The role of the placenta in fetal thyroid hormone physiology

An Eerdekens, Neonatal Intensive Care
No conflict of interest
• Introduction
• Thyroid hormones: crucial for fetal development
• The role of the mother and the placenta
• What about preterm birth?
• Conclusions
INTRODUCTION
THYROID HORMONES: CRUCIAL FOR FETAL DEVELOPMENT
THYROID HORMONES:
DEVELOPMENTAL HORMONES

HYPERTHYROIDISM
- Intolerance to Heat
- Fine, Straight Hair
- Bulging Eyes
- Facial Flushing
- Enlarged Thyroid
- Tachycardia
- Cyanotic BP
- Breast Enlargement
- Weight Loss
- Muscle Wasting
- Finger Clubbing
- Tremors
- Diarrhea
- Menstrual Changes (Amenorrhea)
- Localized Edema

HYPOTHYROIDISM
- Intolerance to Cold
- Receding Hairline
- Facial & Eyelid Edema
- Dull-Blunt Expression
- Extreme Fatigue
- Thick Tongue
- Slow Speech
- Hair Loss
- Apathy
- Lethargy
- Dry Skin (Coarse & Scaly)
- Muscle Aches & Weakness
- Constipation
- Menstrual Disturbances
- Late Clinical Manifestations
  - Subnormal Temp
  - Bradycardia
  - Weight Gain
  - COP
  - Thickened Skin
  - Cardiac Complications
THYROID HORMONES: DEVELOPMENTAL HORMONES

Thyroxine (T-4)

3,5,3'-triiodo L-thyronine (T3)

(Tata 1999)

(Fantie 2008)
THE ROLE OF THE MOTHER AND THE PLACENTA
Human chorionic gonadotropin

Thyroid hormones T4 and T3

Thyroid hormone transporters
MCT8, MCT10, LAT1, LAT2, OATP1A2, OATP4A1

Hypothalamus
TRH

Anterior pituitary
TSH

Thyroid

T4 and T3

Cellular transport target tissues

Thyroid hormone binding proteins
- Transthyretin
- Albumin
- α-1-antitrypsin
- α-1-acid-glycoprotein

Thyroid hormone receptors

Expression T3-responsive target genes
Maternal hypothyroxinemia early in pregnancy
Iodine deficiency $\rightarrow$ $\uparrow$ T3 synthesis instead of T4
$\rightarrow$ less T4 through the placenta
$\rightarrow$ less supply to the fetal brain
$\rightarrow$ impact on neurodevelopment of the infant

Pop, 2003
Velasco, 2009
Li, 2010
Costeira, 2011
Ghassabian, 2014
Koorevaar, 2016
Congenital hypothyroidism

Maternal-Fetal Transfer of Thyroxine in Congenital Hypothyroidism Due to a Total Organification Defect or Thyroid Agenesis

Thomas Valuma, M.D., Margaret H. Gons, M.D., Ph.D., and Jan J. M. de Vilder, Ph.D.

Bernal, Endotext, (2000)
WHAT ABOUT PRETERM BIRTH?
Maternal thyroid hormone transfer

Fetal thyroid hormone secretion
Maternal thyroid hormone transfer

Fetal thyroid hormone secretion

Transient hypothyroxinaemia of prematurity (THOP)
Temporary ↓ (f)T4 levels, normal / ↓ TSH levels
Maternal thyroid hormone transfer

Sudden interruption maternal thyroid hormone supply

Limited thyroid gland reserve

Persistent fetal thyroid hormone metabolism

Immaturity of hypothalamic-pituitary-thyroid axis

Fetal thyroid hormone secretion

Non thyroidal illness

Medication

Transient hypothyroxinaemia of prematurity (THOP)
Relevance of THOP?

