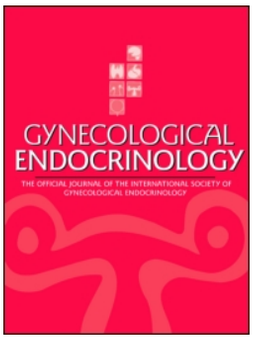

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HYPOTHYROIDISM IN PRE-ECLAMPSIA

D2-Thr92Ala, thyroid hormone levels and biochemical hypothyroidism in preeclampsia

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Abstract

Aim: To identify if there is a relationship between the deiodinase *D2-Thr92Ala* genetic variant, thyroid hormone levels and biochemical hypothyroidism in preeclampsia.
Materials and methods: We genotyped 125 women with preeclampsia and 131 normal pregnant women using PCR-RFLP. Serum thyroid hormone levels were determined using ELISA.
Results: Our study showed higher TSH and FT4 levels and lower FT3 levels in women with preeclampsia compared to normal pregnant women, with statistical significance for women with mild and severe preeclampsia. The risk to develop pregnancy-induced hypertension (PIH), mild or severe preeclampsia was increased in carriers of at least one *D2-Ala92* allele. TSH and FT4 levels were significantly higher and FT3 levels were significantly lower in preeclamptic women with severe preeclampsia if they carried the *D2-Ala*92 allele compared to non-carriers. Pregnant women with PIH and mild preeclampsia, carriers of at least one *D2-Ala92* allele, delivered at lower gestational age neonates with a lower birth weight compared to non-carriers, but the results were statistically significant only in severe preeclampsia.
Conclusion: The *D2-Thr92Ala* genetic variant is associated with the severity and the obstetric outcome of preeclampsia, and it also influences thyroid hormone levels. The study demonstrates non-thyroidal biochemical hypothyroidism – as a result of deiodination effects due to D2 genotypes.

Keywords

Biochemical hypothyroidism, D2 genotypes, genetic and biochemical evaluation, preeclampsia, thyroid hormones levels

History

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Introduction

The thyroid gland produces two hormones, triiodothyronine (T3) and thyroxine (T4) [1]. The synthesis of these thyroid hormones starts with thyroxine and requires the presence of iodine in different foods or water. T3 and T4 are released in the blood as FT4 and FT3 and are transported by thyreoglobulin. T4 can be converted to T3, which means that T4 is a reservoir for T3, and the conversion of T4 to T3 represents an important step in the maintenance of circulating T3 levels [2]. They bind to nuclear receptors and have a role in brain and tissue development, regulating protein, carbohydrate and lipid metabolism [1].

The synthesis of thyroid hormones is regulated by the intervention of the hypothalamus and pituitary gland via TRH and TSH. The highest quantity of T3 in the circulation (~89%) is produced outside the thyroid gland through the deiodination of T4 by two deiodinases, D1 and D2 [1,3,4].

Deiodinases are enzymes that contain selenium in their active center, implicated in the conversion of thyroxine (T4) to triiodothyronine (T3) [1,3,5]. D2 deiodinase is responsible for T4 to T3 conversion in the brain, myocardium, skeletal muscle, brown fat tissue, pituitary, thyroid, heart and placenta [1].

The presence of genetic variations in genes encoding deiodinases can influence thyroid hormone metabolism and bioactivity. One of these genetic variations, a missense mutation, *Thr92Ala*, located in the D2 deiodinase gene (chr 14q24.2-q24.3), is a single base pair substitution, Thr with Ala in nucleotide 92 of the D2 gene, associated with reduced tissue D2 activity. This results in lower T3 levels. This polymorphism is known to be associated with arterial hypertension [6,7,8].

Normal pregnancy involves physiological changes of thyroid hormone levels with altered thyroid function. Approximately 2.5% of women had TSH values higher than 6 μU/ml, while ~0.4% of women had TSH levels higher than 10 μU/ml. However, there is little information regarding thyroid function in obstetrical complications such as preeclampsia [9].

