Pregnancy and Graves Disease

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Abstract
Grave’s disease account for about 85% of hyperthyroidism during pregnancy. If not properly managed, it can result in severe maternal, fetal and neonatal morbidity and mortality. Antithyroid drugs are the main treatment for Grave’s disease during pregnancy. The lowest possible dose should be used to maintain maternal free thyroxine level at or just above the upper limit of pregnancy fetal thyroid function depends on the balance between the trans-placental passage of pregnancy maternal antibodies and thyroid inhibiting and anti-thyroid drugs.

Keywords
Grave’s disease; Pregnancy; Hyperthyroidism

Background
Grave’s disease (GD) is an autoimmune condition caused by antibodies stimulating the Thyroid Stimulating Hormone Receptor (TSHR) GD affect 0.2% of pregnant woman [1]. Establishing the correct diagnosis and effectively managing GD in pregnancy is challenging. Pregnancy alter thyroid physiology and laboratory testing, anti-thyroid drugs (ATA) are associated with teratagonicity and maternal, fetal and newborn complication are directly related to control of GD and in few cases to the level of serum maternal thyroid stimulating immunoglobulin (TSI) [2]. Fetal and neonatal hyperthyroidism occurs in 1% to 5% of women with active or past history of GD and is associated with increase fetal/neonatal morbidity and mortality if not diagnosed and treated [3]. All women of reproductive age with GD or past history of GD should receive preconception counseling.

Causes of hyperthyroidism in pregnancy
GD and gestational transient thyrotoxicosis account for the majority of hyperthyroidism in pregnancy. Other cause listed in Table 1.

Non-autoimmune hyperthyroidism
• Gestational transient thyrotoxicosis
• Multiple gestation
• Trophoblastic disease
• TSH Receptor mutation
• TSH-producing pituitary adenoma

Iatrogenic
• Excessive Levothyroxine intake
• Over treatment
• Factitious

Drug
• Iodine
• Amiodarone
• Lithium

Diagnosis of GD in pregnancy
Sign and symptoms of GD in pregnancy are similar to those of non-pregnant GD. The diagnosis should be suspected in a hyperthyroid pregnant women who
a) Was having symptoms prior to pregnancy
b) Had a prior diagnosis of hyperthyroidism
c) Had previous birth to an infant with thyroid dysfunctions

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Citation: Al Kahtany NH, Al Saeed AH, Suwaidan NAB. Pregnancy and Graves Disease. Endocrinol Diabetes Open Access. 2019 Apr;2(1):110

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Thyroid Disease

- Grave’s Disease
- Chronic Thyroiditis
- Painless Thyroiditis
- Sub-acute Thyroiditis
- Toxic adenoma
- Toxic multinodular goiter

Table 1: Causes of hyperthyroidism in pregnancy [4]

The diagnosis of GD in pregnancy should always be confirmed by measuring FT3 and FT4 and TSH. Since Radioactive iodine scan are absolutely contraindicated in pregnancy making definitive can be challenging. Presence of diffuse, goiter, orbitopathy and hyperthyroid symptoms prior to pregnancy are some of the feature that favor the diagnosis of GD. Presence of thyroid receptor antibodies (TRAb) also confirm diagnosis of GD.

HCG Mediated hyperthyroidism

Serum human chorionic gonadotropin level rise immediately after fertilization and peak at 10-12 weeks of gestation, after which the level tend to fall. The β sub-unit of HCG and TSH are identical and as result of this, HCG weak thyroid stimulating activity and my cause subclinical or mild overt hyperthyroidism during the period of highest serum HCG concentration. Few example of HCG mediated hyperthyroidism are:

1. Gestational transient thyrotoxicosis (GTT)
2. Hyperemesis gravidum
3. Trophoblastic hyperthyroidism

Gestational transient thyrotoxicosis (GTT) and Hyperemesis gravidum

At 10-12 weeks of gestation which is the time for peak rise in serum HCG concentration, serum total T4 and T3 concentrations increase and TSH is reduced, thus in some women high HCG can cause biochemical hyperthyroidism. This is self- limiting condition and subsides by 14-18 weeks of gestation when HCG level tend to fall. This phenomenon is termed as gestational transient thyrotoxicosis, GTT affect 1.5% of pregnant women early in pregnancy and it is not due to intrinsic thyroid disease. GTT may present with palpitation, anxiety tremor and heat intolerance.