Histological Structure of the Cerebral Cortex

Berbel P et al., 2010
Human studies: conflicting data

Heterogeneity in definition of THOP study populations

Difficulties in thyroid hormone measurements reference values in preterm infants
Human chorionic gonadotropin

↑ T4 and T3

Thyroid hormone transporters
MCT8, MCT10, LAT1, LAT2, OATP1A2, OATP4A1

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α-1-acid-glycoprotein

Thyroid hormone receptors

Expression T3-responsive target genes
= result of complicated pregnancy

Knobel, 2005
<table>
<thead>
<tr>
<th>Identified in the human placenta</th>
<th>Thyroid hormone transporters</th>
<th>Deiodinases</th>
<th>Thyroid hormone binding proteins</th>
<th>Sulfotransferases and arylsulfatases</th>
<th>Thyroid hormone receptors</th>
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<tbody>
<tr>
<td>MCT8, MCT10, LAT1, LAT2, OATP1A2, OATP4A1</td>
<td>MCT10</td>
<td>D2, D3</td>
<td>Transthyretin (TTR)</td>
<td>Limited placental activity</td>
<td></td>
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<tr>
<td></td>
<td>LAT1</td>
<td></td>
<td>Albumine α1-antitrypsin</td>
<td>TRα1, TR α2, TRβ1 and TRβ2 mRNA expression</td>
<td></td>
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<tr>
<td></td>
<td>LAT2</td>
<td></td>
<td>α1-acid glycoprotein</td>
<td>TRα1, TR α2, TRβ1 protein expression</td>
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<tr>
<td></td>
<td>OATP1A2</td>
<td></td>
<td>TBG is not synthesized by the placenta</td>
<td></td>
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<tr>
<td></td>
<td>OATP4A1</td>
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</table>

<table>
<thead>
<tr>
<th>Compensation mechanisms (+ method)</th>
<th>↑ MCT 8 (gene and protein expression)</th>
<th>↓ MCT 10 (gene- and protein expression)</th>
<th>No proven compensation mechanisms</th>
<th>TTR toename (immunohistochemistry)</th>
<th>↑TRα1, TR α2, TRβ1 (immunohistochemie)</th>
</tr>
</thead>
</table>

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<thead>
<tr>
<th>Clinical condition?</th>
<th>Severe IUGR</th>
<th>Severe IUGR</th>
<th>Preeclampsia and IUGR</th>
<th>-</th>
<th>IUGR</th>
</tr>
</thead>
</table>

MATERNAL FACTORS
- Age
- Small stature
- High altitude
- Genotype
- Stress
- Pre-eclampsia
- Substance use/abuse
- Undernutrition
- Overnutrition
- Hypertension
- Prior IUGR

PLACENTAL AND CORD ABNORMALITIES
Placental insufficiency: reduced amino acid transport, reduced oxygen delivery, reduced neuroactive substance production
- Incorrect cord insertion
- Placental tumour
- Single umbilical artery
- Circumvallate placenta

INFECTIONS
- 'TORCH' infections
- Malaria

FOETAL FACTORS
- Congenital heart disease
- Congenital diaphragmatic hernia
- Trisomy
- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13 (Patau syndrome)
- Turner’s syndrome

Fleiss et al. Frontiers in Endocrinology (2019)
= result of complicated pregnancy

Romero, 2014
Preterm birth

- Spontaneous preterm birth (SPB)
- Indicated preterm birth (IPB)

IPB due to pregnancy associated vascular disease:
- Gestational hypertension
- Preeclampsia
- HELPP-syndrome
- +/- association IUGR

(Goldenberg, Culhane et al. 2008)
Differences in placenta histology

**SPB**
- More acute onset

**IPB due to pregnancy associated vascular origin**
- Chronic evolution

Massive chorioamnionitis in immature placenta. Exudate is present in the amnion and chorion. The placenta had a purulent surface and marked funisitis. H&E. X60. (Baergen 2005)

“Tenney-Parker” changes in a placenta at 25 weeks gestation. There is obvious acceleration of villous maturation and increased syncytial Knots, H&E. X64. (Baergen 2005)
Tenney Parker changes = Developmental shift
→ villous phenotype
  ❖ richly capillarized
  ❖ highly branched terminal villi
→ to enhance the placenta’s ability to transfer oxygen to the foetus
Hypothesis

