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The Relation Between Gestational Thyroid Parameters and Depression: A Reflection of the Downregulation of the Immune System During Pregnancy?

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Objective: To assess the relation between thyroid parameters and an episode of major depression at different trimesters during pregnancy, taking into account possible confounders. *Design*: Prospective follow-up of 1017 pregnant women from the general population with assessment of thyroid parameters and depression using syndromal diagnosis interviews at 12, 24, and 36 weeks' gestation. *Main outcome:* The prevalence of major depression decreased from 5.3% to 2.9%, and that of elevated concentrations of thyroid peroxidase antibody (TPO-Ab) titers from 8.4% to 6.5% toward the end of term. Subclinical hyperthyroidism not related to TPO-Ab (odds ration [OR] 3.6; 95% confidence interval [CI]: 1.2–0.2) and TPO-Ab (OR 2.1; 95% CI: 1.1–5.8) at 12 weeks' gestation, and TPO-Ab (OR 2.8; 95% CI 1.9–7.1) at 24 weeks' gestation were independently related to major depression. Anxiety and the occurrence of stressful life events were related to depression at all trimesters. *Conclusions:* The occurrence of major depression and high titers of TPO-Ab show a similar pattern of decline throughout pregnancy. During early gestation, thyroid autoimmunity seems to be related to depression while at the end of term—when there is maximal downregulation of the immune system—autoimmunity does not seem to play an important role with regard to the occurrence of depression.

Introduction

Traditionally, pregnancy has been thought of as a period of well-being and happiness. But in addition to the physical challenges women face during their pregnancy, they also must cope with shifting hormones and lifestyle changes. Emotional difficulties, specifically mood changes, may frequently be encountered during pregnancy. In recent reviews, up to 10% of the women were shown to suffer from depressive symptomatology (minor depression) during pregnancy and up to 5% of a major depressive episode (1,2).

Depression during pregnancy has been recognized to affect fetal health and to interfere with obstetrical outcome: gestational hypertension and subsequent preeclampsia, spontaneous abortion, bleeding during pregnancy, neonatal growth retardation, spontaneous early labor, fetal death, low-birth–weight babies, low Apgar scores, admission to a neonatal care unit, perinatal and birth complications, and high cortisol levels in offspring at birth (3–8).

Moreover, women who suffer from a major depressive episode during pregnancy are at high risk to suffer from postpartum depression with all its possible negative consequences for the mother–infant relationship (9).

The relationship between thyroid dysfunction and depression in general has been well documented for many decades as reviewed elsewhere (10–12). Several symptoms of hypothyroidism are similar to those of depression (fatigue, cognitive problems, sleeping problems, low mood). Moreover, many patients with depression, although biochemically euthyroid, show alterations in their thyroid function: abnormal thyrotropin-releasing hormone (TRH) response, high prevalence of thyroid antibodies, and thyroxine (T_4) levels in the high–normal ranges.

Several authors reported an association between high titers of thyroid peroxidase antibodies (TPO-Ab) and depression in general, while others did not (13– 20). These conflicting results are mainly explained by methodological issues such as different use of definition of depression

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(depression at a symptom level versus at a syndrome level), small samples and use of biased population (psychiatric inpatient clinics versus the general population).

Although up to 2%–4% of the pregnant women present with thyroid dysfunction (currently treated or in the past) and up to 8%–10% show elevated TPO-Ab titers, the relation between thyroid dysfunction and depression during pregnancy has hardly been investigated. This is the more surprising, while the immune system of a pregnant woman is susceptible to major alterations (because of the classic downregulation to keep the paternal allograft) as reflected by a substantial decrease of antibody titers during pregnancy, to the thyroid as well as to other organs. There are only two reports showing conflicting results: Kuijpens et al. (17) found that women with elevated TPO-Ab during early gestation were at increased risk for depression, while Oretti et al. (21) found no differences in the prevalence of gestational depressive symptoms in relation to antibody status. However, both studies suffered from methodological shortcomings and used relatively small samples.