A severe form of GTT is hyperemesis gravidum which characterized by significant nausea, vomiting and weight loss of up to 5 kg.

These symptoms along with negative TRAB and absence of Grave’s ophthalmopathy, goiter and prior history of GD favour the diagnosis of GTT.

Laboratory test

TSH: Current guidelines recommend that trimester specific TSH ranges be used in the evaluation of thyroid function during pregnancy [5-7]. Recommended TSH ranges are:

- 0.1-2.5 MIU/L in first trimester
- 0.2-3 MIU/L in second trimester
- 0.3-3 MIU/L in third trimester

The lower end of TSH is not well established in pregnancy, and normal value can be as low as 0.02 [8,9]. TSH concentration may be below the non-pregnant reference range in up to 10% of normal pregnant women with 0.5-1% of women with completely suppressed TSH level [10].

Total T4 and FT4, total T3 and free T3

In the latter half of pregnancy increased thyroid binding globulin (TBG) and decrease serum albumin concentration can affect the widely available FT4 automated immunoassay resulting in significant variability between assay. FT4 continuously decline throughout pregnancy. Consequently assay and trimester specific pregnancy ranges are necessary if FT4 is used.

During pregnancy, TT4 assay is more consistent between assay an estrogen-driven increase in TBG lead to steady rise in TT4 from the first trimester until mid-gestation when TT4 plateaus after week 16, the non-pregnancy reference range may be adjusted by factor of 1.5 and used to assess thyroid status. Free and total T3 (FT3/ TT3) are rarely useful in the diagnosis and management of GD in pregnancy.

TSH Receptor antibodies (TRAb): In pregnant patient undergoing Adverse pregnancy outcome of maternal GD

Mother and Fetus: GD during pregnancy can lead to poor maternal and fetal outcomes. Maternal complication include miscarriage, still birth, preterm delivery, preeclampsia, heart failure, thyroid storm and small for gestational age [14,15].

The fetal and neonatal complications of maternal hyperthyroidism include, goiter formation and hyperthyroidism which can lead to intrauterine growth restrictions and failure to thrive in neonate [3].

In pregnant women with GD fetal hyperthyroidism can re sult from placental transfer of TRAb that can stimulate the fetal thyroid gland one report estimates that the frequency of fetal hyperthyroidism ranges from 1 to 5% in women with GD during pregnancy [16].

Although more rare, fetal hypothyroidism is also known complication that can rise from shifting in the balance between thyroid stimulating and thyroid blocking antibodies [17].

Management of GD in pregnancy

Antithyroid drugs are the mainstay of treatment in pregnancy Carbimazole and propylthiouracil have all been used for the treatment of GD in pregnancy. Radioactive iodine is absolutely contraindicated in pregnancy. Surgery is rarely indicated in pregnancy because it carries risk of spontaneous abortion and premature delivery. Surgery is indicated for patient who developed severe adverse effects to antithyroid drugs or the hyperthyroidism is not controlled in antithyroid drugs. The optimal time of surgery is in the second trimester [18].

Role of beta Adrenergic drugs in controlling hyperadrenergic symptoms in pregnancy is limited. They can only be used for few weeks as their continued use can lead to intrauterine growth retardation. The prolonged used of beta blockers in pregnancy is also associated with fetal apnea, bradycardia and hypoglycemia.

The lowest dose of antithyroid drugs needed to maintain TT4 1.5x the upper limit of non- pregnant reference range or FT4 at the upper limit of reference range should be used. Care must be taken to avoid over treatment with antithyroid drugs.

