Therapy of Hypothyroidism in Pregnancy

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Abstract : *This report presents the prospective analysis of 46 pregnant women with hypothyroidism who were treated before and during pregnancy with thyroid hormone substitutional therapy. Novothyral in a constant dose was administered to 23.9% of pregnant women compared to the non-pregnant patients. The greatest number of pregnant women (76.1%) received Vobenol in a dose ranging from 75-200 μg. Depending on the clinical and laboratory analysis, Vobenol dose was increased in 40.0% of women with idiopathic and in 22.6% with postoperative hypothyroidism. The dose of the drug was not lowered during the whole pregnancy course in any of the patients. The delivery occurred in 82.6% of patients. In 13.2% of women delivered prior to term, while spontaneous abortion was present in 17.4% of the treated patients. There were 5.3% stillbirths which corresponds to the rate of perinatal mortality.One infant was born with hydrocephalus while the others were healthy. The authors are of the opinion that it is necessary to achieve normal metabolic status before pregnancy which should be maintained with substitutional therapy during the whole pregnancy. (Thai J Obstet Gynaecol 1993;5:25-31.)*

Key words : hypothyroidism, pregnancy, substitutional therapy

It is clear today that in patients with hypothyroidism the pregnancy outcome is significantly better in adequately treated pregnant women, but the question of substitutional therapy mechanism effect on the fetus remains still open.

The placental transfer of thyroid hormones (TH) is not completely clear and there is a general statement that in physiological conditions it is limited in the direction mother-fetus and vice versa[1]. Thyroid hormones in early pregnancy do not pass the placental barrier[1]. However, by the end of pregnancy, and especially during delivery, a certain quantity may be transfered into fetal circulation, indicating more the exchange of hormones than real transport. It has been reported that the placenta contains an enzyme that deiodinates thyroxine (T4) into inactive metabolite reverse triiodothyronine (rT3) and also inactivates triiodothyronine (T3) by conversion to diiodothyronine, substrates

that are not transfered into the fetus[2]. It is possible that this enzyme plays a major role in preventing the maternal TH transport into the fetal circulation. Considering that thyroid-stimulating hormone (TSH) does not enter into the fetus either, the question of thyrotropin-releasing hormone (TRH) placental transport arises, which might have the role of mediator in fetal thyroid function. Special interest has been aroused by the hypothesis that fetal TH, especially near term, may pass the placenta and compensate the thyroid status of a hypothyroidal pregnant woman[3,4]. It seems that TH transfer into fetal circulation in a large amount depends on the mutual effect of TH and plasma proteins. Since the binding capapcity of the maternal hormones, especially of thyroxine surpasses their fetal capacity, the TH transfer from the fetus may be expected.

The majority of investigators are of the opinion that the TH placental transfer is not necessary when the fetal pituitary-thyroid axis remains intact. There are investigators who determined the development of athyreosis in children of euthyroid mothers and, in contrast to this, a normal development of children born to hypothyroid mothers, indicating the relative autonomous maternal and fetal thyroid functions[1].

The aim of this study was to investigate the course and outcome of pregnancies in women with hypothyroidism on thyroid hormone substitution therapy, especially the dose requirements of thyroxine.

Patients and Methods

The study involved 46 pregnant women with hypothyroidism which had developed as a consequence of vairous etiopathogenetic factors which were treated before and during pregnancy with thyroid hormone substitutional therapy. All patients were regularly follow-up and delivered at the Clinic of Gynaecology and Obstetrics, University Clinical Center in Belgrade. The analysis was completely prospective, performed in the ten-year period, from 1981-1990.

The follow-up of the basic disease was performed in collaboration with the internist, endocrinologist with the evaluation of clinical parameters and routine laboratory analyses and radioimmunologic assessment of thyroxine (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) (INEP kits) in pregnancy trimesters, and of free hormones (FT4 and FT3 with Amersham kits) in the first and last trimesters, while the pregnancy course was monitored with available means for evaluation of fetal status and the feto-placental unit. The range of normal TSH values were from 0.6-6mU/l,from 64-164 nmol/l for T4, from 1.4-3nmol/l for T3, from 9.5-25.0 pmol/l for FT4 and from 2.9-8.9 pmol/l for FT3.

The control group included 20 healthy pregnant women with normal gravidity course, term delivery with normal endocrinology status deter-

mined before pregnancy.

The majority of pregnant women received Vobenol (since commercially available), a synthetic L-thyroxine preparation (one tablet contains 100 μg of levothyroxine sodium). In the initial phase of this study a smaller number of patients received Novothyral, also a synthetic preparation, which is a combination of T3 and T4 (one tablet of Novothyral contains 20 μg of T3 and 100 μg of T4).