The current study investigated the relation between depression and thyroid parameters during pregnancy taking into account important methodological aspects: a large sample of pregnant women of the general population, a diagnosis of depression at a syndrome level rather than a symptom level, repeated measurements at three different trimesters of gestation, and inclusion of possible confounders of depression.

Materials and Methods

Subjects

Between August 2002 and November 2004, 1702 women scheduled antenatal control at 12 weeks' gestation in five community midwife practices. In order to avoid language problems because of the use of several questionnaires and possible confounding of ethnic origin, only Dutch Caucasian women ($n = 1507$) were invited to participate in screening of maternal thyroid function. Seventy-nine percent ($n = 1191$) of women signed an informed consent for participation; the nonresponders did not differ from the responders with regard to age, parity, and educational level (data not shown). Women taking thyroid medication ($n = 10$), those who became pregnant after hormonal stimulation ($n = 8$), those with a multiple pregnancy ($n = 8$) as well as women with type 1 diabetes ($n = 5$) were excluded. Also excluded were all women ($n = 69$) who did not participate in all assessments and who did not complete all questionnaires. Therefore, 1017 (91%) women were eligible for this study.

In addition to the written informed consent obtained from the participants, the Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven approved this study.

Assessments

Dependent variable: depression

A syndromal diagnosis of depression was assessed using the Composite International Diagnostic Interview (CIDI), a short version of the depression module (22). The CIDI is a fully structured diagnostic interview developed to allow lay interviewers to obtain the data necessary to make a psychiatric diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text Revision* (*DSM-IV-TR I*) (22) and *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (*ICD-10*) (23) criteria. The women were seen by one midwife (H.W.; 2/3 of the assessments) and a team of five psychology students (as a part of a graduating research program). They all received CIDI training and were blinded for biochemical results of the women. Only women suffering from major depression were diagnosed as a case.

Independent variable: thyroid hormones and thyroid autoimmunity

Thyrotropin (TSH) was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles, CA). The interassay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/L and 2.9mIU/L, respectively.

The free thyroxine (FT_4) concentration was measured with a solid-phase immunometric assay (IMMULITE Free T_4). The interassay coefficients of variation for this technique were 6.7% and 4.4% at concentrations of 11.6 pmol/L and 31.5 pmol/L, respectively. For both parameters, the abovementioned nonpregnant reference ranges were used: 0.45–4.5 mIU/L and 10.3–25.7 pmol/L, 0.45–4.5 mIU/L and 10.3–25.7 pmol/L, respectively. The following categories of thyroid dysfunction were defined.

Clinical (overt) thyroid dysfunction: TSH and FT_4 outside reference ranges referring to hyperthyroidism (decreased TSH and increased FT_4) and hypothyroidism (increased TSH and decreased FT_4). Similarly, subclinical thyroid dysfunction was defined by an abnormal TSH with FT_4 level within reference range. Hypothyroxinemia and hyperthyroxinemia were defined by an FT_4 concentration at or below the 10th percentile and at or above the 90th percentile, respectively, with a TSH concentration within reference range.

Finally, the IMMULITE Anti-TPO Ab kit was used for the determination of antibodies against thyroid peroxidase (TPO). The interassay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/L and 526 kU/L, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. A woman with TPO-Ab titers greater than 35 IU/mL at 12 weeks' gestation was defined as immunologically compromised irrespective of a possible decrease of the titer throughout pregnancy resulting in low titers at 24 or 34 weeks' gestation. Women were defined as TPO-Ab–negatives when the titer was below 35 IU/mL at 12 weeks' gestation.

