FISIOLOGI HORMON TIROID DAN RISIKO TERATOGENISITAS OBAT ANTI TIROID SELAMA KEHAMILAN

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PIN PAPDI, 4-6 Oktober 2019
Hotel Shangri La Surabaya
Hyperthyroidism During Pregnancy

0.05%-3.0% of pregnancy
1 to 2 of every 1000 pregnancy

• Graves’ Disease (GD) 80-95%

• Gestational Transient Thyrotoxicosis (GTT)
# Causes of hyperthyroidism in pregnancy

<table>
<thead>
<tr>
<th>Thyroid Disease</th>
<th>Iatrogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ Disease</td>
<td>Excessive levothyroxine intake</td>
</tr>
<tr>
<td>Chronic thyroiditis</td>
<td>overtreatment</td>
</tr>
<tr>
<td>Painless thyroiditis</td>
<td>factitious</td>
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<tr>
<td>Subacute thyroiditis</td>
<td></td>
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<tr>
<td>Toxic adenoma</td>
<td></td>
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<tr>
<td>Multinodular goiter</td>
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</tbody>
</table>

## Non-autoimmune hyperthyroidism

<table>
<thead>
<tr>
<th>Drugs</th>
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<tbody>
<tr>
<td>Gestational transient thyrotoxicosis</td>
</tr>
<tr>
<td>Multiple gestations</td>
</tr>
<tr>
<td>Trophoblastic disease</td>
</tr>
<tr>
<td>Hyperplacentosis</td>
</tr>
<tr>
<td>Hyperreactio luteinalis</td>
</tr>
<tr>
<td>TSH receptor mutation</td>
</tr>
<tr>
<td>TSH-producing pituitary adenoma</td>
</tr>
</tbody>
</table>

Nguyen CT et al., Clinical Diabetes and Endocrinology 2018,4:4
Thyroid Gland During Pregnancy

The gland increase 10% in size
In Iodine-replete countries

The gland increase 20-40% in size
In areas of iodine deficiency

Production of T3&T4 increases 50%, along with a 50% increase in the daily iodine requirement.
These physiological changes may result in hypothyroidism in the later stages of pregnancy in iodine deficient women who were euthyroid in the first semester.

Alexander EK et al., Thyroid 2017, 27(3): 315-
Thyroid physiology and function in normal pregnancy

- There is an increased excretion of iodine in the urine accounting for the increase in thyroid volume in areas of moderate and severe deficiency but not in iodine-sufficient regions.

- Iodine deficiency during pregnancy is associated with maternal goiter and reduce maternal thyroxin (T4) level, which is seen in area endemic cretinism.

- A recommended daily iodine intake of 250 ug/day (WHO), represents an increase from 200 ug/day.

- Changes in thyroid hormone during gestation relate to the necessity of delivering thyroxin to the foetal cells, particularly neuronal cells.

Lazarus JH. British Medical Bulletin 2011;97:137-148
• Adequate concentrations of T4 are essential for neural development and this T4 can only be maternally derived from, at least during the first trimester
Gestational variation in thyroid function in normal women

Alteration in serum concentration of hCG, TSH, and FT4 during pregnancy.

Lazarus JH., British Medical Bulletin 2011;97:137-148
hCG or a molecular variant acts as a TSH agonist so that elevated levels contribute to the cause of gestational transient hyperthyroxinaemia seen in about 0.3% of pregnancy.

Hyperemesis gravidarum, which sometimes requires hospitalization because of development of dehydration and ketosis, may be associated with hyperthyroidism due to excess hCG, stimulation and hyperthyroidism is also seen in some cases of hydatiform mole where excess hCG is secreted.

