**Prospero registration**

**Citation**

Joris Osinga, Arash Derakhshan, Tim Korevaar. Definition and prevalence of thyroid dysfunction in pregnancy: a systematic review and individual patient data meta-analysis. PROSPERO 2021 CRD42021270078 Available from: <https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021270078>

**Review question**

Primary:

1. Systematic review: to provide an overview of all available population based, assay-specific reference ranges for TSH and FT4 during pregnancy

2. Individual patient data meta-analysis using consortium data: To quantify the prevalence of thyroid function test abnormalities in pregnancy

Secondary

3. Systematic review: to analyze and compare differences in the in- and exclusion criteria of the reference populations published and in the subsequent reference intervals calculated.

4. Systematic review: To assess the impact of using additional exclusion criteria for the reference population by simulating these in the Consortium on Thyroid and Pregnancy.

5. To quantify the differences in the prevalence of thyroid function test abnormalities using trimester-specific reference ranges and study-period-specific reference ranges (defined as a reference range across the gestational age for that specific study) for TSH and FT4

6. To assess and quantify within assay-variability for TSH and FT4 reference ranges

7. To quantify thyroid function abnormalities when using fixed cut-off values.

**Searches**

Embase, MEDLINE (Ovid), Web of Science without language or publication date restrictions

Search date 2021-04

**Types of study to be included**

Non-selected, population-based prospective cohorts

**Condition or domain being studied**

Thyroid dysfunction during pregnancy is associated with adverse pregnancy outcomes such as miscarriage, gestational hypertension, gestational diabetes, pre-eclampsia, preterm birth, small for gestational age neonates and lower offspring IQ. Diagnosing thyroid dysfunction during pregnancy is complicated due to changes in maternal thyroid physiology. To account for these differences, the American Thyroid Association (ATA) recommends calculating population-based, assay-specific, trimester-specific, reference ranges in TPOAb negative pregnant women without known thyroid disease. When calculating reference ranges in pregnancy is not feasible, the guideline advises using reference ranges calculated in a similar population and using the same assay. Following the ATA recommendation, the next step is using fixed cutoff values for TSH. To this date, no comprehensive overview of available reference ranges for TSH and FT4 (calculated in accordance with the ATA recommendation) and the prevalence of thyroid disorders exists. Such an overview could provide the needed data for implementing the correct reference range in hospitals around the world. Moreover, from a physiological point of view, trimester-specific reference range s are unlikely to adequately reflect the hormonal changes during pregnancy. It is unclear to what extent the use of trimester-specific ranges affect the identification of individuals classified with an abnormal thyroid function test.

**Participants/population**

- Non-selected, population-based prospective cohorts

- Serum TSH and/or FT4 reference intervals

- Exclusion criteria conform the latest ATA guideline of 2017: known thyroid disease, use of thyroid hormone altering medication, TPO antibody positivity, pregnancies conceived through IVF.

**Intervention(s), exposure(s)**

No interventions are studied.

Exposures are taken into account in the comparison of reference intervals: gestational age at time of blood sampling, Tg antibodies, type of assay used to determine thyroid hormones

**Comparator(s)/control**

Not applicable.

**Context**

Exclusion criteria: Fertility treatment, twin pregnancy, thyroid medication usage, pre-existing thyroid disease.

**Main outcome(s)**

1. Overview of available population based, assay-specific reference ranges of TSH and FT4 in pregnancy

2. Population based, assay- and trimester-specific reference ranges for TSH and fT4 and prevalence of thyroid function abnormalities in pregnancy

***Measures of effect***

Systematic review: TSH will be displayed as mU/L, FT4 as pmol/L

IPD meta-analysis: Net Reclassification Index will be used to compare different methodologies for calculating reference intervals and subsequent prevalences of thyroid dysfunction.

**Additional outcome(s)**

Secondary outcomes:

1. Quantification of differences in the selection of reference populations, and the subsequent effect on reference intervals

2. Intra-assay differences in TSH and FT4 reference ranges.

The difference in TSH and FT4 reference ranges and the prevalence of thyroid function test abnormalities according to

3. A study-period-specific approach

4. Fixed TSH cutoffs as specified by the ATA

5. TgAb status

as compared to the current guideline recommendations.

**Data extraction (selection and coding)**

All studies retrieved through the systematic search will be screened, title and abstract, for inclusion by two authors (JO and AD). The full text of all included studies will be retrieved and assessed for eligibility by two independent reviewers (JO and AD). Any disagreement will be resolved by a third reviewer (TK). All included studies will be summarized in an excel file with all relevant results.

**Risk of bias (quality) assessment**

All studies will be assessed for (selection) bias and will be accounted for in the results.

**Strategy for data synthesis**

Primary analysis:

1. Qualitative overview of systematic search (flowchart), overview of available population based, assay-specific reference ranges of TSH and FT4 in pregnancy (table)

2. Trimester- and assay-specific reference ranges of TSH and FT4 will be calculated using the 2.5th and 97.5th percentile per cohort, after exclusion of TPOAb positivity, and compared to cohort-specific reference ranges. Prevalence of thyroid function abnormalities will be calculated.

Secondary analyses:

1. Simulation of using additional exclusion criteria (based on the findings of the systematic review) for defining the reference population in the Consortium on Thyroid and Pregnancy, and the comparison of the calculated reference intervals

2. Similar methodology as for primary analysis (2), without the division into trimester groups. The Net Reclassification Index analysis will be used to compare differences in prevalence of thyroid function abnormalities.

3. The participating cohorts will be divided into groups based on assay. Trimester- and assay-specific reference ranges of TSH and FT4 will be calculated using the 2.5th and 97.5th percentile per cohort, after exclusion of TPOAb positivity. Prevalence of thyroid function abnormalities will be calculated and compared using the Net Reclassification Index analysis.

4. The calculated prevalences will be compared with calculated prevalences using fixed cut-off values 2.5, 3.0 and 4.0 mU/L for TSH.

5. Similar methodology as for primary analysis (2) on subset with data on TgAb status, with and without exclusion of TgAb positivity. Referance ranges and prevalence of thyroid test abnormalities will be calculated and compared using the Net Reclassification Index analysis.

**Protocol violations**

During the systematic review it became apparent there was a large heterogeneity in the methodology of calculating reference intervals of TSH and FT4 during pregnancy. We decided to focus our efforts on comprising an overview of clinically useful reference intervals for thyroid function hormones during pregnancy. Methodological varieties often encountered in literature were simulated as planned in the Consortium on thyroid and pregnancy, and were used as the basis of the overview of reference intervals.

Ultimately, we did not perform primary analysis point 2) the calculation of prevalences of thyroid function test abnormalities in pregnancy. Moreover, we did not perform secondary analysis point 5), 6) and 7) in this study. Since no prevalences were calculated, the Net Reclassification Index was not performed in this study.

Furthermore, in the registration was noted that one of the exclusion criteria was: pregnancy conceived through IVF, since this did not lead to meaningful differences in reference intervals, these participants were included in all analyses unless specified otherwise.