Given the D2 role in T4 to T3 conversion and also in TSH regulation, the objectives of our study were: (1) To investigate the biochemical and genetic thyroid status in preeclampsia compared to normal pregnancy by determining serum TSH, FT4 and FT3 levels and also, by determining D2 genotypes in both women with different types of preeclampsia and women with normal pregnancy. (2) To establish if there is a relationship between this genetic variant and the severity of preeclampsia, as well as its influence on prognosis and hormone profile. (3) To demonstrate the development of non-thyroidal biochemical hypothyroidism as a result of deiodination effects.

Materials and methods

Materials

In this study, we included women diagnosed with preeclampsia in the Department of Obstetrics and Gynecology, Clinic I.

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We investigated 125 women with preeclampsia and 131 normal pregnant women. Women with preeclampsia were divided into 36 (28.8%) women with pregnancy-induced hypertension (PIH), 57 (45.6%) women with mild preeclampsia and 32 (25.6%) women with severe preeclampsia. The diagnostic criteria were as follows: PIH – systolic and diastolic blood pressure higher than 140 mmHg/90 mmHg, but lower than 160 mmHg/110 mmHg, in the absence of proteinuria; mild preeclampsia – systolic and diastolic blood pressure higher than 160 mmHg/110 mmHg and proteinuria higher than 300 mg/24 h collection. Severe preeclampsia – systolic blood pressure and diastolic blood pressure higher than 160 mmHg/110 mmHg and proteinuria higher than 500 mg/24 h collection. Also, women with severe preeclampsia had one of the following symptoms: thrombocytopenia, oliguria, severe fetal growth restriction, cyanosis [10]. The exclusion criteria were: chronic hypertension, liver, kidney, thyroid or other metabolic diseases, thyroid medication. Normal pregnant women had a gestational age at delivery of more than 35 weeks. All the included pregnant women had singleton pregnancies. Maternal complications were: eclampsia (0.9%) and HELLP (3.2%). In preeclampsia group, fetal complications included: intrauterine growth restriction – IUGR (30.4%), intrauterine death (3.2%), fetal distress (17.6%). 43.2% of the neonates had a birth weight lower than 2500 g. Also, 28% of the neonates had an Apgar score less than 7.

The study was approved by our local Ethics Committee and was conducted in the Medical Biochemistry Department, University of Medicine of Cluj. The selection of patients and controls was done in the Department of Gynecology, Clinic I.

Methods

In order to identify the *D2-Thr92Ala* genotypes, we used PCR-RLFP analysis. We collected 2 ml blood on EDTA and we isolated the DNA from leukocytes using an extraction kit from ZYMO RESEARCH. The PCR conditions were as follows: 20 ng genomic DNA were amplified in 25 µl using 0.2 µM each primers (forward primer: 5′-GATAGTAAAGAATAACAGCCTTGGCT-3′, and reverse primer 5′-CAGCTATCTTCTCCTGGATACCA-3′), 2.0 mM $MgCl_2$, 200 nM dNTPs and *2U Taq polymerase*. In order to amplify a 395 bp fragment, we used an iCycler (BIORAD) and the following programs: initial denaturation at 95 °C for 10 min, 34 cycles of denaturation at 95 °C for 10 s, primer annealing at 60 °C for 20 s, primer elongation at 72 °C for 20 s and a final extension of the primers at 72 °C for 5 min. After PCR amplification, 5 µl of PCR were digested in 10 µl mixture containing 5U *RsaI* restriction enzyme. The digested mixture was incubated at 37 °C for 3 h. The digested profile was examined in 3% agarose gel electrophoresis stained with ethidium bromide solution. The wild type *D2-Thr92* allele yielded an undigested fragment of 395 bp, while the variant *D2-Ala92* allele yielded 330 bp and 65 bp fragments (Figure 1-Supplemental file) [11]. All the reagents were from Fermentas (Thermo Fischer Scientific, USA), except for primers, which were provided by Eurogentec (Kanela Corporation, Japan).

In order to determine serum thyroid hormone (TSH, FT4, FT3) levels, we used ELISA methods. The ELISA kit was from Adaltis Italia SPA. The normal range for thyroid hormones was: TSH: 0.4–4.5 µU/ml, FT3: 1.8–4.2 pg/ml, FT4: 0.76–2.24 ng/dl.