Lazarus JH. British Medical Bulletin 2011;97:137-148
Profile of changes in heterodimeric
• intact hCG (upper graph),
• serum TSH(middle graph) and
• free T4(lower graph) levels as a function
of gestation time in women with single (◉) (n=17) and twin (◎) (n=13) pregnancies

Modified with permission from J.P. Grun et al: Clin Endocrinol (Oxf), in press(134) Blackwell Science Ltd

The Thyroid-stimulating activity of hCG

Fig. 10. Schematic representation of the thyroid-stimulating activity of hCG, based on the spill-over mechanism due to the homologies between both the TSH and hCG molecules and between the TSH and LH-CG receptors.
Physiological adaptation to pathological alterations of the thyroid economy during pregnancy

<table>
<thead>
<tr>
<th>Physiologic change</th>
<th>Thyroid function test change</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Thyroid binding globulin</td>
<td>↑ serum total T4 and T3 concentration</td>
</tr>
<tr>
<td>First trimester hCG elevation</td>
<td>↑ Free T4 and ↓TSH</td>
</tr>
<tr>
<td>↑ Plasma volume</td>
<td>↑ T4 and T3 pool size</td>
</tr>
<tr>
<td>Thyroid enlargement (in some women)</td>
<td>↑ T4 and T3 degradation resulting in requirement for increase production</td>
</tr>
<tr>
<td>↑ Iodine clearance</td>
<td>↓ Serum thyroglobulin</td>
</tr>
<tr>
<td></td>
<td>↓ Hormone production in iodine deficient areas</td>
</tr>
</tbody>
</table>
KOMPLIKASI DAN RISIKO TERATOGENISITAS OBAT ANTI TIROID SELAMA KEHAMILAN
Risk factors for complications associated with hyperthyroidism in pregnancy

Risk Factors
- Long-standing GH
- Gestational hypertension
- Twin Pregnancy
- Anemia
- Frequent infections (i.e., UTIs)
- Late presentation to obstetric clinic
- Inconsistent use of medications
- Abnormal outcomes in prior pregnancy

Possible Complications

Maternal
- Miscarriages
- Gestational hypertension
- Preeclampsia
- Congestive heart failure
- Thyroid storm

Obstetrical
- Premature delivery
- Placental abruption
- Premature rupture of membrane
- Gestational hypertension

Nguyen CT et al., Clinical Diabetes and Endocrinology 2018,4:4
Risk factors for complications associated with hyperthyroidism in pregnancy

Fetal
- Congenital malformations
- Hyperthyroidism
- Developmental dysplasia of the hip associated with first-trimester maternal hyperthyroidism
- Intrauterine growth restriction (IUGR)
- Small for gestational age (SGA) infants
- Prematurity
- Stillbirth

Neonatal
- Prematurity
- Hyperthyroidism
- Neonatal central hypothyroidism
- Low birth weight

Nguyen CT et al., Clinical Diabetes and Endocrinology 2018,4:4
## Birth Defect Associated with ATD

<table>
<thead>
<tr>
<th>MMI</th>
<th>PTU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplasia cutis</td>
<td>pre-auricular sinus/fistula and cyst</td>
</tr>
<tr>
<td>Choanal atresia</td>
<td>urinary tract abnormalities in males</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td></td>
</tr>
<tr>
<td>Omphalocele</td>
<td></td>
</tr>
<tr>
<td>Urinary tract malformation</td>
<td></td>
</tr>
<tr>
<td>Eye defect</td>
<td></td>
</tr>
<tr>
<td>Ventral septal defect</td>
<td></td>
</tr>
<tr>
<td>Dyssomorphic facies</td>
<td></td>
</tr>
<tr>
<td>Athelia</td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td></td>
</tr>
</tbody>
</table>

Nguyen CT et al., Clinical Diabetes and Endocrinology 2018,4:4
**DEFINITION**

- Choanal atresia is defined as congenital stenosis of the posterior nasal apertures.
- It is the absence of communication between the posterior nasal cavity and the nasopharynx.

Eye defects

Goiter congenital

Dysmorphic facies

athelia
choanal atresia associated with maternal hyperthyroid treated with metimazole

BARBERO ET AL.

www.interscience.wiley.com
A 1-year-old girl whose mother suffers from Graves disease. The mother was taking CMZ 40 mg with thyroxine 100 mcg daily at conception, which was unplanned. When it was discovered she was pregnant, the thyroxin was stopped and CMZ gradually reduced reaching 10 mg daily by term. The mother remained euthyroid throughout pregnancy.
Antithyroid drug use in early pregnancy and birth defects: time windows of relative safety and high risk?