Statistical data analysis was done with Student t-test of proportions, χ^2 and Fisher's tests of real probability, while the variance analysis was done for tendency evaluation of examined parameters according to pregnancy trimesters.

Results

In order to obtain the most precise interpretation of the results all pregnant women were divided into two groups according to the disease causes:

I-Postoperative hypothyroidism (31) of very heterogeneous structure, developed as a consequence of subtotal thyroid gland resection (26), due to Graves disease (8), non-toxic goiter (6), follicular adenoma (5), carcinoma (7), or total thyroidectomy due to carcinoma (5).

II-Idiopathic hypothyrodism (15) involved patients (4) with mettabolic impairment during pregnancy which in spite of increased daily doses of Vobenol (200 μg) persisted throughout the pregnancy (IIa).

The analysis of Table 1 indicates that in all patients with hypothyroidism the TSH concentrations increased above normal values, significantly higher comparing to the control group.

The concentration of T4 was significantly lower in relation to the corresponding trimester in the control group. T3 values did not indicate greater deviations compared to the healthy pregnant women.

Patients with idiopathic hypothyrodism with impaired metabolic status during gravidity (IIa) were separately analyzed.

Graphicon 1 shows that in pregnant women with hypothyroidism the FT4 concentration was significantly lower value while concentration of FT3 had unsignificant lower value compared to the healthy pregnant women.

Table 2 shows that Novothyral in a constant dose was administered to 11 pregnant women (23.9%) compared to non-pregnant patients. The

Graph 1 FT4 and FT3 in pregnancy

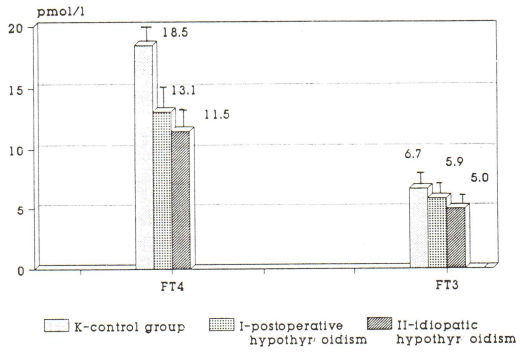

Table 1 The value of thyroxin (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) in pregnancy trimesters

Groups	Trimesters	T4 (nmol/l)		T3 (nmol/l)		TSH mU/l	
		$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
K n=20	I	123.4	12.8	2.21	0.27	5.92	0.85
	II	136.9	12.9	2.37	0.15	5.74	0.83
	III	144.3	11.7	2.52	0.18	5.52	0.79
	test	F = 13.542 p < 0.001		F = 7.951 p < 0.001		F = 0.988 p > 0.05	
I n=31	I	109.2	14.3	2.37	0.31	9.37	1.13
	II	112.9	11.3	2.49	0.23	9.17	1.03
	III	113.2	15.9	2.47	0.27	8.91	1.09
	test	F = 1.057 p > 0.05		F = 1.315 p > 0.05		F = 1.586 p > 0.05	
II n=11	I	108.5	18.5	2.20	0.36	11.5	2.8
	II	117.8	22.6	2.29	0.41	10.4	2.3
	III	122.1	16.4	2.34	0.33	10.0	3.0
	test	F = 1.822 p > 0.05		F = 0.875 p > 0.05		F - 1.071 p > 0.05	
IIa n=4	I	74.5	27.5	1.55	0.47	35.2	8.1
	II	88.0	8.6	1.877	0.13	37.3	10.1
	III	53.0	2.9	1.48	0.06	56.0	7.1
	test	F = 1.102 p > 0.05		F = 3.836 p > 0.05		F = 2.736 p > 0.05	

K - control group
I - postoperative hypothroidism
II - idiopathic hypothyroidism

greatest number of pregnant women (76.1%) received Vobenol (since commercially available) in a dose from 75 μg to 200 μg. Depending on the clinical and laboratory analysis, Vobenol dose was increased in 14 (30.4%) of pregnant women with the progression of gestation. The dose of the drug was not lowered during the pregnancy in any of the patients.