Possible confounders

Because anxiety has been shown to be a highly comorbid condition of depression anxiety symptoms were measured using the 10-items anxiety subscale (range, 10–50) of the SCL-90 scale of Derogatis (24). The SCL-90 is a self-rating scale consisting of six subscales measuring all kinds of psychopathology. The item score ranges from 1 to 5. The SCL-90 has been validated in The Netherlands and its use as

well as the use of several subscales has only revealed appropriate psychometric properties (25). Normally, no cutoff levels are used but in the present study scores at and above the highest 90th percentile defined high levels of anxiety. Several other confounders as described in literature were assessed at one or more trimesters such as: demographic features, lifestyle habits, an earlier episode of depression in the woman's life or in her parents. Moreover, the occurrence of major life events during pregnancy prior to the assessment was carefully assessed using the adapted version of the Recent Life Events List (26). Finally, the effect of several obstetrical factors (parity, planning of pregnancy) was also investigated.

Statistical Analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS; SPSS Inc., Chicago, IL). Difference in prevalence rates was evaluated using χ^2 statistics. Univariate logistic regression analysis was performed with depression according to the CIDI as the dependent variable (OR, 95% CI). Subsequently, a multiple logistic regression analysis was performed again with a syndromal diagnosis by the CIDI as the dependent variable.

Results

The characteristics of the participants are shown in Table 1. In Table 2, the prevalence rates of depression according to the CIDI are shown as well as mean scores on the subscale anxiety at three different trimesters. Moreover, thyroid parameters are shown. As can be seen in Table 2, the prevalence rate of depression according to CIDI remained at 5% until the second trimester and dropped below 3% toward end gestation (χ^2: 7.2, $df = 2$, $p = 0.027$). During the interview, there were no depressed women who showed suicidal ideation, thus no treatment was proposed.

There were 117 women (11.5%) who at least had one episode of major depression during pregnancy. The mean scores of the anxiety subscale of the SCL-90 gradually increased during pregnancy. Thyroid parameters showed a decrease of mean concentrations of FT_4 and an increase of mean TSH toward the end of gestation. The number of women with subclinical hyperthyroidism decreased significantly toward the end of gestation (χ^2: 30, $df = 2$, $p < 0.001$), while the prevalence of subclinical hypothyroidism fluctuated with regard to different trimesters (χ^2: 5.3, $df = 2$, $p = 0.07$). Finally, the number of women with elevated titers of TPO-Ab decreased gradually toward the end of term (χ^2: 2.6, $df = 2$, $p = 0.27$). In the

Table 1. Characteristics of a Sample of 1017 Pregnant Women from the General Population Assessed at 12 Weeks' Gestation

	n *(%)*
Demographic features	
Age (mean, SD)	29 (0.5)
Marital status	
With partner	997 (98)
Single	26 (2)
Educational level	
Low	91 (9)
Middle	458 (45)
High	387 (38)
Academic	81 (8)
Working outside home	874 (86)
Lifestyle habits	
Smoking	113 (13)
Alcohol intake	112 (13)
Body mass index	
<20	61 (6)
Between 20 and 25	467 (46)
Between 26 and 30	336 (33)
>30	153 (15)
Obstetrical features	
Parity	
Primiparity	468 (46)
Multiparity	549 (54)
Pregnancy, not planned	76 (7.5)
Previous miscarriage	195 (19.2)
Risk factors of depression	
Previous history of depression in woman herself	123 (12.1)
History of depression in first line relatives	185 (18.2)
The occurrence of a major life event:	
During first trimester	252 (25)
During second trimester	221 (22)
During third trimester	211 (20)

SD, standard deviation.

