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BMJ Open

The Brabant study: design of a large prospective perinatal cohort study among pregnant women investigating obstetric outcome from a biopsychosocial perspective

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ABSTRACT

Background Pregnancy is characterised by many biological and psychosocial changes. Adequate maternal thyroid function is important for the developing fetus throughout gestation. Latent class analyses recently showed three different patterns of change in thyroid function throughout pregnancy with different associations with obstetric outcome. Maternal distress during the pregnancy (anxiety and depression) negatively affects obstetric outcome. Pregnancy distress in turn may be affected by personality traits and attachment styles. Moreover, during the pregnancy, substantial social changes occur in the partner relationship and work experience. The aim of the Brabant study is to investigate the association between thyroid function trajectories and obstetric outcomes. Moreover, within the Brabant study, we will investigate how different trajectories of pregnancy distress are related to obstetric outcome, and the role of personality in this association. We will evaluate the possible role of maternal distress and attachment style on maternal–fetal bonding. Finally, we will study social changes in the perinatal period regarding partner relationship and well-being and performance at work.

Methods and analysis The Brabant study is a longitudinal, prospective cohort study of an anticipated 4000 pregnant women. Women will be recruited at 8–10 weeks gestation among community midwife practices in South-East Brabant in the Netherlands. Thyroid function parameters (TSH and fT4), thyroid peroxidase antibody and human chorionic gonadotrophin will be assessed at 12, 20 and 28 weeks gestation. Moreover, at these three time points women will fill out questionnaires assessing demographic and obstetric features, life style habits and psychological and social variables, such as depressive symptoms, personality, partner relationship quality and burnout. Data from the obstetric records will also be collected.

Ethics and dissemination The study has been approved by the Medical Ethical Committee of the Máxima Medical Center Veldhoven. Results will be submitted to peer-reviewed journals in the relevant fields and presented on national and international conferences.

Strengths and limitations of this study

- ► Prospective design with three measurements of both biological and psychological variables during the pregnancy, which enables the use of latent class analysis.
- ► A multifactorial approach.
- ► A large sample size.
- ► Use of self-report with validated questionnaires instead of interviews.

INTRODUCTION

Pregnancy is a life-changing event characterised by substantial physiological, psychological and social changes, which can have an impact on the physical and mental health of pregnant women, partner relationships and work.

Maternal thyroid function

Adequate maternal thyroid function is important during pregnancy, both for mother and fetus. Impaired thyroid function has been associated to various obstetric problems including preterm birth (PTB), gestational diabetes (GD), small for gestational age (SGA), abnormal fetal position and pre-eclampsia (PE).[1–3] Some studies have observed an association between outcomes and both TSH and fT4, whereas others have reported a relationship either with TSH but not fT4 or vice versa.[4 5] Similarly, studies investigating the consequences of maternal thyroid dysfunction on infant neurodevelopment have reported disparate findings.[2] Such inconsistencies have always been difficult to reconcile but may result from the use of thyroid function reference ranges derived from cross-sectional data.

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This cross-sectional approach does not address longitudinal changes in thyroid function that occur in individual women during the course of their pregnancy. It is likely, therefore, that more accurate information can be obtained if longitudinal TSH and fT4 measurements from the same women during each trimester are used in epidemiological studies. Latent class analysis (LCA) is a statistical approach to model temporal changes within heterogeneous population samples.[6] This technique has extensively been discussed in detail elsewhere using thyroid function data collected during pregnancy between 2003 and 2004 (n=1100). This resulted in new insights of three thyroid function trajectories, assessed at each trimester throughout pregnancy, taking both TSH and fT4 into account.[7] Preliminary further analysis of these data showed that women of two trajectories (representing 8% of the total sample) were at risk for obstetric complications including PE, PTB, SGA and abnormal fetal position at birth (breech) compared with the reference group. However, the power of these analyses was low, especially when performed in primiparous and multiparous women separately. Also, human chorionic gonadotrophin (hCG) assessments were not performed. A recent study showed that the beneficial effect of hCG on fT4 production is hampered in thyroid peroxidase antibody (TPO-Ab) positive women.[8] Therefore, future LCA should also take into account the assessment of hCG.