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¹Department of Endocrinology, Aalborg University Hospital, DK-9000 Aalborg, Denmark and
²Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Abstract

Background: Antithyroid drugs (ATDs) may have teratogenic effects when used in early pregnancy.

Objective: To review the association between the time period of ATD exposure in early pregnancy and the development of birth defects.

Methods: We identified publications on birth defects after early pregnancy exposure to the ATDs methimazole (MMI; and its prodrug carbimazole (CMZ)) and propylthiouracil (PTU). Cases of birth defects after ATD treatment had been initiated or terminated within the first 10 weeks of pregnancy were identified and studied in detail.

Results: A total of 92 publications were read in detail. Two recent large controlled studies showed ATD-associated birth defects in 2–3% of exposed children, and MMI/CMZ-associated defects were often severe. Out of the total number of publications, 17 included cases of birth defects with early pregnancy stop/start of ATD treatment, and these cases suggested that the high risk was confined to gestational weeks 6–10, which is the major period of organogenesis. Thus, the cases reported suggest that the risk of birth defects could be minimized if pregnant women terminate ATD intake before gestational week 6.

Conclusion: Both MMI and PTU use in early pregnancy may lead to birth defects in 2–3% of the exposed children. MMI-associated defects are often severe. Proposals are given on how to minimize the risk of birth defects in fertile women treated for hyperthyroidism with ATDs.
Time period in gestational weeks of maximal sensitivity to abnormal development in human

The gestational week when start or stop of MMI/CMZ therapy was reported in 24 cases of MMI/CMZ-associated birth defects where change of medication had occurred in early pregnancy

Therapy shifts in the Danish Registry study

Shifted from MMI/CMZ to PTU may give little protection against birth defects, because 13 of 149 children (8.7%) had birth defects. MMI-associated defects were only observed when a shift had been performed at or after 7 weeks of pregnancy, whereas the two PTU-related defects occurred when PTU had been started at 6 weeks of pregnancy. On the other hand, when defects were not related to MMI or PTU, shifts were more evenly distributed over time.

Withdrawal of ATD therapy in early pregnancy
Case of MMI/CMZ embryopathy from the Danish study on birth defect

The neonate was diagnosed with choanal atresia, esophageal atresia with tracheal fistula, jejunal atresia/stenosis, kidney cysts, omphalocele, and cardiac defects (ventricular and atrial septal defect). Based on the data reviewed above, it may be speculated that these severe malformation might not have occurred if the MMI therapy had been terminated already in gestational week 5.

Risk of congenital anomalies associated with antithyroid treatment during pregnancy: a meta-analysis

Xiang Li, * Gui-Yang Liu, Jian-Li Ma, Liang Zhou
The First Affiliated Hospital of Chinese PLA General Hospital, Department of Pharmacy, Beijing, China.

To evaluate the association of either propylthiouracil or methimazole treatment for hyperthyroidism during pregnancy with congenital malformations, relevant studies were identified by searching Medline, PubMed, the Cochrane Library and EMBASE.

We intended to include randomized controlled trials, but no such trials were identified. Thus, we included cohort studies and case-control studies in this meta-analysis.

A total of 7 studies were included in the meta-analyses. The results revealed an increased risk of birth defects among the group of pregnant women with hyperthyroidism treated with methimazole compared with the control group (odds ratio 1.76, 95% confidence interval 1.47–2.10) or the non-exposed group (odds ratio 1.71, 95% confidence interval 1.39–2.10). A maternal shift between methimazole and propylthiouracil was associated with an increased odds ratio of birth defects (odds ratio 1.88, 95% confidence interval 1.27–2.77). An equal risk of birth defects was observed between the group of pregnant women with hyperthyroidism treated with propylthiouracil and the non-exposed group (odds ratio 1.18, 95% confidence interval 0.97–1.42). There was only a slight trend towards an increased risk of congenital malformations in infants whose mothers were treated with propylthiouracil compared with infants whose mothers were healthy controls (odds ratio 1.29, 95% confidence interval 1.07–1.55). The children of women receiving methimazole treatment showed an increased risk of adverse fetal outcomes relative to those of mothers receiving propylthiouracil treatment.