Table 2. Prevalence Rates of Depression and Thyroid Parameters at Three Different Trimesters During Gestation in 1017 Women of the General Population

	12 weeks	*24 weeks*	*36 weeks*
Depression according to CIDI (N, %)	54 (5.3)	46 (4.5)	30 (2.9)
Anxiety (Mn, SD)	12.1 (3.3)	12.4 (3.4)	12.7 (3.6)
Thyroid parameters (N, %)			
TSH (Mn, SD)	1.2 (0.8)	1.3 (0.65)	1.5 (0.74)
FT_4 (Mn, SD)	16.1 (2.5)	13.8 (2.0)	13.3 (2.1)
Subclinical hyperthyroidism	30 (2.9)	7 (0.7)	4 (0.4)
Subclinical hypothyroidism	33 (3.2)	17 (1.7)	25 (2.5)
Hyperthyroxinemia	78 (7.7)	72 (7.1)	72 (7.1)
Hypothyroxinemia	85 (8.4)	99 (9.7)	86 (8.5)
TPO-Ab > 35	85 (8.4)	68 (6.6)	58 (5.7)
Women who were TPO-Ab positive (>35 IU/ml) at 12 weeks' gestation, n = 85			
TPO Mean (SD)	356 (322)	170 (146)	108 (92)
Range IU/mL	36–1900	9–1300	9–1100
FT_4 10th percentile (pmol/l):	13.3	11.2	10.8
FT_4 90th percentile (pmol/l):	18.9	16.4	15.9

CIDI, Composite International Diagnostic Interview; SD, standard deviation; TSH, thyrotropin; FT_4, free thyroxine; TPO-Ab, thyroid peroxidase antibody.

group of women with elevated titers at 12 weeks' gestation ($n = 85$), the mean concentration of TPO-Ab decreased toward the end of term as well as the upper range level: from 1900 to 1100 IU/mL. Of the 85 women with TPO-Ab greater than 35 IU/mL at 12 weeks' gestation, there were 17 women who were negative at 24 and 36 weeks' gestation (TPO_1+ / TPO_2− / TPO_3−), 10 who were positive at 12 and 24 weeks' and negative at 36 weeks' gestation (TPO_1+ / TPO_2+ /TPO_3−) and 58 women who were positive at all three assessments (TPO_1+ / TPO-2+, TPO_3+). The preva-

Table 3. Univariate Logistic Regression Analysis in 1017 Women at Three Different Assessments During Gestation

	OR	*95% CI*
12 weeks' gestation		
Low education	1.8	0.8–4.1
Working outside home	1.6	0.6–3.4
Obstetrical features		
Unplanned pregnancy	4.5	2.2–8.7
Nulliparity	1.2	0.7–2.1
Miscarriage earlier in life	1.4	0.6–1.9
Life style habits		
Smoking during gestation	3.1	1.7–5.8
Alcohol intake	1.2	0.4–1.9
High BMI (>25)	1.5	0.7–3.1
Risk factors of depression		
Previous history of depression in life	2.7	1.4–5.2
Depression in family	1.6	0.8–3.2
Occurrence of stressful life event in first trimester	2.6	1.8–6.3
Anxiety: (scores > 90^{th} percentile)	7.9	4.1–14.2
Thyroid parameters		
Subclinical hypothyroidism	1.1	0.6–4.9
Subclinical hyperthyroidism	2.8	1.2–8.5
Hypothyroxinemia (FT_4 <10^{th} percentile)	1.2	0.8–2.3
Hyperthyroxinemia (FT_4 >90^{th} percentile)	2.4	0.5–6.7
Increased TPO-Ab titers (>35)	1.6	1.2–3.8
24 weeks' gestation		
Low education	1.6	0.6–3.6
Working outside home	1.4	0.5–3.7
Obstetrical features		
Unplanned pregnancy	1.2	0.6–2.6
Nulliparity	1.3	0.6–2.4
Miscarriage earlier in life	1.2	0.8–1.8
Life style habits		
Smoking during gestation	1.8	0.8–3.8
Alcohol intake	1.9	0.5–2.7
High BMI (>25)	2.1	1.2–3.9

Table 3. Univariate Logistic Regression Analysis in 1017 Women at Three Different Assessments During Gestation (*Cont'd*)

