

# Maternal Euthyroid Hyperthyroxinemia May Reduce Preterm Birth Rate in Multiparous Women

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## Abstract

Hypothyroidism, defined as thyrotropin (TSH) above and free thyroxine (fT4) serum level below the reference range, as well as hyperthyroidism, defined as suppressed TSH and elevated thyroid hormones exceeding the upper limit of the reference range, may have major impacts on fertility and pregnancy outcome. Ideally, euthyroidism, defined as TSH and fT4 in the reference range, should be established and preserved during pregnancy prior to gestation. High estrogen levels during pregnancy stimulate the synthesis of maternal thyroxine-binding-globulin (TBG) in the liver, increasing TBG serum concentration by 2 - 3 fold compared to the initial value and affecting thus maternal fT4 serum level. As a consequence, maternal thyroid function adapts by increasing synthesis and secretion of thyroxine. TBG-induced elevation of serum thyroxine either total or free in the absence of hyperthyroidism is defined as euthyroid hyperthyroxinemia. Since TBG concentration declines first after delivery, pregnancy-induced euthyroid hyperthyroxinemia constitutes a physiological metabolic state. Depending on functional capacity, maternal thyroid may exhaust, resulting in hypothyroxinemia, which increases the risk of fetal neurodevelopmental impairment and preterm birth. The study aims to determine whether L-Thyroxine (L-T4) replacement, sustaining pregnancy-induced maternal euthyroid hyperthyroxinemia during the whole pregnancy by keeping fT4 level in the high normal reference range might reduce preterm birth rate. Preterm birth rate of women with singleton gestation and L-T4-induced high normal fT4 level constituting the study group (n = 918) was compared with the preterm birth rate of women with singleton gestation (n = 6414) who completed a questionnaire concerning L-T4 administration during pregnancy. Two groups were formed. In group A we compared the preterm

birth rate between women with L-T4-induced high normal fT4 level and a control group without L-T4 administration during pregnancy. In group B we compared the preterm birth rate of women already receiving L-T4 prior to conception, maintaining dosage to keep fT4 level in the high normal reference range during gestation to a control group with L-T4 intake during pregnancy. The preterm birth rates in group A declined by 51% ( $p = 0.01$ ) and in group B by 87% ( $p = 0.001$ ) in multiparous women, while in primiparous the preterm birth rate was similar between study and the control group. Sustaining a high normal fT4 level during pregnancy with L-T4 may significantly reduce preterm birth rate in multiparous women.

## Keywords

Preterm Birth, Euthyroid Hyperthyroxinemia, Thyroid, Pregnancy

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## 1. Introduction

Despite remarkable progress in perinatal medicine, preterm birth remains an unresolved obstetrical challenge with an estimated worldwide prevalence of 11% of all live-births, accounting for nearly 15 million babies born before 37 weeks of gestation. Over 50% of all neonatal deaths are due to prematurity and many survivors may have long-term adverse health deficits [1].

Preterm birth has multifactorial causes. These encompass advanced age or teenage pregnancy, parity, ethnicity, history of cervical cone biopsy, low as well as high body mass index, tobacco use, assisted conception with in vitro fertilization, and gamete intrafallopian transfer, especially for singleton gestations, systemic and genital-tract infection, and low parental socioeconomic status, being the most important factors [2] [3] [4] [5].

In the last decades numerous epidemiological studies suggest that maternal hypothyroxinemia during pregnancy increases the risk for delayed neurobehavioral development and cognitive function in childhood [6]. Pregnancy outcome, especially the risk of preterm birth, might also be jeopardized by maternal hypothyroxinemia, although most results from epidemiological studies are not unique and a clear interrelationship between maternal hypothyroxinemia and preterm birth is not well established [7]. Rather, no effect of maternal hypothyroxinemia in pregnancy outcome could be found in two recently published studies [8] [9].