Because important obstetric complications such as PE, PTB, breech position and SGA show a relatively low incidence rate (5%–10%) and primiparous women are at substantial higher risk compared with multiparous women, large samples are needed to evaluate possible associations in two distinct groups.

Maternal mental health: mental distress

Pregnancy is characterised by many changes and adaptations, most of which are outside of the woman's control (eg, bodily changes and physical complaints). Within a vulnerability-stress model, all these physical, physiological and psychosocial changes could trigger pregnancy distress symptoms (depressive and negative affect (NA) symptoms) in already vulnerable women.[9] Depressive symptoms during the pregnancy are common and affect up to 20% of the childbearing women,[10] also in Dutch pregnant populations.[11] The prevalence for self-reported anxiety symptoms is even higher, up to 25% during the last trimester of pregnancy, according to a recent meta-analysis.[12] Pregnancy distress has been associated with several aspects of poor pregnancy outcome, including pregnancy-induced hypertension, PTB and SGA.[13–17] Poor maternal thyroid function has also been associated with increased depressive symptoms during the pregnancy.[18 19] A protective factor against negative effects of depressive symptoms may be mindfulness, as shown before.[20] Non-reacting was positively associated with birth weight.

Coping with perinatal changes is likely to be particularly challenging for women who experience a high need for control and predictability.[21] In the general population, an important determinant of depression is obsessive-compulsive personality disorder (OCPD).[22 23] As such, expecting mothers with OCPD might be at an increased risk of distress symptoms during gestation. So far, OCPD has hardly been investigated in association with maternal mental health.[24]

Another predictor of mental health in general is attachment style. Adult attachment style is defined as the systematic pattern of relational expectations, emotions and behaviours that results from the internalisation of a particular attachment history.[25 26] Individuals who are insecurely attached tend to have relationships of lower quality, report lower marital satisfaction, experience higher levels of stress and are at increased risk of depression.[27] Maternal attachment insecurity has also been linked with negative parenting characteristics and child outcomes[28] and it may, therefore, be related to affective feelings toward the child during the pregnancy and the postpartum period. This may in turn trigger poor mother-infant bonding and may interfere with the child's emotional development.

Partner relationship

The birth of a child is one of the most invasive events in a romantic relationship. Previous research has shown that the transition to parenthood sets off significant changes in partners' satisfaction with their relationship.[29 30] Typically, these studies showed that marital satisfaction increases during pregnancy (coined as the 'honeymoon effect'),[31] after which it declines steeply directly after childbirth.[31 32] In this project, we aim to unravel which groups of parents are especially at risk of becoming less happy with their relationship in the transition to parenthood. Subsequently, we aim to develop interventions aimed at protecting the quality of their relationship.

Work

The majority of pregnant women in the Netherlands has a paid job. Contrary to most other European countries, women return to work already at around 12 weeks post partum. The partner has as little as 1-week leave post partum. Recent research by the Statistics Netherlands has shown that 15% of the Dutch working population suffers from mental or emotional exhaustion due to work (burn-out symptoms).[33] These symptoms are particularly prevalent among young women between 25 and 35 years old (18%).[33] Moreover, women between 25 and 45 years are twice as likely to be absent from work compared with men. This difference can partly be explained by physical and psychological problems during the pregnancy and post partum.[34] In the current study, physical and psychological factors affecting work-related well-being and performance of women during the pregnancy and the postpartum period will be investigated.