Table 2 Therapy before and during pregnancy

Characteristics	N	Novothyral			Vobenol				
		n	2* 1/2	2* 1	n	75 μg	100 μg	150 μg	200 μg
Without changing the dose	32 69.6	11 23.9	7 15.2	4 8.7	21 45.7	8 17.4	8 17.4	5 10.9	- -
Increase the dose	14 31.4	14 -	1 -	13 -	30.4	-	-	2.1	28.3
Total	11 46	7 23.9	4 15.2	35 8.7	8 76.1	8 17.4	6 17.4	13 13.0	28.3
I	8 31	7 25.8	1 22.6	23 3.2	6 74.2	6 19.3	4 19.3	7 12.9	22.6
II	3 15	1 20.0	2 6.7	12 13.3	2 80.0	2 13.3	2 13.3	6 13.3	40.0

I - postoperative hypothyroidism
II - idiopathic hypothyrodisim

Table 3 Pregnancy outcome

Groups	N	Pregnancy outcome		
		Delivery		Abortion
		Total	Preterm	
I	31	26 (83.9%)	3 (11.5)	5 (16.1%)
II	15	12 (80.0%)	2 (16.7)	3 (20.0%)
Total	46	38 (82.6%)	5 (13.2)	8 (17.4%)

I - postoperative hypothyroidism
II - idiopathic hypothyroidism

Table 3 shows that 82.6% of our patients were delivered, 13.2% had preterm deliveries, while 17.4% had spontaneous abortions of which 6.5% were in the first trimester of pregnancy. There were two stillbirths so perinatal mortality was 5.3%.

Discussion

Since Howitz, in 1892, first reported that dried lamb thyroid gland given orally to the patients with hypothyroidism has an active effect, preparations with various biological activity were used. Novothyral, administered to a small number of subjects in the initial phase of this study, caused serum peaks immediately after the absorption, followed by a sudden fall. Pure thyroxine is nowadays generally accepted as the drug of choice and the only preparation which is ca-

pable to achieve adequate physiological control. There is disagreement on the optimal daily thyroxine doses in pregnancy; some authors suggest unchanged, constant doses compared to non-pregnant conditions while others suggest higher or lower doses depending on hormonal parameters[5-7]. The discrepancy in data on daily thyroxine doses is probably a consequence of a different clinical status, especially of the etiologic factors of hypothyroidism. In 30.4% of our subjects, the dose of Vobenol was increased with the progression of gestation based on clinical and laboratory findings. It is reported that pregnant women who underwent thyroidectomy are most suitable for evaluation of L-thyroxine appropriate doses[7]. However, there is disagreement here as well. While some authors describe unchanged doses, and even insignificant decrease of doses compared to non-pregnant conditions[6], others assume that it is necessary to increase thyroxine doses due to the metabolic and hormonal changes which normally occur in pregnancy[7].

Although the data on the effects of hypothyroidism on the course and outcome of pregnancy and the status of the newborns are contradictory, the majority of authors observed differences which occurred depending on the treatment before and during gravidity. According to the referential data since 1897, Potter[8] reported the improvement of pregnancy outcome in patients with hypothyroidism treated with subsitutional therapy.

Spontaneous abortions occurred in 17.4% of our pregnant women with hypothyroidism, in the first trimester in 26.7%, and preterm delivery occurred in 13.2%, which is concordant to the results of the other investigators. The reported incidence of spontaneous abortion is 14.3% as much as 50% of them in the first trimester, and preterm deliveries from 8.9% to 20.8%[6, 9, 10]. In our subjects there were 5.3% of stillbirths which corresponds to the rate of perinatal mortality. The data on stillbirths reported by other authors have a wide range, from 1.8% to 12.5% with perinatal mortality from 3.6% to 12.5%[6, 9,10], and even to 20% in older publications. High prevalence of congenital malformations is of remarkable importance, from 10% to 20% as well as impaired mental and somatic development is 50% to 60% of surviving newborns[11]. By applying intelligence test Man[11] found that it was much lower in children of untreated pregnant women with hypothyroidsm compared to the children born to adequately treated hypothyrotic mothers. The incidence of congenital anomalies in recent reports ranges from 7% to 9%[6, 10], but it can not be explained only by thyroid function disorders. We reported that one newborn was born with hydrocephalus in the group of pregnant women with autoimmune hypothyroidism so the incidence of anomalies was 2.6%. The development of hypothyroidism was not observed in the newborns.

In conclusion one can say that

pregnancies in women suffering from hypothyroidism must be followed up from the very beginning, as a high risk pregnancy, since the pregnancy and puerperium itself influence the course and outcome of the pregnancy. It is necessary to achieve eumetabolic status in these patients before pregnancy which should be maintained during the whole gestational period in order to lower the incidence of complications of the mother and her fetus. During the pregnancy the control of the feto-placental unit by all available means is recommended. Special care must be put on the control of the basic disease, particularly the dosage of TSH, total and free TH, in order to determine the optimal daily doses of thyroxine according to the clinical and laboratory parameters.

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