# TPO and Pregnancy

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- Thyroid autoimmunity (TAI) is prevalent amongst women of reproductive age.
- TAI describes the presence of circulating anti-thyroid autoantibodies that are targeted against the thyroid and can occur with or without affecting thyroid function.

- thyroid peroxidase antibodies (TPOAb)
- thyroglobulin antibodies (TGAb)
- thyrotropin receptor antibodies (TRAb)

are the three most clinically important.

- Thyroid peroxidase antibodies (TPOAb) are the most common anti-thyroid autoantibodies;
- present in 90% of cases of Hashimoto's thyroiditis, 75% of Graves' disease and 10-20% of nodular goitre or thyroid carcinoma.
- However, around 10-15% of biochemically euthyroid individuals will also have an elevated TPOAb titre.

- Higher TPOAb positive rates were found in women with a BMI >34.9 kg/m2 and with increasing TSH concentrations but significantly lower rates in women of Black ethnicity compared with Caucasians.

- Here we will discuss the associations between TPOAb and adverse pregnancy outcomes.
- Despite this association the aetiology remains unknown.

# Several theories

- The first theory is that the presence of circulating thyroid antibodies is not directly related to the pregnancy loss, but rather represents a marker of an underlying autoimmune imbalance. An imbalance which, in turn, could explain a greater rejection rate of the foetus.

- The second theory proposes that despite apparent biochemical and clinical euthyroidism, the presence of TAI could be represent a reduced ability of the thyroid gland to adapt adequately to the necessary changes associated with pregnancy; due to the reduced functional reserve characteristic of chronic thyroiditis.

- The third theory suggests that as increasing age has been associated with increasing titres of TPOAb; that age itself is the risk factor rather than the TPOAb.
- It is most likely that the increased risk of adverse pregnancy outcomes associated with TAI is of multifactorial origin.

# Adverse outcomes associated with TPO antibodies in pregnancy

- MATERNAL
- FETAL/CHILD RISKS

# MATERNAL

- *TPOAb and miscarriage*
- *TPOAb and pre-term birth*
- *TPOAb and thyroid disease in pregnancy*
- *TPOAb and other antenatal adverse events*
  - *Pre-eclampsia*
  - *Gestational diabetes*
  - *Placental abruption*
  - *Polyhydramnios*
  - *Premature rupture of membranes*
  - *Anaemia*
- *TPOAb and post-partum complications*
  - *Post-partum thyroiditis*
  - *Post-natal depression*
  - *Future thyroid disease*

# FETAL/CHILD RISKS

- *TPOAb and behavioural/intellectual development*
- *TPOAb and birthweight*
- *TPOAb and hearing loss*
- *TPOAb and other fetal risks*

# *TPOAb and miscarriage*

- A systematic review of over 12,000 women, published in 2011, showed that the presence of thyroid autoantibodies leads to a significantly increased odds of miscarriage for women from all populations compared to women without autoantibodies.
- The meta-analysed results showed: subfertility population (OR 3.15 [95% CI 2.23-4.44] $p<0.001$); recurrent miscarriage population (OR 4.22 [95% CI 0.97-18.44] $p=0.06$) and "unselected" or other (OR 4.28 [95% CI 2.06-8.92] $p<0.001$)

- two further prospective studies by Liu et al. in 2014 and Bhattacharyya et al. in 2015, totalling over 3000 women, have also found an increased risk of miscarriage in women with TPOAb.

- The most recent study of TPOAb and pregnancy loss was by Plowden et al. in 2016. They found that anti-thyroid antibodies were not associated with pregnancy loss, however when looking in detail at the numbers, despite a total of 1228 women enrolled for thyroid screening, only 29 women tested positive for TPOAb and conceived a pregnancy. Of this 29 there were only 3 losses, the small numbers explain why no association was found.

- Overall, there is substantial high-quality evidence to demonstrate that TPOAb are linked to higher rates of miscarriage.

# *TPOAb and pre-term birth*

- Two meta-analyses with large sample sizes He et al. (n=35000 women) and Thangaratinam et al. (n=12,000 women) both demonstrated an increased odds of pre-term birth with TPOAb compared to women without TPOAb.
- The metaanalysis by Thangaratinam et al. found an increased odds of pre-term birth of 2.07 (95% CI 1.17-3.68, p=0.01) while the other study by He et al. also showed an increased relative risk of pre-term birth of 1.69 (95% CI 1.19-2.41, p=0.003)

- These findings have been further substantiated by an individual patient data (IPD) meta-analysis recently published by Korevaar et al. in 2019 which found that TPOAb positivity was significantly associated with an increased odds of preterm birth (OR 1.33 95% CI 1.15-1.56) when adjusting for maternal age, body mass index, ethnicity, smoking status, gestational age at blood sampling and fetal sex.