TSH may remain suppressed during antithyroid drugs therapy even when TT4 or FT4 has normalized. Current guidelines by ATA, AACE and ES recommend the use of PTU in the first trimester of pregnancy and consideration to switch to Carbimazole after the first trimester [19]. These recommendations are based on concern of rare congenital abnormalities associated with Carbimazole use during embryogenesis in the first trimester, PTU can be dosed at 50-150 mg every 8 hour depending on the severity of the patient symptomatology. When switching from Carbimazole to PTU, a ratio of 1:20 is used (i.e Carbimazole 15 mg=300 mg of PTU per day dosed as 100 mg every 8 hour depending on the severity of the patient. After the first trimester Carbimazole 5-20 mg can be given as single dose. Occasionally, in very symptomatic patient up to 30-40 mg can be used daily.

Propranolol 10-20 mg every 6-8 hour can be used to control hyperadrenergic symptoms and tapered and discontinued as tolerated. TSH, TT4 or FT4 should be checked every 2-4 weeks as clinically indicated and dose of antithyroid titrated based on clinical and biochemical response. Antithyroid drugs may be discontinued.
in women with mild disease requiring low dose of antithyroid drugs and mildly elevated TRAB (Table 2).

Adverse effect of ATD

Antithyroid drugs are associated with development of both minor and major adverse effects minor side effects include cutaneous reaction (rash, urticaria), gastrointestinal upset and arthralgia (Table 3).

Ai Yoshihara et al. [21] treated 91 newly detected pregnant women with GD with ATD (40 patients with Carbimazole and 51 with PTU) and study the adverse events, in this study the frequency of cutaneous reactions in patients treated with Carbimazole was 12.5% compared to 5.9% in patient treated with PTU. Among the major side effects agranulocytosis is the most feared complication of ATD. Agranulocytosis is defined as an absolute granulocyte counts less than 300 per cubic millimeter. In large series of patients studied by Tajiri et al. [22], agranulocytosis was reported in 0.37% of patients receiving PTU and 0.35% of patients receiving Carbimazole.

Hepatotoxicity is another major side effect of antithyroid medication. Immuno-allergic hepatitis occur in 3.9% of patients treated with PTU. It has been estimated that 4 out of approximately 4000 pregnant women treated with PTU in US developed severe injuries in injury each year [23,24]. Vasculitis is the third major adverse

<table>
<thead>
<tr>
<th>Minor adverse effects:</th>
<th>Major adverse effects</th>
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<tbody>
<tr>
<td>Skin reactions</td>
<td>Agranulocytosis</td>
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<tr>
<td>Arthralgia</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Hepatotoxicity (PTU)</td>
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<tr>
<td>Altered taste (PTU)</td>
<td>Polyarthritis</td>
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<thead>
<tr>
<th>Factor</th>
<th>Lower chance of recurrence</th>
<th>Higher chance of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Duration of therapy</td>
<td>more than 6 months</td>
<td>less than 6 months</td>
</tr>
<tr>
<td>• ATD Dose</td>
<td>&lt;5-10 mg/d</td>
<td>&gt;10mg/day</td>
</tr>
<tr>
<td>• Serum TSH on ATD</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>• TRAb</td>
<td>Normal or slightly elevated</td>
<td>high level</td>
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In 30-40% of women ATD may be discontinued after 30-34 weeks of gestation [20]. Fetal hypothyroidism is an indication to decrease or stop ATD.

Table 2: Clues to the risk of recurrent hyperthyroidism if antithyroid drugs are stopped

<table>
<thead>
<tr>
<th>Table 3: Side effects of antithyroid drugs</th>
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<tbody>
<tr>
<td>• Agranulocytosis</td>
</tr>
<tr>
<td>• Vasculitis</td>
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<tr>
<td>• Hepatotoxicity (PTU)</td>
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<tr>
<td>• Polyarthritis</td>
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<tr>
<th>Table 4: Birth defect associated with ATD</th>
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<tr>
<td>• Pre-auricular sinus/fistula and cyst</td>
</tr>
<tr>
<td>Urinary tract abnormalities in male</td>
</tr>
</tbody>
</table>

events associated more often with the use of PTU than Carbimazole anti neutrophil, cytoplasmic antibody positive vasculitis have been reported from Asian patients treated with PTU [25].

Teratogenic potential of ATD

Medical literature is full of studies which show an association between the use of ATD for treatment of GD in pregnancy and development of congenital malformation in the fetus [26]. This association is widely reported with the use of Carbimazole [27].

