in the second or third trimester) increases the risk for fetal or neonatal hyperthyroidism by placental transfer, which begins by the 20th week and peaks by the 30th week [44,33,45]. Neonatal hyperthyroidism occurs in 1 to 5% of infants of women with a history of GD, even if the mother had undergone thyroidectomy or radioiodine ablation [16]. The fetus should be monitored by ultrasound for signs of hyperthyroidism (sustained tachycardia >160 bpm, goiter, intra-uterine growth restriction, advanced bone age, craniosynostosis, nonimmune hydrops) or hypothyroidism (goiter, retarded bone age) [7,8,46,47]. We had only 1 neonatal hyperthyroidism (with positive TRAb) in the studied group (3.3% of live children born to GD women). TRAb monitoring was not regular in every patient; however, more

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frequent ultrasound monitoring of the fetus was undertaken, especially in women who still needed treatment or had uncontrolled hyperthyroidism in late pregnancy, in line with the ACOG guidelines [48].

4.6. *Maternal outcomes*

Patients diagnosed prior to pregnancy have been counseled regarding the risks and benefits of every treatment option (surgery, radioiodine or medical therapy). According to the current guidelines, the preferred ATD for those planning a pregnancy, as well as for those diagnosed *de novo* during early pregnancy, is PTU, due to the lower reported prevalence of birth defects [7,8]. Patients currently on MMI may shift to PTU as soon as pregnancy is diagnosed (as currently recommended) or continue with MMI [7,8] notably when the dose is low, and PTU is not easily available, as is the case in our country and others [35]. Data from large trials and recent meta-analyses have shown that shifting MMI to PTU in early pregnancy (usually in a 1: 20 ratio) was still associated with an increased risk for birth defects [36,11,38]. We agree with the authors of a recent position paper of several Italian Societies of Endocrinology and Obstetrics-Gynecology that in MMI-treated women, contraceptive methods are not routinely necessary (they may be offered until disease control is obtained), and in those with an unplanned pregnancy, therapeutic abortion is not warranted [35].

In women who are controlled on low-dose ATD [MMI ≤5-10 mg/day or PTU ≤100-200 mg/day], who have already been treated for at least 6 months (or are euthyroid on a stable dose checked 2 months apart [8]), who do not have large goiters or TRAb > 3 times the upper limit of normal), ETA and ATA guidelines suggest withdrawing ATD as soon as pregnancy is diagnosed [7,8], with close monitoring of symptoms and thyroid function tests every 1 to 2 weeks, aiming to avoid ATD treatment during the first trimester [18,33]. In our series, ATD withdrawal in the first trimester was undertaken in 40% of women treated for at least 6 months before pregnancy. Two of those patients had borderline high TRAb levels. Hyperthyroidism relapsed in 14.2% (1 patient) in about 8 weeks and ATD was resumed. Reviewing the data, a few other patients may have been good candidates for this strategy, which was not recommended at that time. However, more studies are needed in order to evaluate the benefits and risks of this procedure. Of note, the recent guidelines of the Association of Canadian Obstetrics and Gynecology do not mention this strategy [48].

From the beginning of the second trimester onwards, treatment with MMI is preferred, in view of the potential PTU – induced liver toxicity, but PTU may also be continued [7,8]. In our series of patients, 17.4% of women switched from MMI to PTU usually in the first trimester and continued with it until delivery, with no adverse effects.

In women with newly diagnosed with GD during gestation, the guidelines recommend to use the lowest doses of thionamides that control thyroid function (usually PTU 50 mg 2 or 3 times daily, MMI 5-10 mg daily, or CMZ 5-15 mg daily) [7,8]. This was possible in most of our patients, except in those with moderate to severe hyperthyroidism diagnosed during pregnancy, in whom the starting doses have usually been higher (10 – 45 mg/day).

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4.7. *Maintenance, remission and relapse*

In order to maintain optimal control of the thyroid function in both mother and fetus, frequent monitoring of TSH, free T4, and/or total T4 or T3 level is recommended throughout pregnancy (every 4 weeks in women on stable doses of ATD, or even more frequently when dose adjustments are made) [7,8,33]. This was not possible in all our cases in real-life, usually due to patient non-compliance or to the incomplete available data - a recognized limitation of our retrospective analysis. However, with careful selection, counseling, and monitoring of the pregnant women with hyperthyroidism, satisfactory control of the thyroid function during pregnancy was obtained, notably in women treated more than 6 months before conception: TSH level was below normal in 37%, 35% and 22% of pregnancies in T I, II and III respectively; FT4 was increased in 5.8% (T I) and transiently subnormal in 11.75% in TII and III; abnormal values have been more frequently found in women with hyperthyroidism diagnosed shortly before or during gestation (Table 4).

Graves' disease may enter remission during late pregnancy (due to the progressive decrease of TRAb titers), and ATD may be stopped [14]. In our series, 55% of long-term treated pregnant women and 42.8% of those diagnosed during pregnancy were treatment free in the last trimester. However, Graves' disease frequently relapses during the postpartum period, which indeed was the case in 83.3% of our patients in the following 10 months. Relapse of thyrotoxicosis was noted also in 3 of the 5 women (60%) considered in previous stable remission/cure of GD (Table 1). In this case, the prevalence may be overestimated, patients with recurrence being more prone to present to the endocrinologist. The differential diagnosis with postpartum thyroiditis may pose difficulties, since these patients may have remanent TRAb and radioiodine uptake is not readily performed in breastfeeding women. Regular monitoring of TSH and FT4 is thus warranted in the postpartum period, notably in the first 3 to 12 months [7,8]. Breastfeeding is possible in women treated with MMI < 20 mg/day or PTU < 250 mg/day, taken in divided doses after feeding [8,49] and we recommend it.

5. Conclusions

Few studies analyze the management of hyperthyroid pregnant patients and the outcomes for the mother and child. In this small retrospective study, we were able to demonstrate that women with hyperthyroidism treated with antithyroid drugs generally have normal pregnancies. Several factors contribute to the success: correct identification of the etiology of hyperthyroidism; careful patient counseling before conception with regard to treatment options, the infrequent risks of birth defects associated with antithyroid drugs, and the necessity to get a stable control of the thyroid function before pregnancy; frequent TSH and FT4 monitoring allows to maintain the use of the minimal treatment dose possible and good control of the thyroid function. Withdrawal of antithyroid drugs is possible in carefully selected patients in early pregnancy in order to avoid the sensitive period to teratogenesis; it was also possible in about half of the patients with Graves' disease during late pregnancy. We recommend a multidisciplinary

approach (endocrinologist + obstetrician) to reduce fetal-maternal risks. Extensive prospective studies are still needed to evaluate the currently recommended management strategies in women with hyperthyroidism during pregnancy.

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Informed Consent Statement: "All the patients have signed an informed consent for the use of their medical data for scientific research".

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