Statistical analysis

FT3, FT4, TSH levels were presented as mean ± SD and the comparison between the groups of women with preeclampsia and normal pregnant women was made using the Student's *t*-test. Allele and genotype frequencies were calculated and comparisons were performed using the $\chi 2$ test. We also calculated the odds ratio (OR) and 95%CI. We considered statistical significance for *p* values less than 0.05. All analyses were done using the SPSS 17.0 (Chicago, IL).

Results

In this study, we investigated 125 pregnant women diagnosed with different types of preeclampsia, mean age 29.07 ± 5.04 years, and 131 normal pregnant women, mean age 28.41 ± 4.67 years. The mean gestational age was 34.72 ± 4.28 weeks ($p < 0.001$) in women with preeclampsia compared to 38.79 ± 1.61 weeks for normal pregnant women. Birth weight was 2665.155 ± 987.239 g ($p < 0.001$) in newborns with preeclamptic mothers and 3299.83 ± 341.386 g in newborns with normal pregnant mothers. Preeclamptic women had mean TSH, FT4 and FT3 levels of 3.51 ± 2.42 µU/ml ($p < 0.001$), 1.26 ± 0.61 ng/dl ($p < 0.001$) and 2.48 ± 0.86 pg/ml ($p = 0.001$) compared to normal pregnant women, who had mean TSH, FT4 and FT3 levels of 2.34 ± 1.5914 µU/ml, 0.97 ± 0.29 ng/dl and 2.65 ± 0.63 pg/ml, respectively. The distribution of TSH, FT4 and FT3 levels in all preeclampsia groups compared to the normal pregnant group is presented in Table 1. We mention that the mean range for TSH, FT4 and FT3 levels was within the normal laboratory reference ranges in the preeclampsia group and also in the normal pregnant group. In the preeclampsia group, women with TSH levels higher than 4 µU/ml delivered neonates with a mean birth weight of 2275.24 ± 837.26 g ($p = 0.002$), while women with TSH levels lower than 4 µU/ml delivered neonates with a birth weight of 2784.69 ± 911.37 g.

The frequencies of heterozygous *D2-Thr92/Ala92* and homozygous *D2-Ala92/Ala92* genotypes in preeclampsia compared to normal pregnancy were: 40.8% versus 22.1% and 36% versus 12.2%, respectively. Women carriers of at least one *D2-Ala92* allele had a 6.33-fold ($p < 0.001$) increased risk to develop preeclampsia. The distribution of *D2-Thr92Ala* genotypes and the risk to develop different types of preeclampsia in carriers of at least one *D2-Ala92* allele and also in homozygous carriers of *D2-Ala92/Ala92* genotypes are presented in Table 2.

Looking at the influence of D2 genotypes on thyroid hormone levels, we found that TSH levels were 3.7 ± 2.49 µU/ml ($p < 0.001$) in preeclamptic women carriers of at least one *D2-Ala92* allele compared to 2.03 ± 1.75 µU/ml in non-carriers. Also, FT4 and FT3 levels were 1.26 ± 0.61 ng/dl versus 1.23 ± 0.59 ng/dl (p = NS) and 2.46 ± 0.9 pg/ml versus 2.67 ± 0.44 pg/ml (p = NS), respectively, in carriers of at least one *D2-Ala92* allele compared to non-carriers. The influence of *D2-Thr92Ala* genotypes on thyroid hormone levels (TSH, FT4 and FT3) is shown in Table 3.

The influence of *D2-Thr92Ala* genotypes on pregnancy outcome (gestational age at delivery and birth weight) is shown in Table 3.

Discussion

Hypertension is one of the most important complications of pregnancy. Preeclampsia is a multisystem disorder of unknown cause, which develops in the second trimester of pregnancy, after 20 gestational weeks, characterized by reduced placental perfusion and vascular endothelial dysfunction. It is recognized by hypertension, proteinuria (albuminuria) and/or edema [12]. Even though preeclampsia is the major cause of maternal and fetal morbidity and mortality, accounting for 8–36% of all deaths during the course of pregnancy or perinatal deaths, the pathophysiology of preeclampsia remains unknown [13,14]. This is why preeclampsia is a public health issue.