Underlying pregnancy complication → Affect on trans-placental TH supply → Predisposition to THOP
Methods

Spontaneous preterm birth (SPB)  
Indicated preterm birth* (IPB)  
Healthy term controls

Blood sample at partus
- TSH
- Total T4
- Free T4 index (fTI)
- Total T3
- TBG
- TPO antibodies

- Weight placenta
- Fresh peri-umbilical samples
- RNA (PCR) and protein expression (Western blotting):
  - MCT8
  - MCT10
  - DiO1
  - DiO2
  - DiO3
- H&E staining, maturation score
- Automatic calculation diameter villi

Cord blood sample
- TSH
- Total T4
- Free T4
- Total T3
- TBG

* due to pregnancy associated vascular origin

Eerdekens et al., 2018
Results

319 mothers were screened and included in a larger project during pregnancy

117 singleton pregnancies

- 31 pregnancies resulting in spontaneous preterm birth (SPB)
- 45 pregnancies resulting in indicated preterm birth with vascular origin (IPB)
- 41 uncomplicated term deliveries (Controls)

202 were excluded:
- 121 samples couldn't been collected
- 14 did not meet the inclusion criteria postfactum due to congenital malformations
- 45 multiple pregnancies
- 22 indicated preterm birth without vascular cause

Eerdekens et al., 2018
Results

- Preterm birth:
  - Lower educational level
  - Higher caesarean section rate

- IPB: higher health risk profile
  - Higher BMI
  - More tobacco use

- SPB: lower median GA than IPB

- Preterm birth:
  - Lower mean placenta weight

- IPB:
  - Lower weight placenta / GA

- Preterm birth:
  - Lower birth weight

- IPB:
  - More IUGR

Eerdekens et al., 2018
Results

Eerdekens et al., 2018
Gestational age matched subset

Eerdekens et al., 2018
Results

Eerdekens et al., 2018
Results

Eerdekens et al., 2018
Results

Eerdekens et al., 2018
Chronic maternal pregnancy associated vascular pathology

Thyroid activation (increased TSH)

Early tissue maturation

Activation thyroid hormone metabolism (DIO2, DIO3, MCT10)

Increased T3 levels

Foetal maturation?
Further implications?

Early fetal maturation $\rightarrow$ ↑ chance of survival in uncertain times

BUT

At the cost of altered perinatal programming in several organ systems
EX-PRETERM ADULTS ARE CHRONIC PATIENTS

- neuro-psychological and behavioural problems
- hypertensive disorders
- metabolic syndrome

Raju, 2017
Maternal or fetal administration of glucocorticoids → increase of fetal T3 levels, but not T4 levels → decreased placental D3 activity

Maturational effects of glucocorticoids → reduced size of thyroid gland → disturbed functioning of HPT axis in offspring

Maternal smoking and high BMI → disturbed fetal gland development and endocrine function in 2nd trimester of pregnancy

Very preterm infants → alterations in thyroid function at preschool age
Relation to maternal glucocorticoid levels

Follow up of preterm infants
Obesity pandemic
½ pregnant women in United States is obese!
(Davis AM, 2020)

Table 2. Short-term and long-term outcomes associated with obesity in pregnancy

<table>
<thead>
<tr>
<th>Complications</th>
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<tbody>
<tr>
<td>Maternal</td>
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<tr>
<td>Preconception</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Immediately postpartum</td>
</tr>
<tr>
<td>Persistent postpartum</td>
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<tr>
<td>Fetal or neonatal</td>
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</tbody>
</table>

* After gestational diabetes.
† After pre-eclampsia.

(Poston, 2016)
If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.

Hippocrates
General conclusions

Thyroid hormones are crucial for fetal development

Placental compensation mechanisms in case of chronic hypoxia? Long term effects
General conclusions

Nature, 2020 (Red Méthot)
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