The official recommendations concerning diagnosis and treatment of thyroid disease in USA and Europe vary. The American College of Obstetricians and Gynecologists does not recommend routine screening for thyroid disease in pregnancy. Even treatment of subclinical hypothyroidism is questioned because convincing data for adverse pregnancy outcome are lacking. The American Thyroid Association agrees with the exception that women with subclinical hypothyroidism associated with thyroid peroxidase antibody (TPO) positivity should be treated with L-T4. Finally, Endocrine Society Guidelines of 2011 al-

ready left the choice of treatment to the discretion of the caregiver [10] [11] [12].

The European Thyroid Association acknowledges that maternal hypothyroxinemia may impair neuropsychological development in the offspring. Therefore, universal thyroid screening is considered to be justified by the majority of authors, although it is stated that well controlled studies are lacking. They acknowledge that subclinical hypothyroidism and isolated hypothyroxinemia detected in the first trimester should be treated with L-T4 to avoid neuropsychological impairment in children and adverse pregnancy outcome [13].

In 2011, we demonstrated a lower preterm birth rate in multiparous women by keeping maternal fT4 serum level with L-T4 in the high normal reference range [14]. The aim of this study is to confirm our previously published results by expanding the former study population and comparing the preterm birth rate with a control group with known administration of L-T4 during pregnancy. Considering emerging concerns, we additionally analyzed the potential relationship between high-normal maternal fT4 levels in early pregnancy and increased risk for small gestational age (SGA) newborns [15] [16].

## 2. Subjects and Methods

This clinical trial is a retrospective nonrandomized observational study with prospectively designed data. All pregnant women below 12 weeks of gestation presenting for their first medical consultation for prenatal care in a medical office in Southern Germany were offered a serological thyroid scan. An early ultrasound of the crown-rump length was used to correct gestational age when the difference using the last menstrual period was equal to or greater than 7 days. The serological thyroid scan included basal TSH, free triiodothyronine (fT3), free thyroxine (fT4) and thyroid antibodies. Thyroid antibodies were not further considered for this study evaluation. To all pregnant women with fT4 values below the upper third of the reference range (high normal values), L-T4 was prescribed with the intention to keep fT4 levels in the upper third of the reference range (high normal values) until delivery. If fT4 values were found to be in the upper third of the reference range L-T4 was not administered until the values began to decline. Maternal fT4 serum levels were regularly assessed after an interval of 24 hours from the last L-T4 intake every 4 weeks during routinely performed serological scans for pregnancy care and if necessary, the L-T4 dose was adjusted. Additionally, each woman ingested supplements containing 150 or 200 µg iodide and 400 µg folic acid. Preterm birth was defined as delivery before completed 37 weeks of gestation. Overall, 918 pregnant women with singleton gestation, 383 primiparous and 535 multiparous were included in the study group covering a time span from august 2001 until December 2015. The control group encompassed 6414 pregnant women with singleton gestation, 4338 primiparous and 2076 multiparous from the “Baby Care” surveillance program who had completed a questionnaire about preterm birth risks, daily nutrition, and medication intake during pregnancy with particular consideration of L-T4 administration.

“Baby Care” is a written advisory program for early detection of pregnancy risks with special emphasis on preterm birth. Based on a questionnaire, all relevant risk factors for preterm birth are inquired. It includes further individual counseling with respect to medication in pregnancy, specific personal recommendations to reduce preterm birth risks and a 7-day food record of the German Society for Nutrition to determine the individual intake of micronutrients. Since 2000, this voluntary program is available by gynecological offices and health insurance companies throughout Germany with a database of more than 60.000 participants.

In our previously published study [14], the preterm birth lowering effect of induced high normal fT4 serum levels with L-T4 was only prevalent in multiparous women. To rule out heterogeneity of the risk factors and to avoid possible selection, we first compared the odds ratios of preterm birth risks in a sample of multiparous of the study and control groups. From the n = 535 multiparous women in the study group, n = 60 (11%) had also completed the “Baby Care” questionnaire. This sample was compared with a sample n = 243 of participants of the “Baby Care” program who completed the questionnaire from the same regional origin in South Germany (Table 1).

**Table 1.** Comparison of the prevalence of risk factors for preterm birth between study group and control group from the same regional origin in South Germany.