We found that propylthiouracil was a safer choice for treating pregnant women with hyperthyroidism according to the risk of birth defects but that a shift between methimazole and propylthiouracil failed to provide protection against birth defects.

KEYWORDS: Hyperthyroidism; Congenital anomalies; Propylthiouracil; Methimazole; Pregnancy; Meta-analysis.


Received for publication on September 18, 2014; First review completed on January 12, 2015; Accepted for publication on March 10, 2015
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The effect of PTU use on congenital malformations

Li X et al. CLINIC 2015;70(6):453-459
The effect of MMI use on congenital malformations

Li X et al. CLINIC 2015;70(6):453-459
The effect of shifts between MMI and PTU use on congenital malformations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PTU&amp;MMI Events</th>
<th>PTU&amp;MMI Total</th>
<th>No ATD Events</th>
<th>No ATD Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 2013</td>
<td>16</td>
<td>159</td>
<td>190</td>
<td>3543</td>
<td>50.4%</td>
<td>1.97 [1.15, 3.38]</td>
</tr>
<tr>
<td>Korelitz 2013</td>
<td>14</td>
<td>126</td>
<td>390</td>
<td>5932</td>
<td>49.6%</td>
<td>1.78 [1.01, 3.13]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>285</strong></td>
<td><strong>9475</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>1.88 [1.27, 2.77]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.17 (P = 0.002)
The effect of anti thyroid drugs on congenital malformations

Conclusion that PTU was safer choice for the treating pregnant women with hyperthyroidism according the risk of birth defects but that a shift between MMI and PTU failed to provide protection against birth defect

Li X et al. CLINIC 2015;70(6):453-459
Of the 135 pregnancies, 4 infants (3%) were born with congenital anomalies to mothers treated with either PTU or MMI

• 3 of the fetal anomalies: 99 women treated PTU (3%) and 1 in 36 women treated MMI (2.7%)

• Concluded that PTU and MMI were equally safe and effective in the treatment of hyperthyroidism during pregnancy
  (Chattaway JM and Klepser TB. The Annals of Pharmacotherapy 2007;41: 1018-1022)

A meta-analysis from 10 studies involving 5059 participants exposure to different ATDs during pregnancy

• Result indicated that exposure of MMI/CMZ only during pregnancy significantly increased the risk of neonatal congenital malformations compared to no ATD exposure (OR 1.88; CI 95% 1.33 to 2.65; P=0.0004)

• No differences were observed between PTU exposure and no ATD exposure (OR 0.81; CI 95% 0.58 to 1.15; P=0.24)

• Exposure MMI/CMZ significantly increased the risk of neonatal congenital malformations compared to that exposure PTU (OR 1.90; CI 95% 1.30 to 2.78; P=0.001)
  (Song R et al., PLOS ONE July 3, 2017)
Kesimpulan

• Pada kehamilan kebutuhan hormon tiroid meningkat untuk memenuhi kebutuhan janin pada trimester pertama kehamilan

• Pada daerah kekurangan kadar jodium terjadi pembesaran kelenjar tiroid dan hipotiroid. Asupan Jodium 250 ug/hari

• Trimester pertama kehamilan peningkatan hormon tiroid terkait dengan peningkatan hCG menyebabkan GTT (0.3% kehamilan)

• Hipertiroid pada kehamilan yang tidak mendapat terapi dengan baik akan menyebabkan komplikasi baik pada ibu, janin dan neonatus

• OAT trimester pertama kehamilan yang aman diberikan adalah PTU terkait dengan efek teratogensitas (cacat lahir).
TERIMA KASIH