Objectives

The primary objective of the Brabant study is to investigate whether obstetric outcomes (PE, PTB, gestational diabetes mellitus (GDM), SGA, term of gestation at

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Table 1 Time points for the measures

Measure	Pregnancy			Post partum
	12 weeks	20 weeks	28 weeks	10 weeks
Blood samples (thyroid function parameters, hCG)	X	X	X	
Questionnaires	X	X	X	X
Baseline characteristics (age, marital status, education level, etc)	X			
Obstetric variables	X	X	X	X
Depressive symptoms (EDS)	X	X	X	X
Pregnancy distress (TDPS)	X	X	X	
Mindfulness (non-reacting subscale of TFMQ)		X		
Personality (BFI-2S)			X	
OCPD (symptom checklist)				X
Attachment style (ECR-SF)				X
Bonding (PPBS)			X	X
Partner relationship quality (DAS, PRS)	X	X	X	X
Employee well-being and performance (UBOS, VBBA V.2.0)	X		X	

BFI, Big Five Inventory; DAS, Dyadic Adjustment Scale; ECR-SF, Experiences in Close Relationships Scale Short Form; EDS, Edinburgh Depression Scale; hCG, human chorionic gonadotrophin; OCPD, obsessive–compulsive personality disorder; PPBS, Postnatal Bonding Scale; PRS, Partner Responsiveness Scale ; TDPS, Tilburg Pregnancy Distress Scale; TFMQ, Three Facet Mindfulness Questionnaire; UBOS, Utrecht Burnout Scale; VBBA, Vragenlijst Beleving en Beoordeling van de Arbeid.

delivery, mode of delivery) are related to different trajectories of gestational thyroid function. The secondary objective is to investigate how different trajectories of pregnancy distress are related to obstetric outcome, and the role of personality in this association. Tertiary objective is to evaluate the possible association between thyroid dysfunction and pregnancy distress. A fourth objective is to evaluate the possible role of maternal distress and attachment style on maternal–fetal bonding and to study the social changes in the perinatal period with regard to partner relationship. Finally, we will investigate the effect of mental health during pregnancy on well-being and performance at work.

METHODS AND ANALYSIS

Design and setting

The current study is a longitudinal, prospective cohort study among pregnant women, from 12 weeks pregnancy up until 10 weeks post partum with a clear option of prospective follow-up including the children until preschool age. The current paper describes the perinatal part of the Brabant study. Pregnant women will be recruited among community midwife practices in the South-East part of the North-Brabant province in the Netherlands (Tilburg, Eindhoven and Den Bosch). In this area, 15 000 pregnancies occur annually. The regional organisation responsible for blood collection for primary and secondary care laboratories (De Bloedafname) will perform blood sample collection. The laboratory of clinical chemistry and haematology of the Máxima Medical Centre Veldhoven is responsible for analysis of TSH, fT4, TPO-Ab and hCG and storage of the blood samples.

Recruitment

In the Netherlands, about 84% of pregnant women start antenatal care in a midwife practice, the other 16% are high risk and start within the hospital setting.[35] Considering early abortion rate and the exclusion criteria, it is estimated that around 9000 pregnant women will be eligible for participation each year. Pregnant women (18+ years) who have an understanding of the Dutch or English language and have their first antenatal visit before 12 weeks gestation are eligible for participation.

Exclusion criteria are: multiple pregnancy, known endocrine disorder before pregnancy (other than thyroid function problems), diabetes type I, rheumatoid arthritis, severe psychiatric disease (schizophrenia, bord00erline or bipolar disorder), HIV, drug or alcohol addiction problems or any other disease resulting in treatment with drugs that are potentially adverse for the fetus and need careful follow-up during the pregnancy. Moreover, women must have access to the internet.

Pregnant women visit the community midwife for the first time around 6–8 weeks gestation. During this visit, eligible pregnant women will be informed, both orally and written, about the study by their midwife. When they agree to participate, they will sign a full written informed consent. In the past 25 years, five cohorts of pregnant women have been formed in the same area with the same design showing an average response rate between 70% and 76%.[36] Recruitment started with a pilot in 2018 and

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is now ongoing. Recruitment is expected to be finished mid-2022.