	Study group	Control group	Odds ratio	CI (95%)
<b>Risk factors of preterm birth</b>	<b>n = 60</b>	<b>n = 243</b>		
Low and middle school education status	88.3%	60.2%	5.01	2.19 - 11.49
Thyroid disease in last 12 months	23.3%	9.1%	3.06	1.46 - 6.42
Smoking at diagnosis of pregnancy	27.6%	13.5%	2.45	1.23 - 4.87
Diabetes in last 12 months	1.7%	0.4%	4.10	0.25 - 66.55
Hypertension in last 12 months	5.0%	3.3%	1.55	0.40 - 6.01
Hospital admission(s) in last 12 months	21.7%	17.7%	1.29	0.64 - 2.58
Body mass index ( $\geq 25$ , $< 25$ )	28.3%	25.5%	1.15	0.61 - 2.17
Gynecological surgery ever	44.0%	41.2%	1.12	0.60 - 2.09
Former preterm birth	13.3%	12.4%	1.08	0.47 - 2.50
Self-assessed health status	25.0%	24.5%	1.03	0.53 - 1.98
Psychological Stress	32.1%	33.6%	0.94	0.50 - 1.75
Vaginal infection(s) in last 12 months	11.1%	12.5%	0.88	0.09 - 8.56
Former miscarriage(s)	25.0%	32.1%	0.71	0.37 - 1.34
Further complications in former pregnancies	40.0%	50.4%	0.66	0.37 - 1.16
Age $\geq 30$ years/ $< 30$ years	71.7%	81.5%	0.57	0.30 - 1.10
Former induced abortion	6.7%	11.1%	0.57	0.19 - 1.70
Fertility treatment	8.3%	27.7%	0.24	0.09 - 0.62

CI = Confidence interval.

With regard to lower school qualification, smoking habits and thyroid disease, **Table 1** indicates a significantly higher prevalence in the study group compared to the control group, while the prevalence of the other risk factors did not differ. According to a meta-analysis, smoking is a relevant risk factor for preterm birth with a calculated odds-ratio of 1.27 (1.21 - 1.33), as well as low education level with an odds-ratio up to 1.4 [17] [18]. Thus, the study group had higher prevalence of risk factors for preterm birth in multiparous women.

To compare the preterm birth rates in the study and control group, two collectives were formed. In group A we compared the preterm birth rate between women with L-T4-induced high normal fT4 level and a control group without L-T4 administration during pregnancy. In group B we compared the preterm birth rate of women already receiving L-T4 prior to conception, maintaining dosage to keep fT4 level in the high normal reference range during gestation to a control group with L-T4 intake during pregnancy.

Group A encompassed in the study group 615 pregnant women, 240 primiparous and 375 multiparous. Those women who did not ingest L-T4 prior to gestation were prescribed L-T4 to keep the fT4 level in the high normal reference range (upper third). If these women had preexisting high normal fT4 levels, L-T4 was first started when levels began to decline. The control group consisted of 5579 pregnant women, 3781 primiparous and 1798 multiparous without L-T4 administration during pregnancy.

Group B consisted in the study group of 303 pregnant women, 143 primiparous and 160 multiparous. These women were already taking L-T4 prior to conception. The administration of L-T4 was continued but if fT4 was not in the high normal reference range (upper third) the dose was increased in order to elevate maternal fT4 serum levels in the high normal reference range. The control group encompassed 835 pregnant women, 557 primiparous and 278 multiparous who according to the questionnaire had administered L-T4 during gestation. **Table 2** indicates the study group A and B by mean age, parity status and induced high normal fT4 levels.

We further examined whether induced maternal high normal fT4 levels with L-T4 might increase the prevalence of SGA newborns. SGA was defined as a birth weight below the 5<sup>th</sup> percentile for gestational age.

The study was approved by the Ethics Commission of the National Medical Association of Baden-Wuerttemberg, Germany.