# *TPOAb and thyroid disease in pregnancy*

- Several studies have shown that TPOAb positive women who are euthyroid are more likely to develop impaired thyroid function during pregnancy, particularly subclinical hypothyroidism (SCH) but also have the potential to progress to overt disease.

- Owing to this increased risk of thyroid disease, and the known harmful effects of SCH and overt hypothyroidism on pregnancies, the Endocrine Society Clinical Practice Guidelines (ESCPG) and the American Thyroid Association (ATA) guidelines recommend thyroid function monitoring for women with known thyroid autoimmunity during pregnancy.

- It is recommended that women with TPOAb are offered thyroid function testing around 6-8 weeks gestation with a further re-test 4 weeks later if normal.
- Treatment with levothyroxine should only be commenced if an abnormality in thyroid function is detected, as there is currently no evidence to support levothyroxine treatment of euthyroid women with TAI improves pregnancy outcomes.

# *Pre-eclampsia*

- In a cohort of over 600 women, those with TPOAb were found to have a higher risk of preeclampsia, however when studied in detail this was in conjunction with apparent thyroid dysfunction (RR = 3.7, p = 0.003).
- A high quality meta-analysis by Van De Boogard et al. showed no association between thyroid antibodies and hypertension or pre-eclampsia.
- Conclusion: that there is no strong evidence linking TPOAb to hypertensive disorders.

# *Gestational diabetes*

- A study by Karakosta et al. found that the combination of TPOAb and high TSH in early pregnancy was associated with an increased risk for gestational diabetes [relative risk (RR) 4.3, 95% confidence interval (CI) 2.1-8.9)].
- This finding was supported by the results of a literature review in 2014 which reported a higher prevalence of TPOAb in gestational diabetes compared to healthy controls.
- In contrast the results of a large cohort study of 1193 women in 2016 found no association between TPOAb and development of gestational diabetes.
- In the absence of a high quality meta-analysis of the existing studies we cannot confirm or refute a link between gestational diabetes and TPOAb positivity

# *Placental abruption*

- There has been suggestion that TPOAb positivity is associated with placental abruption.
- Abbassi-Ghanavati et al. showed a 3 fold increased rate of abruption.
- This finding was supported by a larger study by Haddow et al. amongst over 10,000 women.
- Further studies are needed to confirm this association, although the evidence thus far does suggest a link.

# *Polyhydramnios*

- Chen et al. studied 208 women and found the incidence of polyhydramnios was significantly higher in TPOAb+ve women compared to TPOAb –ve (15.4% vs. 2.7%, $p<0.02$).

# *Premature rupture of membranes*

- The same study group which found a link with TPOAb and polyhydramnios also found an association between TPOAb positivity and premature rupture of membranes.
- This finding was supported by the large study by Haddow et al..

# *Anaemia*

- In 2016 a study by Meena et al. found a link between TPOAb positivity and maternal anaemia.
- BUT there have been no large prospective cohort studies or metaanalyses looking at the relationship between TPOAb positivity and polyhydramnios or maternal anaemia.

# *Post-partum thyroiditis*

- TPOAb positivity has been associated with a significantly increased risk of postpartum thyroiditis (PPT) in several studies.
- Chen et al. found the prevalence of PPT to be significantly higher in TPOAb-positive than TPOAb-negative group (42.31% versus 7.14%, $P < 0.001$).
- The meta-analysis by Van de Boogard showed a statistically significant increased pooled odds of developing PPT in women with TPOAb (OR 11.54 95% CI 5.44-23.88).
- In view of this link with post-partum thyroiditis we would recommend that TPOAb positive women are routinely offered thyroid function testing 6 weeks following delivery.

# *Post-natal depression*

- Associations with postnatal depression have been not so consistent.
- A study of TPOAb and post-partum depression at 48 hours post-delivery found no association.
- Another study reported that TPOAbs were independently associated with depression at 12 weeks' gestation (OR, 95%CI: 2.4 (1.1± 6.0)) and at 4 (3.8 (1.3 ± 7.3)) and 12 weeks (3.6 (1.2 ± 7.1)) postpartum.
- The presence of TAI or a higher TSH level during the postpartum period has been independently associated with depressive symptoms or dysphoric mood, even when clinical depression was not present.

- Similarly, another study found that TPOAb positive women had significantly higher depressive symptoms in the antenatal period compared with TPOAb-negative women, and TPOAb-positive women continued to have significantly higher depression, anger, and total mood disturbance scores postpartum, regardless of development of postpartum thyroiditis.

