## Abstract: 43O

**Thyroglobulin antibody positivity induces maternal hyperglycaemia and increases placental weight in a Lewis rat model**

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Autoimmune thyroiditis (AIT) is the most common autoimmune disease impacting up to 20% of women of reproductive age. The disease is characterised by the presence of thyroid antibodies (TAs), and lymphocytic infiltration of the thyroid gland. This condition is infrequently diagnosed because in the absence of chances to thyroid stimulating hormone (TSH) concentrations, it is unlikely that TAs will be tested. TAs in pregnancy increase the risk of pre-term birth and gestational diabetes mellitus (GDM) in the absence of changes to TSH or thyroid hormones. We aimed to use a rat model of AIT to explore how AIT impacts risk of maternal and fetal complications in pregnancy.

Thyroglobulin antibody positivity (TgAb+) was induced before pregnancy in female Lewis rats by immunisation with porcine thyroglobulin in Freund's adjuvant and exposure to sodium iodide in drinking water. We then explored how TgAb+ affects maternal random blood glucose prior to pregnancy and maternal glucose tolerance on embryonic day 16 (E16) by performing an intraperitoneal glucose tolerance test (IPGTT). On E20, rats were anesthetised by intraperitoneal administration of 50/50 mix of ketamine/xylazil (1mL/kg body weight), prior to euthanasia by exsanguination. Maternal organs, placentas and fetuses were removed, weighed, and immediately snap frozen for molecular analysis.

Maternal TgAb+ increased maternal plasma free thyroxine (FT4) concentration by E20. However, there was no change to TSH concentration and no overt thyroid pathology. Maternal glucose tolerance on E16 was unaffected by TgAb+, however maternal random blood glucose prior to pregnancy and on E20 was increased. This was accompanied by reduced random plasma insulin levels at these same time points. The placental hormone that regulates β-cell expansion in pregnancy, rat placental lactogen, was significantly increased, suggesting that low insulin levels are likely a consequence of high FT4, not insufficient β-cell expansion in pregnancy. While maternal TgAb+ was associated with a slight increase in body weight in male and female fetuses, this did not reach statistical significance. Placentas were significantly larger which was associated with increased junctional zone glycogen accumulation and altered labyrinth zone (LZ) expression of genes that regulate angiogenesis and syncytialisation. Genes that may be important for achievement of term gestation were also reduced in the LZ.

This model indicates that maternal TgAb+ may lead to elevations in maternal random blood glucose levels due to low insulin levels. As this was present prior to pregnancy, it is not representative of a GDM-like phenotype, but rather a pre-pregnancy diabetes-like phenotype which is likely due to high FT4. Nevertheless, the outcomes seen in the fetuses were characteristic of a diabetic pregnancy, including a slight increase in fetal weight, increased placental weight and glycogen accumulation. Future studies should investigate the role of TgAb+ in placental endocrine function, their contributions to maternal metabolic disease in pregnancy and impact on premature delivery. Maternal TgAb+ should be monitored in pregnancy as it may increase risk of maternal and fetal complications even in the absence changes to TSH.