Preeclampsia can be caused by placental perfusion due to incomplete fetal trophoblast invasion in the womb and maternal

Table 1. Thyroid hormone status: women with different types of preeclampsia compared to women with normal pregnancy.

Normal pregnancy ($n = 131$)	Preeclampsia ($n = 125$)		PIH ($n = 36$)		Mild preeclampsia ($n = 57$)		Severe preeclampsia ($n = 32$)	
TSH (μU/ml)	TSH (μU/ml)	*p**	TSH (μU/ml)	*p**	TSH (μU/ml)	*p**	TSH (μU/ml)	p*
2.34 ± 1.59	3.51 ± 2.42	<0.001	2.36 ± 1.51	NS	3.26 ± 2.14	0.0004	5.24 ± 2.82	<0.001
FT3 (pg/ml)	FT3 (pg/ml)	*p**	FT3 (pg/ml)	*p**	FT3 (pg/ml)	*p**	FT3 (pg/ml)	*p**
2.85 ± 0.63	2.48 ± 0.86	0.001	2.74 ± 0.63	NS	2.44 ± 0.78	<0.001	2.28 ± 1.13	<0.001
FT4 (ng/dl)	FT4 (ng/dl)	*p**	FT4 (ng/dl)	*p**	FT4 (ng/dl)	*p**	FT4 (ng/dl)	*p**
0.97 ± 0.29	1.26 ± 0.61	<0.001	1.11 ± 0.49	0.028	1.19 ± 0.54	0.006	1.54 ± 0.75	0.01

PIH: pregnancy-induced hypertension.
*Comparison of pregnant women with preeclampsia versus pregnant women with normal pregnancy; $p < 0.05$ – statistical significance was considered for p values less than 0.05.

Table 2. Distribution of *D2-Thr92Ala* in the preeclampsia groups and the normal pregnant group.

	D2-Thr92Ala Genotypes							
Study groups	Thr/Thr	Thr/Ala	Ala/Ala	Thr/Ala + Ala/Ala	OR, 95%CI*	*p**	OR, 95%CI**	*p***
Normal pregnant group ($n = 131$)	86 (65.6%)	29 (22.1%)	16 (12.2%)	45 (34.4%)				
Preeclampsia ($n = 125$)	29 (23.2%)	51 (40.8%)	45 (36%)	96 (76.8%)	6.33 [3.65–10.97]	<0.001	4.04 [2.14–7.65]	<0.001
PIH ($n = 36$)	16 (44.4%)	7 (19.4%)	13 (36.1%)	20 (55.6%)	2.39 [1.13–5.05]	0.001	4.06 [1.72–9.58]	0.001
Mild ($n = 57$)	4 (7%)	32 (56.1%)	21 (36.8%)	53 (93%)	25.32 [8.61–74.4]	<0.001	4.19 [1.98–8.88]	<0.001
Severe ($n = 32$)	9 (28.1%)	12 (37.5%)	11 (34.4%)	23 (71.9%)	4.88 [2.08–11.44]	<0.001	3.77 [1.53–9.24]	0.003

PIH: pregnancy-induced hypertension.
*Comparison of pregnant women with different types of preeclampsia versus normal pregnant women (carriers of at least one *D2-Ala92* allele;
**Comparison of pregnant women with different types of preeclampsia versus normal pregnant women (carriers of the homozygous genotypes); OR: odds ratio; 95%CI: 95% confidence intervals; $p < 0.05$ – statistical significance was considered for p values less than 0.05.

Table 3. Influence of *D2-Thr92Ala* on thyroid hormone levels and pregnancy outcome.