**Table 2.** Overview of the study group A and control group B.

Group A				Group B			
Primiparous		Multiparous		Primiparous		Multiparous	
Study*	Control	Study*	Control	Study*	Control	Study*	Control
n = 240	n = 3781	n = 375	n = 1798	n = 143	n = 557	n = 160	n = 278
Ma ± SD	Ma ± SD	Ma ± SD	Ma ± SD	Ma ± SD	Ma ± SD	Ma ± SD	Ma ± SD
28.3 ± 5.1	30.6 ± 4.1	30.6 ± 4.1	32.4 ± 4.3	30.3 ± 4.6	31.7 ± 3.9	32.8 ± 5.0	33.4 ± 4.3

\* = fT4 in the high normal reference range (upper third), Ma ± SD = Mean age ± Standard deviation.

### Laboratory Analysis

Serum basal TSH and fT4 were measured using a third-generation electrochemiluminescence immunoassay (Elecsys 1010/2010–MODULAR ANALYTICS E170 from Roche Diagnostics GmbH–Mannheim, Germany). Between 2001 and 2010, trimester specific reference values for TSH and fT4 were not available, so the reference range for non-pregnant women was used as recommended [11]. Reference values for TSH were 0.27 - 4.2  $\mu\text{U/ml}$  and for fT4 12.14 - 19.62 pmol/l. Intra- and inter-assay coefficients of variation were 3.0% and 7.2% for TSH, and 1.4% and 3.5% for fT4. From 2011 to 2015 trimester specific reference ranges for TSH and fT4 were used. The TSH reference range for the first trimester was 0.1 - 2.5  $\mu\text{U/ml}$ , for the second trimester it was 0.2 - 3.0  $\mu\text{U/ml}$  and for the third trimester it was 0.3 - 3.0 - 3.5  $\mu\text{U/ml}$ . The reference range for fT4 in the first trimester was 11.6 - 19.3 pmol/l, in the second trimester 9.0 - 16.7 pmol/l and in the third trimester 9.0 - 15.4 pmol/l.

### Statistical analysis

We compared treated women and controls in group A as well as group B separately for primiparous and multiparous. Since number and distribution regarding age were different between cases and controls in these groups, a weighting adjustment was performed and preterm birth rates were evaluated by means of the Chi-Square test with a p-value < 0.05 considered as statistical significant.

## 3. Results

In group A the preterm birth rate for primiparous in the study group was 9.3% versus 7.3% in the control group indicating no statistical difference ( $p = 0.16$ ). For multiparous, the preterm birth rate in the study group was 3.4% versus 7.0% in control group, resulting in a reduction of 51%, which is highly significant (Table 3).

In group B the preterm birth rate for primiparous in the study group was 5.6% versus 10.2% in the control group. This is a reduction by 45%, however not yet significant ( $p = 0.08$ ). For multiparous, the preterm birth rate in the study group was 1.2% versus 9.4% in the control group, resulting in a highly significant reduction by 87% (Table 4).

To keep maternal fT4 serum levels in the high normal reference range in group A, the following L-T4 doses indicated by mean  $\pm$  SD and [median] were administered. During first, second and third trimester the L-T4 dose was 39  $\mu\text{g} \pm 48.6 \mu\text{g}$  [0], 107.8  $\mu\text{g} \pm 51.7 \mu\text{g}$  [100  $\mu\text{g}$ ] and 152.4  $\mu\text{g} \pm 54.18 \mu\text{g}$  [150  $\mu\text{g}$ ], respectively. The corresponding TSH readings indicated by mean  $\pm$  SD and [median]

**Table 3.** Comparison of preterm birth rates in group A.

	Primiparous	Multiparous
Study group* (n = 615)	9.3%	3.4%
Control group (n = 5579)	7.3%	7.0%
Significance $p < 0.05$	$p = 0.16$	$p = 0.01$

\* = fT4 in the high normal reference range (upper third).