- It may be that women with thyroid anitbodies are predisposed to mood disturbances preconceptually and that postnatal symptoms may not be a new development and may be occurring independently of thyroid dysfunction.

# *Future thyroid disease*

- TPOAb-positivity has been strongly associated with future development of thyroid disease in women. It is therefore important that women are counseled and monitored appropriately.
- It is recommended annual thyroid function testing to ensure any progression to thyroid disease is detected.

# FETAL/CHILD RISKS

- Maternal thyroid antibodies have been linked to long term developmental risks to the offspring but a causative association is yet to be established.

# TPOAb and behavioural/intellectual development

- A study of over 3000 children born to mothers with TPOAb found that elevated titres of TPOAbs during pregnancy impacted on children's risk of problem behaviour, in particular, attention deficit/hyperactivity.
- Brown et al. found that the prevalence of maternal TPO-Ab was significantly increased in pregnancies giving rise to autism cases (6.15%) compared to controls (3.54%).
- Li et al. reported lower motor and intellectual development at age 25–30 months in the offspring of euthyroid women who were TPOAb positive compared to children of TPOAb-negative controls.

- Another study by Williams et al. found lower perceptual performance and motor scores in children of TgAb-positive mothers, and lower perceptual performance scores in children with TgAb-positive cord blood.
- However, no neurodevelopmental outcomes were associated with maternal or infant TPOAb status.
- It is important that women with TPOAb are aware of the potential risk of neurodevelopmental delay and/or behavioural problems in their children.

# *TPOAb and birthweight*

- A suggestion of low birthweight being associated with TPOAb was made by Chen et al..
- Monen et al. found no association found between TPOAb and small for gestational age babies.
- A comprehensive systematic review by Tong et al. also found no association between TPOAb and intra-uterine growth restriction.
- In contrast, Mannisto et al. found that TPO-Ab-positive mothers had more large for-gestational age infants (2.4 vs. 0.8%, P = 0.017) and significantly higher placental weights were observed among TPO-Ab-positive mothers.
- It would seem that with the inconsistent findings there is unlikely to be a relationship between TPOAb and birthweight.

# *TPOAb and hearing loss*

- Elevated TPOAb levels have also been associated with sensorineural hearing loss.
- A study by Wasserman et al. showed a modest, statistically significant, effect of TPOaAbs on cognitive performance observed at 4y of age which lessened in both magnitude and P value by the age of 7years.
- Children with sensorineural hearing loss (SNHL) had lower IQ scores at both ages.

# *TPOAb and other fetal risks*

- A study by Ozdemir et al. compared hypothyroidism associated with autoantibodies to non-autoimmune hypothyroidism. The results showed pregnant women with autoimmune hypothyroidism had higher rates of babies needing NICU admission.
- Negro et al. found an association between TPOAb and neonatal respiratory distress.

# Treatment options

- Levothyroxine
- Selenium
- Oral steroids
- Intravenous immunoglobulin (IVIG)

# *Levothyroxine*

- For women with TPOAb, if they are found to have an elevated TSH above the trimester specific range, levothyroxine treatment can be considered.
- This is regardless of free thyroxine levels, since the hypothyroidism may be progressive as the pregnancy advances.
- However, there is currently no robust evidence of any clinical benefit in treating TPOAb positive women who have subclinical hypothyroidism.

- A systematic review of five studies of levothyroxine treatment in thyroid antibodies showed no significant reduction in miscarriage (RR: 0.58, CI: 0.32-1.06), but only a significant reduction in preterm birth (RR: 0.31, CI: 0.11-0.90).

- There have been 2 randomised trials by Negro et al., including a total of 187 women, which have looked at Levothyroxine treatment for TPOAb.
- Both studies were in euthyroid women with thyroid autoantibodies; one was in unselected women and the other in women scheduled to have IVF treatment.
- These studies showed a reduction in miscarriage rates (36% and 75% relative reductions), and when the results were pooled, there was a statistically significant 52% reduction in miscarriages with levothyroxine treatment (RR: 0.48, 95% CI: 0.25, 0.92).
- One of the two studies reported on preterm birth: this study (n=115) found a 69% reduction in preterm births with levothyroxine treatment (RR: 0.31; 95% CI:0.11, 0.90).