	PIH		Mild preeclampsia		Severe preeclampsia	
	D2-Thr22Ala		*D2-Thr22Ala*		*D2-Thr22Ala*	
Thyroid hormone levels/Pregnancy outcome	*Thr92/Thr92*	At least one *D2-Ala92* allele	*Thr92/Thr92*	At least one *D2-Ala92* allele	*Thr92/Thr92*	At least one *D2-Ala92* allele
TSH, μU/ml	1.95 ± 0.93	2.68 ± 1.82	1.2 ± 0.83	3.42 ± 2.3	3.02 ± 2.06	6.11 ± 2.62
p				0.003		0.002
FT4, ng/dl	0.94 ± 0.34	1.26 ± 0.54	1.15 ± 0.41	1.18 ± 0.54	1.11 ± 0.24	1.71 ± 0.82
p		0.02				0.003
FT3, pg/ml	2.99 ± 0.55	2.53 ± 0.61	3.04 ± 0.09	239 ± 0.79	3.09 ± 2.06	1.97 ± 1.17
p		0.02		<0.001		0.0006
Gestational age at delivery, weeks	34.75 ± 4.83	35.1 ± 4.01	36.75 ± 5.43	34.56 ± 4.5	35.33 ± 3.46	34.13 ± 3.99
Birth weight, g	2939.37 ± 906.35	2567.5 ± 986.65	3550 ± 1059.87	2758.11 ± 788.91	2641.11 ± 804.96	1899.56 ± 762.71
p						0.003

PIH: pregnancy-induced hypertension; TSH, FT4, FT3 levels, gestational age at delivery and birth weight are expressed as mean ± SD; p values less than 0.05 were considered statistically significant; comparisons between groups were performed using the Student *t-test.*

resistance against this invasion. This induces defective spiral artery remodeling, defective placental development, placental ischemia, release of placental factors, oxidative stress, placental thrombosis [15]. In the mother, the disease can cause endothelial dysfunction affecting the liver, the brain or the kidneys. Also, neurological damage such as cerebral hemorrhage, stroke, cerebral edema, pulmonary edema and DIC can occur. For the newborn, the disease is associated with premature birth, placental insufficiency, intrauterine growth retardation and intrauterine death [16].

Latest studies have estimated that preeclampsia is a condition that occurs as a result of the complex interaction of multiple genetic variants located in different genes.

Of more than 70 genes incriminated in preeclampsia, we mentioned the one related to thyroid hormone metabolism and possibly associated with hypothyroidism in this study.

Untreated, hypothyroidism induces high blood pressure. Also, anemia, myopathy, heart failure, preeclampsia, placental abnormalities, intrauterine growth retardation and heart disease can develop. Severe maternal hypothyroidism can cause fetal distress such as brain development abnormalities, severe cognitive deficits, neurological abnormalities and growth deficits [17–19]. Moreover, hypothyroidism is correlated with the severity of preeclampsia. Controversial results have been obtained regarding the association of preeclampsia with hypothyroidism. Some of these studies, such as that of Raoofi et al. (2014), showed a relationship between the severity of preeclampsia and thyroid hormone levels, i.e. an association with hypothyroidism [20]. However, studies such as that of Kharb et al. (2013) suggested higher TSH values and lower T3 and T4 values in preeclamptic women compared to normal pregnant women, while other studies such as that of Kumar et al. (2005) found higher TSH levels without any changes in T3 and T4 levels. Arash et al. (2015) reported higher TSH and FT3 levels and unaltered FT4 levels in preeclamptic women [21–23]. Also, Kharb et al. (2013) evidenced

a correlation between biochemical hypothyroidism found in women with preeclampsia and the severity of the disease [21].

The results regarding TSH levels in pregnancy are also controversial. There are studies that show no alteration of TSH levels in pregnancy, while others evidence higher TSH levels during pregnancy. More important is the fact that maternal hypothyroidism can be associated with hypertensive disorder later in life [24].