**Table 4.** Comparison of preterm birth rates in group B.

	Primiparous	Multiparous
<b>Study group* (n = 303)</b>	5.6%	1.2%
<b>Control group (n = 835)</b>	10.2%	9.4%
<b>Significance p &lt; 0.05</b>	p = 0.08	p = 0.001

\* = fT4 in the high normal reference range (upper third).

were 1.43  $\mu\text{U/ml} \pm 1.5 \mu\text{U/ml}$  [1.25  $\mu\text{U/ml}$ ], 0.48  $\mu\text{U/ml} \pm 0.64 \mu\text{U/ml}$  [0.12  $\mu\text{U/ml}$ ] and 0.32  $\mu\text{U/ml} \pm 0.63 \mu\text{U/ml}$  [0.05  $\mu\text{U/ml}$ ], respectively. The corresponding fT4 readings indicated by mean  $\pm$  SD and [median] were 16.1 pmol/l  $\pm$  2.7 pmol/l [15.7 pmol/l], 16.0 pmol/l  $\pm$  3.5 pmol/l [15.7 pmol/l] and 16.7 pmol/l  $\pm$  3.1 pmol/l [16.7 pmol/l], respectively (**Table 5**).

As indicated in **Table 5**, only during the third trimester median fT4 readings exceeded the upper limit of the reference range, but TSH was in most cases lower than the lower limit of the reference range, suggesting biochemical subclinical hyperthyroidism.

For group B, the following L-T4 doses indicated by mean  $\pm$  SD and [median] were administered. During first, second and third trimester the L-T4 dose was 89.6  $\mu\text{g} \pm 47.1 \mu\text{g}$  [100  $\mu\text{g}$ ], 130.9  $\mu\text{g} \pm 52.3 \mu\text{g}$  [150  $\mu\text{g}$ ] and 167.5  $\mu\text{g} \pm 54.4 \mu\text{g}$  [150  $\mu\text{g}$ ], respectively. The corresponding TSH readings indicated by mean  $\pm$  SD and [median] were 0.82  $\mu\text{U/ml} \pm 1.29 \mu\text{U/ml}$  [0.36  $\mu\text{U/ml}$ ], 0.42  $\mu\text{U/ml} \pm 1.87 \mu\text{U/ml}$  [0.05  $\mu\text{U/ml}$ ] and 0.21  $\mu\text{U/ml} \pm 0.43 \mu\text{U/ml}$  [0.05  $\mu\text{U/ml}$ ], respectively. The corresponding fT4 readings indicated by mean  $\pm$  SD and [median] were 18.3 pmol/l  $\pm$  4.0 pmol/l [17.6 pmol/l], 16.6 pmol/l  $\pm$  2.7 pmol/l [16.5 pmol/l] and 17.2 pmol/l  $\pm$  2.8 pmol/l [17.0 pmol/l], respectively (**Table 6**).

Median fT4 reading during the third trimester only slightly exceeded the upper limit of the reference range but again in group B TSH was mostly lower than the lower end of reference range, suggesting biochemical subclinical hyperthyroidism as well.

Due to the impaired thyroid function of the women in study group B a higher

**Table 5.** Thyroid parameters TSH and fT4 related to L-T4 doses in the study group A (n = 615).

	TSH	fT4	L-T4 -dose
<b>1. Trimester</b>	<b>RR: 0.1 - 2.5 <math>\mu\text{U/ml}</math></b>	<b>RR: 11.6 - 19.3 pmol/l</b>	
<b>Until 12. weeks</b>	(n = 488)	(n = 959)	(n = 957)
<b>Mean + SD [Median]</b>	1.43 $\pm$ 1.5 [1.25]	16.1 $\pm$ 2.7 [15.7]	39.0 $\pm$ 48.6 $\mu\text{g}$ [0]
<b>2. Trimester</b>	<b>RR: 0.2 - 3.0 <math>\mu\text{U/ml}</math></b>	<b>RR: 9.0 - 16.7 pmol/l</b>	
<b>Between 13.-28. weeks</b>	(n = 513)	(n = 2076)	(n = 2076)
<b>Mean + SD [Median]</b>	0.48 $\pm$ 0.64 [0.12]	16.0 $\pm$ 3.5 [15.7]	107.8 $\pm$ 51.7 $\mu\text{g}$ [100 $\mu\text{g}$ ]
<b>3. Trimester</b>	<b>RR: 0.3 - 3.0 - 3.5 <math>\mu\text{U/ml}</math></b>	<b>RR: 9.0 - 15.4 pmol/l</b>	
<b>Over &gt; 29. weeks</b>	(n = 310)	(n = 1134)	(n = 1333)
<b>Mean + SD [Median]</b>	0.32 $\pm$ 0.63 [0.05]	16.7 $\pm$ 3.1 [16.7]	152.4 $\pm$ 54.18 $\mu\text{g}$ [150 $\mu\text{g}$ ]

n = number of readings, RR = pregnancy specific reference range, SD = standard deviation.