	OR	*95% CI*
Risk factors of depression		
Previous history of depression in life	1.7	0.8–3.2
Depression in family	1.8	0.6–3.8
Occurrence of stressful life event in second trimester	4.6	2.8–8.3
Anxiety: (scores >90th percentile)	8.9	5.2–15.8
Thyroid parameters		
Subclinical hypothyroidism	1.6	0.9–5.2
Subclinical hyperthyroidism	—	—
Hypothyroxinemia (FT_4 <10th percentile)	1.4	0.6–4.1
Hyperthyroxinemia (FT_4 <10th percentile)	1.8	0.7–5.3
Increased TPO-Ab titers (>35)	1.9	1.3–4.2
36 weeks' gestation		
Low education	1.6	0.6–4.7
Working outside home	1.5	0.7–3.2
Obstetrical features		
Unplanned pregnancy	1.9	0.7–5.7
Nulliparity	1.5	0.6–3.1
Miscarriage earlier in life	1.9	0.6–2.9
Life style habits		
Smoking during gestation	1.9	0.7–4.8
Alcohol intake	1.3	0.5–2.5
High BMI (>25)	1.1	0.6–3.3
Risk factors of depression		
Previous history of depression in life	3.2	1.4–7.3
Depression in family	1.3	0.5–3.1
Occurrence of stressful life event in third trimester	3.8	1.6–8.6
Anxiety: (scores > 90th percentile)	8.4	3.4–17.9
Thyroid parameters		
Subclinical hypothyroidism	1.4	0.6–9.8
Subclinical hyperthyroidism	—	—
Hypothyroxinemia (FT_4 <10th percentile)	0.4	0.1–2.3
Hyperthyroxinemia (FT_4 <90th percentile)	1.2	0.6–3.1
Increased TPO-Ab titers (>35)	1.5	0.6–5.2

Dependent variable: depression according to CIDI. (O.R., 95% CI).
BMI, body mass index; FT_4, free thyroxine; TPO-Ab, thyroid peroxidase antibodies; CIDI, Composite International Diagnostic Interview; OR, odds ratio; CI, confidence interval.

lence of women who suffered from at least one episode of depression in these different three groups was 11%, 10%, and 17%, respectively, (χ^2: 0.55, $df = 2$, $p = 0.66$).

In Table 3, a univariate logistic regression is shown at three trimesters with the dependent variable (a syndromal diagnosis of depression according to the CIDI) on one hand and several independent variables (several thyroid parameters) on the other. Moreover, the relation between possible confounders and the dependent variable is shown (demographic characteristics, obstetrical features and risk factors of depression in general). As can be seen, at 12 weeks' gestation, a decreased TSH (subclinical hyperthyroidism) and elevated titers of TPO-Ab were significantly related to depression as well as several possible confounders; at 24 weeks' gestation, an elevated titer of TPO-Ab was significantly related to depression as well as other confounders while at 36 weeks' gestation, no thyroid parameters were related to depression.

Subsequently, in Table 4, the set of variables was put into a multiple logistic regression analysis with the dependent variable: a syndromal diagnosis on the CIDI at different trimesters of pregnancy. Only the significant odds ratios are shown.

As can be seen in Table 4, also at a multivariate level thyroid parameters remained significantly related to depression until 24 weeks' gestation. At the first trimester, women with an unplanned pregnancy were significantly at risk to suffer from depression. Moreover, smoking was shown to be an independent risk factor. The other variables at all three assessments, which significantly correlated with depression, were high anxiety and the occurrence of recent major life events.