Our study showed higher TSH and FT4 levels and lower FT3 levels in women with preeclampsia compared to normal pregnant women, but we obtained statistical significance only for women with mild and severe preeclampsia. This means that our results were in agreement with those obtained by Ipadeola et al. (2013), Raoofi et al. (2014), Kumar et al. (2005), which showed an association between the severity of preeclampsia and thyroid hormone status [20,22,25]. Also, our results were in agreement with those of Dyvia et al. (2009), which suggested higher TSH and FT4 levels and lower FT3 levels in preeclampsia compared to normal pregnant women [9]. A possible explanation for the statistical significance obtained by us in severe preeclampsia is that peripheral conversion of T4 to T3 in the liver and kidneys had an important role, and women with severe preeclampsia can associate liver and kidney diseases. Başbuğ et al. (1999) indicated that low FT3 levels can appear because of protein loss in urine, as is shown in mild and especially in severe preeclampsia [26]. There was a positive influence of TSH levels on pregnancy outcome. Thus, preeclamptic women with TSH higher than 4 μU/ml delivered neonates with a significantly lower birth weight compared to preeclamptic women with TSH levels lower than 4 μU/ml. On the other hand, there were no differences in gestational age at delivery according to TSH levels higher than 4 μU/ml. Our results regarding FT3 and FT4 levels are in agreement with those obtained by Kharb et al. (2013), but do not confirm the results regarding TSH levels [21].

With respect to *D2-Thr92Ala* genotypes, the study conducted by Dora et al. (2014) showed the association of this polymorphism with reduced placental D2 activity, but did not confirm the association with gestational outcomes [27]. Regarding the D2 genotype distribution, a higher frequency of the homozygous *D2-Ala92/Ala92* genotypes was found in all types of preeclampsia compared to normal pregnancy. Pregnant women carriers of the homozygous *D2-Ala92/Ala92* genotypes had a significantly higher risk to develop PIH, mild or severe preeclampsia. The risk dramatically increased in carriers of at least one *D2-Ala92* allele.

Regarding the influence of *D2-Thr92Ala* genotypes on thyroid hormone levels, we found that preeclamptic women with PIH, carriers of at least one *D2-Ala92* allele, had significantly increased FT4 levels and significantly decreased FT3 levels compared to non-carriers. TSH levels were increased in carriers of the *D2-Ala92* allele compared to non-carriers, but the results were not statistically significant. Also, preeclamptic women diagnosed with mild preeclampsia, carriers of at least one *D2-Ala92* allele, had significantly higher TSH and significantly lower FT3 levels compared to non-carriers. There was no significant difference in FT4 levels according to D2 genotypes. The results were different in women with severe preeclampsia. TSH and FT4 levels were significantly higher and FT3 levels were significantly lower in preeclamptic women with severe preeclampsia if they carried the *D2-Ala92* allele compared to non-carriers. Also, our results showed higher TSH and FT4 levels and lower FT3 levels in severe preeclampsia compared to mild preeclampsia and PIH.

The studies conducted by Basbug et al. (1999) and Khalik et al. (1999) analyzed the influence of thyroid hormone levels on pregnancy outcome. They showed that preeclamptic women with low gestational age had higher TSH and FT4 levels and lower FT3 levels compared to preeclamptic women with normal gestational age. Also, preeclamptic women with newborns weighing less than 2500 g had higher TSH and FT4 levels and lower FT3 levels compared to preeclamptic women with neonates having a birth weight higher than 2500 g [26,28].

Our study aimed to investigate the influence of *D2-Thr92Ala* genotypes on pregnancy outcome in preeclampsia. The results suggested that pregnant women with preeclampsia, carriers of at least one *D2-Ala92* allele, delivered at lower gestational age neonates with a lower birth weight compared to non-carriers. Even though this influence is seen in PIH and mild preeclampsia, the results were not statistically significant. However, pregnant women with severe preeclampsia, carriers of at least one *D2-Ala92* allele, had a significantly lower gestational age and birth weight compared to women negative for this allele.

Conclusion

In conclusion, the present study investigates the genetic and biochemical thyroid status according to D2 genotypes and thyroid hormone levels in pregnant women with preeclampsia. The study demonstrates the association of the *D2-Thr92Ala* genetic variant with the severity and obstetric outcome of preeclampsia. Because D2 has a role in the conversion of T4 to T3, our study shows an influence of the D2 variant on thyroid hormone levels.

The study demonstrates non-thyroidal biochemical hypothyroidism – as a result of deiodination effects due to D2 genotypes.

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Declaration of interest

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Supplementary material available online