**Table 6.** Thyroid parameters TSH and fT4 related to L-T4 doses in the study group B (n = 303).

	TSH	fT4	L-T4 -dose
<b>1. Trimester</b>	<b>RR: 0.1 - 2.5 <math>\mu</math>U/ml</b>	<b>RR: 11.6 - 19.3 pmol/l</b>	
<b>Until 12. weeks</b>	(n = 216)	(n = 534)	(n = 533)
<b>Mean + SD [Median]</b>	0.82 $\pm$ 1.29 [0.36]	18.3 $\pm$ 4.0 [17.6]	89.6 $\pm$ 47.1 $\mu$ g [100 $\mu$ g]
<b>2. Trimester</b>	<b>RR: 0.2 - 3.0 <math>\mu</math>U/ml</b>	<b>RR: 9.0 - 16.7 pmol/l</b>	
<b>Between 13.-28. weeks</b>	(n = 351)	(n = 1083)	(n = 1084)
<b>Mean + SD [Median]</b>	0.42 $\pm$ 1.87 [0.05]	16.6 $\pm$ 2.7 [16.5]	130.9 $\pm$ 52.3 $\mu$ g [150 $\mu$ g]
<b>3. Trimester</b>	<b>RR: 0.3 - 3.0 - 3.5 <math>\mu</math>U/ml</b>	<b>RR: 9.0 - 15.4 pmol/l</b>	
<b>Over &gt; 29. weeks</b>	(n = 198)	(n = 577)	(n = 577)
<b>Mean + SD [Median]</b>	0.21 $\pm$ 0.43 [0.05]	17.2 $\pm$ 2.8 [17.0]	167.5 $\pm$ 54.4 $\mu$ g [150 $\mu$ g]

n = number of readings, RR = pregnancy specific reference range, SD = standard deviation.

L-T4 dose was needed to increase fT4 serum level towards the high normal reference range during the first trimester, 89.6  $\pm$  47.1  $\mu$ g versus 39.0  $\pm$  48.6  $\mu$ g and became similar to group A during the second and third trimester (Table 5, Table 6). In both groups, TSH readings were very low and fT4, as intended, high, indicating in both groups biochemical subclinical hyperthyroidism. Major influence factors for biochemical hyperthyroidism were frequently disregarded interval between the last L-T4 ingestion and TSH reading, which should be ideally 24 hours before blood drawing and an insufficiently short period of 4 weeks for establishing a new steady-state between peripheral fT4 serum level and the hypothalamus-pituitary axis which affects TSH levels. Nevertheless, L-T4 was generally tolerated very well, without any signs of maternal or fetal hyperthyroidism. Maternal side effects such as palpitations occurred sporadically and resolved by reducing the L-T4 dose. Fetal signs of induced hyperthyroidism controlled by ultrasound check and cardiotocography never occurred.

Concerning the rate of newborns with SGA in the study groups it was 5.5% versus 5.0% (p = 0.4) in control groups, and thus not significantly different.

#### 4. Discussion

The present observational investigation confirms our previous data that L-T4, administered to keep maternal fT4 serum levels in the upper third of the reference ranges, which is high normal during pregnancy, may effectively and safely reduce preterm birth rate in multiparous women, and this applies in particular to women who were already taking L-T4 prior to conception. Regarding our published data in 2011, the presented results suggest that the preterm birth lowering effects of high normal fT4 seem to be independent of the use of trimester specific reference ranges [14]. Our data did not confirm an association between high normal maternal fT4 serum levels and an increased risk for SGA newborns. This is in accordance with a newly published meta-analysis [16].