Patient and public involvement

Lessons learnt from previous pregnant cohorts in the same area were used during the design of the current study.[36] Midwives and pregnant women evaluated the design and questionnaires during a pilot, after which appropriate adjustments were made. Participants will be informed about the results of the Brabant study via email.

Sample size calculation

An important variable of research of the Brabant study is the occurrence of obstetric complications (PE, PTB, SGA and GDM). The sample size calculation is mainly based on the possible relation between different trajectories of thyroid function and these obstetric complications. In a previous LCA analysis of a cohort of 1100 pregnant women, 8% of women belonged to 'abnormal' trajectories at risk for poor thyroid function during the pregnancy and consequently at risk for obstetric complications. Obstetric complications were 2–3 times more prevalent in these two 'abnormal' trajectories compared with the reference group (92% of women).[37] This cohort of women was from the same area as the current study, therefore, we expect similar outcomes. The sample size needed for statistically and clinically relevant differences between the two groups can be calculated according to Cohen.[38] For example, PE is expected to occur in 4% of the women of the reference group, reflecting 92% of the total sample. PE is expected to occur in 8% of the women of the other two trajectories, reflecting 8% of the total sample. With an alpha of 0.05 and beta of 0.80, the sample size of both groups should be 200 women.[38] Similar or higher prevalence figures are known for PTB, SGA and GDM.[39]

With a sample of 4000 at baseline and an expected drop-out of 10%,[40] all obstetric data will be available of 3600 women. Of these, 8% (n=288) will belong to the two high-risk trajectories. This N meets the 200 required.

The prevalence of women with high depressive symptomatology is substantially higher than PE, PTB and SGA and varies between 10% and 15% according to the pregnancy trimester.[41] The prevalence for self-reported anxiety symptoms during the pregnancy is between 18% and 25%.[12] These figures are large enough to perform statistical analysis with adequate power looking at a possible association with thyroid function trajectories. LCA will also be used to evaluate different trajectories of depressive symptomatology throughout gestation in relation to thyroid function and obstetric outcome.

Prevalence figures of both thyroid dysfunction and pregnancy distress during gestation are adequate to evaluate a possible association between these conditions with sufficient epidemiological power.

Data collection

Participants will receive questionnaires by email three times during the pregnancy and will provide three blood samples during the pregnancy (both around 12, 20 and 28 weeks). Moreover, all participants will be asked to complete a questionnaire at 8–10 weeks post partum (see table 1). If necessary, women will receive a maximum of two reminder emails within 2 weeks after receiving the questionnaire.

During the regular blood sampling at 12 and 28 weeks, additional blood will be collected for the Brabant study. At 20 weeks, during the regular ultrasound check-up, women will also be asked to provide a blood sample. Blood samples will be analysed for thyroid function parameters and hCG. Women with thyroid dysfunction (expected n=1%), who according to the literature need immediate treatment, will be contacted by their midwife.[5] At 10 weeks post partum, women will receive another questionnaire with additional questions regarding the birth and health of the newborn child. Data from the questionnaires will be downloaded automatically to the appropriate file types. All data will be coded and stored separately from identifiable participant information (names, addresses, birth dates, etc).

Measures

Thyroid function parameters

TSH, fT4, TPO-Ab and hCG will be measured in serum using electrochemiluminescence assays (Cobas e 601, Roche Diagnostics, Mannheim Germany). The anti-TPO assay is standardised in relation to the International Reference Preparation for anti-TPO MRC 66/387. A TPO-Ab titre >35 IU/mL at 12 weeks gestation will be used as cut-off. This is a widely used cut-off in the literature.[5]

The reference range for trimester-specific normal thyroid function has recently been defined in 2200 pregnant women in the same area.[42] Following the international guidelines of the American Thyroid Association and the American Endocrine Society, women with hypothyroidism that requires treatment (TSH >3.9 mIU/L and fT4 <11.2 pmol/L, or TSH >10 mIU/L and fT4 within reference range) and overt hyperthyroidism (TSH <0.19 mIU/L and fT4 >18.0 pmol/L) will be identified. These cut-offs of both TSH and fT4 refer to the 2.5th and 97.5th percentiles assessed in TPO-Ab negative women at 12 weeks gestation. These women will be referred to their midwife or obstetrician. It is well known that during pregnancy, there are no cut-offs for hCG.