- A more recently published randomised controlled trial (RCT) by Wang et al. has looked specifically at euthyroid TPOAb positive women undergoing in-vitro fertilisation (IVF) treatment. They randomised 600 women to receive either Levothyroxine or no treatment. The Levothyroxine dose was either 25mcg or 50mcg and then titrated according to TSH levels in the pregnancy.
- No differences were found in miscarriage rates or in live birth rates between the groups

- The findings of the largest RCT on the subject, TABLET trial, were published in April 2019. A total of 952 women with a history of either subfertility or miscarriage, confirmed as TPOAb positive and euthyroid, were randomised to receive 50mcg once daily levothyroxine vs placebo. The treatment was commenced preconception and continued until the end of the pregnancy. There was no improvement in live birth outcome at or beyond 34 weeks in those taking LT4 and no difference in any secondary pregnancy or neonatal outcomes, including pregnancy rates and miscarriage.

- When adding the results of the TABLET trial and the trial by Wang et al. to those of the Negro et al. trials, the pooled results show no significant reduction in miscarriage with levothyroxine treatment compared with control.

- There is currently an ongoing trial lead by Vissenberg et al. in the Netherlands (T4LIFE). They have designed a double blind RCT looking at the use of Levothyroxine in TPOAb positive euthyroid women who have had recurrent miscarriage (defined as 2 or more consecutive losses). This trial is still in recruitment phase and so the results are not yet available.

# Selenium

- Selenium is an essential co-factor for the deiodinase enzymes, which are selenoproteins involved in the synthesis and metabolism of thyroid hormones.
- Selenium treatment has been proposed in helping to reduce adverse outcomes for TPOAb positive women in pregnancy.
- In one small study in a region of mild moderate iodine deficiency, selenomethionine 200mcg daily did not change the rates of antenatal hypothyroidism, pre-eclampsia or preterm birth but there was a reduction in post-partum thyroid dysfunction and hypothyroidism.
- A study in mildly iodinedeficient British pregnant women, showed that treatment with 60 μg of selenium daily did not affect TPO concentrations nor TPOAb positivity. There are also concerns of the potential harmful effects of selenium such as increased insulin resistance, which has been observed in non-pregnant adults on long-term selenium supplementation.

- In the non-pregnant population, one small study of 60 women suggested that TPOAb titres could be reduced by selenium and a large trial, CATALYST trial is currently recruiting to assess if selenium supplementation in patients with chronic autoimmune thyroiditis could alter the natural course of the disease and modulate thyroid autoimmunity, the findings of this trial could be applicable to euthyroid TPOAb positive women.

- Owing to the present lack of evidence and potential harm, selenium supplementation cannot be recommended for the treatment of TPOAb positive women during pregnancy.

# *Oral steroids*

- There have been 2 small randomised studies looking at the use of oral corticosteroids in TPOAb positive women undergoing assisted reproductive technology (ART) to improve pregnancy and live birth rates.
- The study by Litwicka et al. (n=60) found improved pregnancy and live birth rates, while a smaller study by Turi et al. (n=48) randomised women prior to intra-uterine insemination and also found higher pregnancy rate.
- The data from these small studies, while promising, is insufficient to make routine recommendations for use of oral steroids to improve pregnancy outcomes in TPOAb positive women.

# *Intravenous immunoglobulin (IVIG)*

- There are three small non-randomized case series which have been published on the use of intravenous immunoglobulin (IVIG) therapy for the prevention of recurrent pregnancy loss in women with TAI, with the live birth rates ranging from 80% to 95%.
- One study had a self-selected control group (consisting of women who refused IVIG therapy) and it reported a highly significant improvement in live births with IVIG-treatment (95% vs. 0% p = 0.001).

# Screening and monitoring

- It is recommended that thyroid function testing should be offered as soon as possible in pregnancy (ie. Around 6-8 weeks gestation) and, if normal, tests should be repeated 4 weeks later to ensure there has been no progression to hypothyroidism.
- If tests are normal at this stage there is no indication to continue monitoring through the rest of the pregnancy.
- Once the pregnancy is completed, regardless of gestation, we would recommend a thyroid function test is performed at 6weeks post-natal, given the risk of progression to post-partum thyroiditis (as outlined earlier).

# Practice points

- TPOAb are present in 10-15% of the population.
- Women with TPOAb should be counselled that they are at higher risk of miscarriage, pre-term birth and of developing thyroid disease in pregnancy but that causation is poorly understood.
- Women should also be counselled on potential fetal risks such as behavioural problems, neurodevelopmental delay and sensorineural hearing loss.
- At present, there is no proven treatment for TPOAb in euthyroid women.

# Practice points

- Given the risk of progression to hypothyroidism with TPOAb in pregnancy, women should be offered thyroid function testing in early pregnancy and continued monitoring if appropriate.
- Routine screening, either preconception or antenatally, for TPOAb is not recommended, however it should be considered for “high risk” populations such as women undergoing assisted reproductive technology and those with history of recurrent miscarriage or preterm birth.