In two recently performed randomized trials, which aimed to treat pregnant women with L-T4 suffering from subclinical hypothyroidism or hypothyrox-



inemia to improve cognitive function of the offspring, no effect on preterm birth rate was observed. As mentioned by the authors, both studies have the limitation that they started too late in gestation with L-T4 treatment. L-T4 was administered after the first trimester at a median gestational age of 13 weeks 3 days in one and at 16 weeks 4 days and 18 weeks in the other study. Furthermore, both studies had only the intention to establish euthyroidism by keeping TSH in the low normal or normal and fT4 in the reference range. It was not considered that pregnancy induces physiological euthyroid hyperthyroxinemia and that fT4 can be safely held in the high normal reference range without impairing maternal or fetal health [8] [9].

High pregnancy estrogen levels selectively induce maternal and fetal serum TBG synthesis in the liver while the other two thyroxine binding proteins, transthyretin (TTR) and albumin, remain unchanged or decline with only minimal effects on fT4 concentration. Maternal TBG concentration increases by 2 - 3 fold compared to the initial value and by increased sialic acid content, TBG serum half-life is prolonged, resulting in TBG excess. At mid-gestation, maternal TBG concentration reaches a plateau, remaining nearly unchanged until term and declining only after parturition. This physiological changeover in maternal serum might presumably be the most important impact for thyroid function during gestation [19] [20].

As a consequence, maternal thyroid function has to adapt, since any change in the affinity or capacity of plasma binding proteins will alter the relationship between circulating total and free hormones. A decreased fT4 level by increased TBG binding triggers normal pituitary-thyroid axis to maintain the appropriate free hormone concentration and stimulates thyroid hormone synthesis and secretion. Since TBG has a 20 fold greater affinity to T4 than to T3, high TBG levels affect serum fT4 more than serum fT3. The T3 and fT3 serum levels remain stable or decline during pregnancy [21]. Of the three binding proteins, TBG has the highest affinity to T4 which is not modified by pregnancy, and it carries the highest proportion of T4 [19] [20].

In the fetus, TBG is the main T4 binding protein, since concentration of TTR and albumin is low. TBG synthesis increases rapidly up to 24 weeks of gestation, and correlates with the crown-rump length. By 24 weeks of gestation more than 83% of T4 is bound to TBG, which is much higher than in non-pregnant women [22] [23]. Between 24 weeks and term, TBG concentration reaches adult levels, tripling the TBG capacity during this period [24] [25].

TBG-induced elevation of serum T4, either total or free, in the absence of hyperthyroidism, concomitant with low, normal or high levels of T3 is defined as euthyroid hyperthyroxinemia and TBG excess is the most common cause of hyperthyroxinemia, naturally occurring during pregnancy [26] [27]. Because TBG concentration declines only after delivery, pregnancy-induced maternal euthyroid hyperthyroxinemia seems to be a physiological metabolic state. Consequently, a decline in maternal fT4 serum level with advancing pregnancy might be a sign of thyroid function exhaustion which leads to progressive TBG

desaturation with persistent high TBG concentration [19].

To achieve the higher T4 demand, maternal thyroid is stimulated by human chorionic gonadotropin (hCG) which has thyrotropic activity during the first trimester. The stimulatory effect of TSH and hCG on maternal thyroid differ significantly from each other. While TSH promotes preferentially T3 synthesis and secretion, hCG preferentially induces the release of T4 in high quantities leading in general to TSH suppression and therefore inhibiting further thyroidal T3 secretion [20] [28] [29] [30]. HCG can override the hypothalamic-pituitary-thyroid feedback system, forcing maternal thyroid to synthesize and secrete high quantities of T4, accompanied by low or suppressed TSH and normal fT3 [25] [26] [27] [31] [32] [33].

Maternal thyroid adaptation is often associated with transitory subclinical hyperthyroidism, which is exclusively defined on laboratory findings, not on clinical complaints. Typical readings are subnormal TSH levels and free thyroid hormones fT3 and fT4 in the mid-to-high reference range [34]. During the first trimester the lower end of the reference range for TSH is poorly defined. TSH values below the classical lower limit of 0.4  $\mu$ IU/ml and in a small percentage even suppressed below <0.01  $\mu$ IU/ml still represent a normal pregnancy, not indicating subclinical hyperthyroidism. Therefore, and based on studies that did not demonstrate maternal or neonatal complications with subclinical hyperthyroidism [35], some authors advocate that it might be reasonable to assume that TSH suppression can be safely maintained throughout pregnancy [11] [20] [36]. Even hCG-induced gestational transient thyrotoxicosis (GTT) is without unfavorable effects on pregnancy outcome [20] [36] [37] [38].