Obstetric data

All relevant data on pregnancy and delivery will be collected from the obstetric record form from the community midwife and/or the obstetrician. Obstetric parameters during the pregnancy such as blood pressure, weight gain, smoking habits and alcohol intake, and obstetric data such as gestational age at birth, usage of anaesthesia, mode of delivery, duration of labour, complications and birth weight will be assessed.

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Depressive and NA symptoms

The 10-item Edinburgh Depression Scale (EDS) will be used to measure symptoms of depression during the pregnancy. It is the most widely used instrument in perinatal research[43] and has also been validated in Dutch postpartum women,[44 45] as well as pregnant women.[46] The items are answered on a 4-point Likert scale and higher total scores indicate more depressive symptoms.

Moreover, the Tilburg Pregnancy Distress Scale (TPDS) will be used.[47] This 16-item scale assesses partner involvement (PI, 5 items) and negative affect (NA, 11 items) including symptoms of worrying about pregnancy and labour. PI, the way a woman perceives her partner to be involved in her pregnancy, has been shown to be a protective factor against mental distress.[40] The items are answered on a 4-point Likert scale and higher total scores indicate more symptoms of NA and less PI, respectively. The TDPS was reported as excellent by other research groups[48] and further research confirmed adequate its psychometric properties.[48]

Mindfulness (as an emotion-regulation strategy) will be assessed at 20 weeks using the 4-item non-reacting subscale of the Three Facet Mindfulness Questionnaire-Short Form (TFMQ-SF),[49] which is originally derived from the short form of the frequently used Five Facet Mindfulness Questionnaire.[50] The items are answered on a 5-point Likert scale and higher total scores indicating better mindfulness skills. The TFMQ-SF has previously been validated in pregnant women.[49]

Personality traits

Specific personality traits have been associated with physical and psychological issues during the pregnancy, such as preterm labour, perinatal insomnia and use of medication, alcohol and smoking.[51–53] Therefore, in the current study, personality will be assessed using the 30-item Next Big Five Inventory (BFI-2S), which measures the Big Five personality dimensions (extraversion, agreeableness, conscientiousness, negative emotionality and open-mindedness). The BFI-abbreviated version is a valid and reliable questionnaire to asses Big Five personality traits.[54]

We previously developed an OCPD symptom checklist during pregnancy. The seven items are answered on a 4-point Likert scale and higher total scores indicating more symptoms of OCPD. This 7-item questionnaire showed adequate psychometric properties and highly significant correlations with EDS scores.[55] Moreover, follow-up research in a sub-sample of postpartum women of this cohort showed that OCPD scores were rather stable over a period of 3 years with r coefficients between 0.62 and 0.72.[56]

Adult attachment style

The Experiences in Close Relationships Scale SF (ECR-SF) questionnaire is a well-validated questionnaire for measuring the underlying dimensions of attachment in adult relationships.[57] The ECR-SF is designed to assess individual differences with respect to attachment-related anxiety and attachment-related avoidance, as measured with two subscales (each six items). Higher scores on the ECR-SF denote an insecurely attached person. Lower scores represent a securely attached person. All items are measured on a 7-point numerical scale ranging from 1 (strongly disagree) to 7 (strongly agree).

Maternal-fetal bonding

Maternal-fetal bonding will be assessed using the 5-item Prenatal and Postnatal Bonding Scale (PPBS).[58] The scale consists of only positive statements to describe maternal feelings towards her (unborn) child, which can be answered on a 4-point Likert scale. A higher score reflects a better mother-fetal bonding. The PPBS showed to be a robust instrument with excellent psychometric properties.

