Supplement 1:

Pre-registered study protocol and details on deviations

Title The association of gestational thyroid function and thyroid autoimmunity with preterm birth.

PROSPERO ID: CRD42016043494
(https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=43494)

Proposed Working Group
(Indicate potential investigators/authors for this project)
First author / Last Author: Tim IM Korevaar / Robin P Peeters

CTP sponsor: n/a

Other collaborators: Interested Steering Committee members and Eric Steegers

Source of funding (if any) / ethical committee approval (if needed): ZonMw / none

Background
(Explain briefly why this subproject is innovative with respect to prior studies done in this field)

Preterm birth is the largest direct cause of child morbidity and mortality in almost all high and middle-income countries.[1] Furthermore, it is an important risk factor for psychiatric, metabolic, cardiovascular and renal disease later in life.[2-4] The estimated incidence of preterm birth in developed countries was 5-12%, yet in the majority of these women no known risk factors can be identified.[5, 6] Severe hypo- or hyperthyroidism during pregnancy is an important risk factor for preterm birth. However, conflicting results have been published on milder alterations in thyroid function tests and thyroid autoimmunity over the last two decades.[7-10] Moreover, meta-analyses and large cohort studies so far have been unable to study effect thresholds and also lacked the ability to quantify effects of overt disease and other small but relevant subgroups. This is a key issue to address as universal thyroid screening and correction of borderline thyroid function might have substantial benefits.

Specific aims
(List the study hypotheses and specific aims of this subproject)

Primary: Investigate the association of gestational TSH, FT4 and TPOAbs with preterm birth.

Secondary: Investigate the association of thyroid disease entities (subclinical hypothyroidism, overt/subclinical hyperthyroidism and hypothyroxinemia) and TPOAb positivity with preterm birth.

Methods
(Describe briefly the methods you plan to use to address the study hypothesis/questions, in particular, what variables you need from the cohort databases to accomplish your goals)

Study population with inclusion/exclusion criteria and cohorts you intend to include
Study cohorts to include: Based on results of a systematic search, see eMethods in Supplement 2.
Study population: Estimated based on appendix 1: N= *TBD*

Basic variables needed (Please be as specific as possible)
Exposures: TSH, FT4, TPOAbs

Covariates (including mediators and modifiers): Gestational age at blood sampling, maternal age, BMI, height, smoking status, parity, education level, marital status, household income, fetal gender (a codebook with the full data request is provided).

Outcomes: Preterm birth (<37 weeks), preterm birth (<34 weeks), spontaneous preterm birth, mean gestational age at birth, premature rupture of membranes.

Exclusion criteria: Fertility treatment, multiple gestation pregnancies, thyroid medication usage, pre-existing thyroid disease.

Planned analyses
(Provide a brief description of the statistical analyses that are planned based on (presumed) underlying biology)

Definition of outcomes:

Primary analysis:
1) The continuous association of maternal TSH, FT4 and TPOAbs with preterm birth outcomes.
- TSH, FT4 and TPOAb SD scores will be calculated per population and studied in order to retain inter-individual differences. Percentile scores will be calculated per cohort and studied to define optimal population-based cut-offs.

Secondary analyses:

1) The association of (sub)clinical disease entities and TPOAb positivity with preterm birth outcomes.
- Percentile scores will be calculated per cohort and different population-based cut-offs for clinical disease entities will be calculated define optimal population-based cut-offs.

2) The association of TgAbs with preterm birth.
- Similar methodology as for TPOAbs.

Pre-specified sensitivity analyses

3) Effects of TSH and FT4 in women with and without TPO and/or Tg antibody positivity.

4) Stratification per week of gestational age of serum measurement.

Pre-specified interactions

4) With known risk factors (maternal age, BMI, smoking, ethnicity).

Additional analysis:
5) Funnel plot to evaluate publication bias.

Statistical analyses:
We will study the above described associations by performing and individual participant based meta-analysis (combining raw data). We will use both a one-step and two-step approach. For the one step, TSH, FT4 and TPOAb concentrations will be standardized to SD scores per cohort and analyzed utilizing models with random intercepts and slopes per cohort. In addition, we aim to extract effect thresholds by calculating percentile scores per cohort and assess the risk of outcomes per percentile. For the two-step approach, TSH, FT4 and TPOAb concentrations will be standardized to SD scores and/or percentile scores per cohort and analyses performed in each cohort will be pooled.

Project Timeline
(Indicate the presumed date when the project will be completed)

Project period:

June 2016: Systematic search and sending invitations
June 2016 – September 2016: Data collection

September – December 2016: Analyses
January 2017: First results discussion with working group and update search
February 2017: Finalize results
March 2017: First draft manuscript

References:

1. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, Rudan I, Campbell H, Cibulskis R, Li M, Mathers C, Black RE. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151-61.
2. Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, MacCabe J, Rifkin L, Hultman CM. Preterm birth and psychiatric disorders in young adult life. Archives of general psychiatry 2012;69:E1-8.
3. Willemsen RH, de Kort SW, van der Kaay DC, Hokken-Koelega AC. Independent effects of prematurity on metabolic and cardiovascular risk factors in short small-for-gestational-age children. J Clin Endocrinol Metab 2008;93:452-8.
4. Vikse BE, Irgens LM, Leivestad T, Hallan S, Iversen BM. Low birth weight increases risk for end-stage renal disease. Journal of the American Society of Nephrology : JASN 2008;19:151-7.
5. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.
6. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta obstetricia et gynecologica Scandinavica 2008;87:590-600.
7. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W, American Thyroid Association Taskforce on Thyroid Disease During P, Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081-125.
8. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2543-65.
9. He X, Wang P, Wang Z, He X, Xu D, Wang B. Thyroid antibodies and risk of preterm delivery: a meta-analysis of prospective cohort studies. Eur J Endocrinol 2012;167:455-64.
10. Sheehan PM, Nankervis A, Araujo Junior E, Da Silva Costa F. Maternal Thyroid Disease and Preterm Birth: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab 2015;100:4325-31.

Deviations from pre-specified protocol
During the course of the study we had to deviate from the pre-specified protocol for certain analyses 1)

we could not calculate valid population-based percentile or SD scores for TPOAb due to skewness of the data and large differences in the limit of detection between the studies, instead we used a single population-based cut-off and sensitivity analyses using high absolute values and multitudes of the upper limit of the normal range; 2) we could not perform analyses on premature rupture of membranes due to limited data availability; 3) we additionally investigated the association with preterm birth <32 weeks as a secondary outcome due to the large differences in results between preterm birth <37 and < 34 weeks. 4) Upon reviewer request we published results on additional adjustment of TPOAb positivity, rather than analyzing the effects in thyroid antibody positive and thyroid antibody negative women. 5) Due to power restrictions we did not stratify analyses per gestational age at serum measurement but instead analyzed the interaction term similar to for example BMI.