L-T4 substitution causes hyperthyroxinemia as well without simultaneously increasing fT3 levels, which usually remain in lower end of the reference range because thyroidal T3 secretion is inhibited by decreased or suppressed TSH [39] [40]. When L-T4 is ingested, the peripheral conversion to T3 is accomplished by autoregulation of 5'-deiodination (D1). Depending on the L-T4 dose D1 may produce T3 or more metabolic inactive reverse-T3 (rT3), when serum T4 concentration is elevated. Additionally, by renal and hepatic sulfation, higher L-T4 doses can be rapidly inactivated. Therefore, L-T4-induced hyperthyroxinemia concomitant with suppressed TSH does not necessarily indicate excessive dose ingestion, although biochemical signs for subclinical hyperthyroidism may be apparent [26] [41] [42].

Transplacental passage of maternal thyroid hormones is controlled by placental type 3 deiodinase (D3) which inactivates T3 over T4 with preference for T3 [43] [44]. Human tracer kinetic studies indicate that during pregnancy D3 inactivates 80% of daily thyroid hormone production, either as T4 or T3. However, it seems evident that transplacental passage of T4 can only be assured by binding to placental TTR, which reduces exposure to D3 to be inactivated [21]. Since the affinity of TTR for T4 is 4 fold higher than for T3 in humans, maternal T3 may be fully subject to the deactivating activity of D3 and even in high concentration cannot cross the placental barrier. Placental TTR binding of T4 contributes es-

essentially to the preferential transmission of maternal T4 over T3 to the fetus [45] [46] [47].

Beside the placenta, fetal tissues, as well as liver, cerebral cortex and the epithelial structures of the embryonic lung, intestine, skin, and urinary tract also express D3. Similar to the uteroplacental unit, fetal D3 activity regulates the transfer of maternal thyroid hormones. The deactivating efficiency prevents fetal hyperthyroidism even when high doses of L-T4 are introduced into amniotic fluid [48] [49] [50].

Our study shows a considerable and significant reduction of the preterm birth rate for multiparous women by induced high normal fT4 level with L-T4. Nevertheless, there might be some assumption that the study group may be selected towards reduced risks of preterm birth. To avoid this assumption, a comparison of preterm birth risks between the study and control groups was performed. With regard to the established risk factors for preterm birth, namely lower school qualification, smoking habits and thyroid disease, the prevalence in the study group was significantly higher than in the control group while all other important risk factors do not significantly differ. Therefore, the preterm birth rate should be even higher in the study group compared to the control group underscoring the preterm birth lowering effect of induced high normal fT4 serum level with L-T4. However, a limitation is the retrospective approach and the restriction of analyses on a few causes for preterm birth, knowing the multifactorial background of this pregnancy complication. Therefore, we cannot exclude the possibility that our results may be subject to other aspects not considered that could also reduce preterm birth rate in multiparous women. The relationship between maternal high normal fT4 level and a possible reduction of preterm birth rate in multiparous women has never been reported before.

## 5. Summary

Based on estrogen-induced TBG excess, maternal euthyroid hyperthyroxinemia is the physiological adaptation to higher metabolic demand during pregnancy. Declining maternal fT4 serum levels are a sign of thyroid exhaustion and may be associated with adverse pregnancy outcome, especially preterm birth in multiparous women. High maternal fT4 serum levels, either endogenously synthesized or exogenously caused by administration of L-T4 are harmless for both mother and fetus and may be associated with a considerably reduced preterm birth rate in multiparous women. This applies in particular to women who are already taking L-T4 prior to conception. L-T4, one of the most widely prescribed drugs, has a safe latitude and is well tolerated during gestation. Keeping maternal fT4 in the upper third of reference range or high normal is easy to manage, harmless, and may be effective to reduce preterm birth rate in multiparous women.

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### Conflict of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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