Partner relationship quality

Relationship quality will be assessed with two different indicators: an 8-item version of the Dyadic Adjustment Scale,[59] aimed to assess the overall satisfaction with the relationship, and a 5-item version of the Partner Responsiveness Scale,[60] aimed to assess the extent to which one partner experiences the other partner to constructively respond to his/her needs. Both these questionnaires have been used in previous research that studied the development of romantic relationships over time (see eg, Pollmann *et al*[61] and Vohs *et al*[62]), and showed good reliability.

Employee well-being and employee performance

Work engagement will be measured with an ultra-short version of the Utrecht Work Engagement Scale.[63] The 7-point Likert answer scale ranges from 1 (never) to 7 (always). The scale has shown appropriate reliability and validity. Burn-out will be measured with three items taken from the 5-item exhaustion subscale of the Utrecht Burn-out Scale.[64] The 7-point Likert answer scale also ranges from 1 (never) to 7 (always). Internal consistency, test–retest reliability and factorial validity for the 5-item version were found to be adequate in prior research.[64 65] The employee's relationship with her supervisor is assessed by two items taken from the 6-item 'relationship with direct supervisor' subscale of the Vragenlijst Beleving en Beoordeling van de Arbeid (VBBA V.2.0).[65 66] The employee's relationship with her colleagues is assessed by two items taken from the 6-item 'relationship with colleagues' subscale of the VBBA V.2.0.[66 67] The two items of both subscales reflect the atmosphere/relationship quality dimension of the original scale. The original scale has adequate reliability and validity. Task and contextual performance are measured with three items taken from the Individual Work Performance Questionnaire using a 5-point Likert scale ranging from one (seldom) to five (always).[68] The questionnaire has been found to be reliable[69] and to display acceptable convergent and discriminant validity.[68]

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Confounders

Confounders used in this study include standard baseline characteristics (demographics, education, lifestyle habits such as smoking, alcohol and body mass index, BMI) a previous history of (family) thyroid function disease or depression/anxiety, typical pregnancy related symptoms such as morning-sickness symptoms (using the Pregnancy-Unique Quantification of Emesis).[70] This information will be collected using self-report via the questionnaires. Moreover, the obstetric record forms will be critically evaluated for the occurrence of possible complications during pregnancy and labour. It is well known that apart from baseline BMI, inappropriate weight gain is an important determinant of both PE and GDM. The national institute of medicine of the US has defined inappropriate weight gain as the relative weight gain in relation to baseline BMI.[71]

Statistical analyses

Descriptive data will be presented as frequencies and corresponding percentages or means and SD. Differences between groups will be analysed using t-tests for continuous variables and χ^2-tests for categorical variables. A $p<0.05$ will be considered significant. Effect sizes of the corresponding statistics will be analysed. Missing data will be imputed using multiple imputation using the SPSS version 25.

To study trajectories of gestational thyroid function, we will perform LCA using MPlus V.7.4.[72] LCA is a longitudinal mixture modelling technique that can identify homogeneous classes within a larger heterogeneous longitudinal data sample. To model thyroid function, we will include TSH and fT4 at all trimesters.[72] Since three time points were included, only linear growth factors can be estimated. The starting point will be a one-class model, after which models will be fitted to increasing numbers of classes. To determine the optimal number of classes, we will apply the following fit indices: Bayesian information criterion, Lo-Mendell-Rubin likelihood ratio test and Bootstrapped likelihood ratio test.[73] Apart from these fit indices, we will also consider entropy, with entropy values closer to 1 indicating clearer delineation of classes.[74] We will further account for parsimony and interpretability of the models, and average posterior probabilities of their classes. We will also take into account whether additional classes include more than 1% of the total sample. We will use this statistical approach both for changes of thyroid function as well as pregnancy distress symptoms assessed at three different trimester throughout gestation.