Discussion

This study in a large sample of pregnant women of the general population shows that the prevalence of major depression varies from 2.9% to 5.4% depending on the time of assessment during pregnancy. In addition, it demonstrates that depending on the time of assessment, different variables predict depression on one hand, while on the other hand some factors are related to depression at all assessments. During early gestation thyroid parameters have an independent relation to depression: decreased TSH levels and elevated titers of TPO-Ab during the first trimester, while dur-

Table 4. Multiple Logistic Regression Analysis in 1017 Women at Three Different Assessments During Gestation

	OR	*95% CI*
12 weeks' gestation		
Unplanned pregnancy	3.0	1.8–6.6
Smoking during gestation	2.2	1.2–4.7
Occurrence of stressful life event in first trimester	2.3	1.6–6.1
Anxiety: (scores >90th percentile)	3.9	1.9–8.1
Subclinical hypethyroidism	3.6	1.2–10.2
Increased TPO-Ab titers (>35)	2.1	1.1–5.8
24 weeks' gestation		
Previous history of depression in life	1.5	1.2–2.1
Occurrence of stressful life event in second trimester	3.1	1.6–6.1
Anxiety: (scores >90th percentile)	6.3	3.2–12.8
Increased TPO-Ab titers (>35)	2.8	1.9–7.1
36 weeks' gestation		
Occurrence of stressful life event in third trimester	2.4	1.3–5.9
Anxiety: (scores >90th percentile)	4.1	1.6–9.8

CIDI, Composite International Diagnostic Interview; OR, odds ratio; CI, confidence interval; TPO-Ab, thryoid peroxidase antibodies.

ing the second trimester, an elevated titer of TPO-Ab is the only thyroid parameter that correlated significantly with depression. Moreover, although not significantly different, women with elevated TPO-Ab at all assessment showed the highest prevalence rate of a major depressive episode compared to those with only elevated titers at early gestation. The reason that significance was not met partly might be explained by the low numbers in the different subgroups.

A recent review of the literature concerning depression during pregnancy using similar methods of syndromal diagnosis showed a prevalence rate of major depression varying from 3.1% to 4.9% depending on the time of assessment, which is in accordance with the findings of the current study (1). The prevalence rate of depression during pregnancy is lower compared to that of depression in the general female nonchildbearing population of similar age (10%–12%) as shown in a large population study of 6000 adults between 18 and 65 years of age in The Netherlands (27). Although a definite explanation is lacking, a possible reason that might partly explain this difference is the downregulation of the immune system during pregnancy. Depression has a multifactorial origin in which biologic, immune, psychological, and environmental factors are thought to play an important role. In psychoneuroimmunology it has long time been described that perturbations of the immune system might be associated with depression or vice versa (28). Because of the downregulation of the immune system it might be argued that the effect of an autoimmune phenomenon as a possible trigger of depression decreases during pregnancy resulting in lower prevalence rates of depression. In the current study, the prevalence rate of depression dropped from 5.3 to 2.9% in line with the prevalence rate of elevated titers of TPO-Ab, which decreased from 8.4% to 6.5% (Table 2).

Several authors investigated a relation between thyroid autoimmunity and depression in general. Some did not find a difference in the prevalence of elevated TPO-Ab between patients with unipolar depression and the nonpsychiatric control group (13) while others reported an increased mean level of thyroid antibodies in depressed patients compared to controls (19) or a higher lifetime prevalence of anxiety and mood disorder in subjects with increased TPO-Ab titers (20) and in perimenopausal women (18). The relation between depression and thyroid dysfunction has been well studied during the postpartum period. Some did not report a relationship between thyroid antibody concentrations (TPO-Ab or microsomal antibody [MsAb]) and depression (14) while others found high TPO-Ab levels to be associated with depression (15,16). The only two reports looking at a possible relation during pregnancy reported inconclusive data. Using a design similar to the current study but in a smaller sample, Kuijpens et al. (17) also found a relation between depression and TPO-Ab, only at 12 weeks' gestation and not at 32 weeks' gestation. However, important confounders were not taken into account such as the comorbidity of anxiety and obstetrical factors such as planning of pregnancy. Oretti et al. (21) found no differences of prevalence rates of depressive symptoms between 61 antibody positive women and 66 antibody negative women. However, they used no syndromal diagnosis of depression and their study did not use a representative sample of the general population, which was the case in the current study.