Carbimazole exposure in utero is associated with the development of birth defects like aplasia cutis, choanal atresia, tracheo-aesophageal fistula, patent vitello intestinal duct and dysmorphic facies. These have been reposted as a components of Carbimazole embryopathy [28].

PTU has traditionally been preferred over Carbimazole in the first trimester because the birth defect associated with PTU are considered less severe and surgically correctable. ATD associated birth defects are most common and severe in those exposed during weeks 6-10. Incidence from Danish registry shows 1.6% birth defect with Carbimazole compared to 0.2% for PTU and 0.07% for non-exposed pregnancy.

Monitoring the fetus

Fetal risk in mother with GD include hyperthyroidism due to inappropriate transplacental passage of maternal TRAb and hypothyroidism due to excessive maternal administration of ATD. TRAb can cross the placenta and act to stimulate or block fetal thyroid hormone production once the fetal thyroid gland becomes functional around 20 weeks of gestation.

TRAb level greater than 3 times the ULN in the latter half of pregnancy predicted neonatal hyperthyroidism with 100% sensitivity and 43% specificity [29].

Indication for Fetal Ultrasound (FUS)

Women with prior fetus or neonate with a thyroid disorder, TRAb greater than 3 times the ULN, fetal trachycardia and poorly controlled hyperthyroidism should have a FUS. Initial FUS is generally performed at 18-22 weeks and then every 4 weeks to assess for gestational age, fetal viability, amniotic fluid volume, fetal anatomy and detection of malformation [29].

US finding of hyperthyroidism

The earliest sonographic sign of fetal thyroid dysfunction is fetal goiter [30,31]. HR.160 bpm for over 10 min, intrauterine growth retardation, advanced bone age or oligohydramnios can be seen in fetal hyperthyroidism [32]. Less commonly fetal thyrotoxicosis can lead to heart failure, fetal hydrops and fetal demise.

Fetal goiter can cause fetal, obstetric and neonatal complication
including polyhydramnios secondary to reduced swallowing ability, cervical dystocia and mechanical obstruction of fetal airway respectively [33,34]. Cesarean delivery may be preferred due to high risk of labor dystocia from dysflexed head.

### Fetal hypothyroidism secondary to ATD

 Fetuses of mother with GD on ATD can developed hypothyroidism and or goiter due to overtreatment with ATD. Sign of hypothyroidism on FU include fetal goiter, growth restriction and delayed bone age. ATD dose reduction or discontinuation should restore normal fetal thyroid function and decrease the size of fetal goiter. Rarely, intra-amniotic levothyroxine injection in conjunction with reduction of ATD dose may be indicated as combination therapy may lead to faster resolution of fetal goiter and recovery from hypothyroidism.

In rare circumstance where the diagnosis remains unclear, cordocentesis remains the method of choice for confirmation of fetal thyroid status. While less hazardous, amniotic fluid hormone levels have not been validated as reliable measure of fetal thyroid function.

### Conclusions

GD in pregnancy is associated with both maternal and fetal complication which can be avoided by rendering the patient euthyroid with the administration of anti-thyroid medications. PTU and Carbimazole are the antithyroid drugs available with almost similar transplacental transfer rates. Use of Carbimazole in pregnancy is associated with malformation. Due to the association of fetal teratogenicity with Carbimazole, PTU is recommended as the drug of choice in first trimester of pregnancy.

Appropriate treatment of maternal hyperthyroidism during pregnancy and dose monitoring of mother and fetus are essential for optimizing outcomes performing prenatal ultrasound directed to the fetal thyroid gland is of utmost important as it enables prenatal diagnosis and treatment by dose modification in order to prevent fetal goiter.

Maternal and fetal morbidity and mortality can be reduced if lowest possible dose of Carbimazole is used to maintain maternal serum FT4 levels at or just above the upper limit of the normal non-pregnant reference range, or serum total T4 level at 1.5 times the lowest possible dose of Carbimazole is used to maintain maternal thyroid function and decrease the size of fetal goiter. Rarely, intra-amniotic levothyroxine injection in conjunction with reduction of ATD dose may be indicated as combination therapy may lead to faster resolution of fetal goiter and recovery from hypothyroidism.

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### References