The possible relation of these three trajectories with obstetric outcome will be investigated using multiple (multinominal) logistic regression, adjusting for age, parity, maternal educational level and EDS score, with appropriate adjustments for non-normality if necessary. Similarly, multiple linear regression will be used to evaluate the possible association of these thyroid trajectories and the depression scores. A similar technique will be applied to assess trajectories of symptoms of depression (EDS), PI and NA. To model the trajectories of these variables, three time points during the pregnancy will be included, using the same LCA methodology as for thyroid function, as described above. We will compare the prevalence of different thyroid function trajectories between the different trajectories of pregnancy distress symptoms using χ^2 tests.

ETHICS AND DISSEMINATION

The Brabant study has been approved by the Medical Ethical Committee of the Máxima Medical Center Veldhoven (protocol number NL64091.015.17). Women will be provided with verbal and written information about the study and will sign a written informed consent when they agree to participate. During the design of the study, special attention was given to the length and nature of the questionnaires, in order to minimalise the burden on the participants. Moreover, two of the three blood samples overlap with the blood samples collected as part of the regular obstetric care, meaning women only need one extra venipuncture, which limits the burden for the participants. Data management will adhere to strict guidelines in compliance with General Data Protection Regulation of the European Union. Results of the study will be submitted to peer reviewed journals in the relevant fields and presented on national and international conferences. These will be drafted according to Strengthening of the Reporting of Observational Studies in Epidemiology reporting guidelines.

DISCUSSION

The extensive perinatal literature is hampered by many studies using a cross-sectional design, especially when psychological and/or obstetric outcome are linked to possible biological determinants. Moreover, the very recent literature of impaired maternal thyroid function in relation to obstetric outcome shows an intriguing paradox: on the one hand, four large randomised controlled trials failed to show any benefit of thyroid hormone treatment during gestation on either obstetric or developmental outcomes.[75–78] On the other hand, a recent meta-analysis in over 40 000 pregnant women showed a clear association between poor thyroid function and preterm birth and the similar consortium showed an association with poor thyroid function and birth weight.[79 80] Apart from possible explanations reported in the literature (intervention started too late), it might be possible that we need further differentiation or more accurate definition of subgroups of women with an abnormal pattern of thyroid function throughout pregnancy who might benefit from an intervention. LCA might contribute to a more accurate definition of the targeted group using a prospective approach rather than a cross-sectional approach.

The major strength of the Brabant study is the aim to overcome these limitations using a prospective design with repeated measurements in a large sample of pregnant women, assessing both psychological and biological

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parameters. The large sample size will enable to look at possible associations between psychological and physiological determinants and obstetric complications that are relatively rare (PE, PTB, SGA), also in primiparous and multiparous women separately, using advanced statistics including LCA. This latter technique will also enable to look at a possible association between thyroid function and distress symptoms in a prospective way. Moreover, the feasibility of the Brabant study is realistic because of the extensive experience of the perinatal research group of Tilburg University that formed up to six pregnancy and postpartum cohorts in the past 30 years, varying from 300 to 2200 women. Over this 30-year period—in the same area as the current study—the participation rate was persistently between 70% and 75% with a drop-out of 7%–10% during the pregnancy. In the current study, all women provide written informed consent to track obstetrical outcomes in the medial record forms. This will result in objective obstetric information detected during clinical practice by midwives and obstetricians. All questionnaires will be completed online with no (face-to-face or telephone) interviews. This limits the possible outcome with regard to syndromal diagnosis of depression and anxiety.

In conclusion, there is a need for longitudinal cohort studies with multiple measurements in large samples of pregnant women. The current study will contribute with a comprehensive and in-depth study of factors affecting obstetric outcome, including thyroid function and pregnancy distress, and other important psychological and social changes, such as the partner relationship and well-being and performance at work during the perinatal period.

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