The finding that subclinical hyperthyroidism during early pregnancy was related to depression is interesting and not to be explained by changes in the immune system during pregnancy. In general, one of the most important causes of subclinical hyperthyroidism is inadequate substitution or suppression dose of women with hypothyroidism and hyperthyroidism, respectively. However, these women were excluded from the study. The 30 women with subclinical hyperthyroidism in the current study had a similar prevalence rate of elevated TPO-Ab titers (6.4%, data not shown) compared to the group as a whole, which suggests that thyroid autoimmunity is not the cause either. In comparison: 18 (55%) of the 33 women with subclinical hypothyroidism (which is most of the time of autoimmune origin) did have elevated titers of TPO-Ab. The 90th percentile cutoff point of hyperthyroxinemia at 12 weeks' gestation was 18.9 pmol/L and only 21% (6 women) of those with subclinical

hyperthyroidism (Table 2) had FT_4 levels between 18.9 and 25.7 pmol/L. This suggests that an association between subclinical hyperthyroidism and depression is unlikely to be explained by thyroid hormone excess. It might be suggested that low TSH (with normal FT_4 levels) especially during early gestation reflects high peaks of hCG, which is known for its effect on the TSH receptor because of a structural analogy with TSH (29,30). High peaks of hCG are related to high levels of estrogens and it might be hypothesized that the relationship between subclinical hyperthyroidism and depression actually reflects a relation between estrogens and depression. Future studies are needed to look directly at a possible relation between hCG levels and depression during early pregnancy.

There is, however, another argument that might support a relationship between depression and thyroid autoimmunity. When looking at the literature concerning the relationship between depression and obstetrical problems on one hand and between elevated titers of TPO-Ab and obstetrical problems on the other hand, it is interesting to see that there are many similarities. Both depression and TPO-Ab have been associated with increased rate of premature delivery, gestational hypertension, and subsequent preeclampsia, spontaneous abortion, bleeding during preganancy, neonatal growth retardation, spontaneous early labor, fetal death, and low-birth–weight babies (3–8,31). It is a matter of speculation whether the negative effect of TPO-Ab on obstetrical outcome might be partly explained by the higher risk of depression in TPO-Ab positive women. In addition to thyroid parameters, smoking and an unplanned pregnancy were shown to be an independent risk factor of depression during early pregnancy. The relation between smoking and depression in general has been well documented (32) and smoking habits might moderate the finding that depression might interfere with low birth weight of the neonate. The fact that an unplanned pregnancy was an important risk factor of depression during early pregnancy has been described earlier and is another argument that these women need special attention during regular antenatal controls (1).

Anxiety was independently related to depression at all trimesters. This is not surprising given the fact that nowadays depression shows a comorbidity with anxiety in up to 80% of the cases. Depression and anxiety very often co-occur (33). Because anxiety has been shown to be an important determinant of impaired obstetrical outcome it might be argued that a possible negative effect of depression on obstetrics might be moderated by anxiety.

At all trimesters, classic psychosocial determinants of depression were independently related to depression such as high levels of anxiety and the occurrence of major life events. These risk factors of depression by no means differ from risk factors of depression in general.

Several limitations of the study need to be mentioned. Anxiety was the most stable risk factor of depression throughout pregnancy but was only assessed using self-rating scales. Because its major negative impact on obstetrics and apparently the offspring syndromal diagnosis should be preferred. Second, when looking at a possible relationship between thyroid parameters and depression it is important to look at possible confounders. In the current study, important psychological confounders were taken into account. Ideally, other biologic parameters (hCG, estradiol, progesterone, cortisol) should also take into account when looking at an independent biologic parameter of depression.

In summary, this study suggests that during pregnancy the model to predict depression contains different parameters at different trimesters of gestation, in line with the downregulation of the immune system: an immune and biologic (TPO-Ab, TSH, and perhaps hCG) component during early gestation with some psychosocial trimester-specific determinants; and a rather stable psychological set of variables (anxiety, major life events) throughout the entire pregnancy.

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