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Treatment of Graves' Disease During Pregnancy

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1. Introduction

1.1 Etiology

Graves' disease is an autoimmune syndrome where thyroid stimulating antibodies bind to and activate the thyrotropin receptor on thyroid cells resulting in hyperthyroidism (Weetman, 2000; Jonklaas, 2011). Specifically, the production of thyroid-stimulating immunoglobulin (TSI) and thyroid-stimulating hormone-binding inhibitory immunoglobulin (TBII) act on the thyroid stimulating hormone receptor to cause thyroid stimulation or thyroid inhibition, respectively.

Graves' disease is the most common cause of hyperthyroidism in the United States with an estimated prevalence of 3 per 1,000 (Jonklaas, 2011, Abalovich, 2007). The occurrence of Graves' disease is similar in Caucasians and Asians, with a lower incidence in African Americans (Weetman, 2000; Jonklaas, 2011). Major risk factors for Graves' disease include female gender and genetic predisposition. Graves' disease is approximately eight times more common in women than men and often occurs in clusters in families (Weetman, 2000). An increased frequency of certain human leukocyte antigens (HLAs) has also been associated with Graves' disease. In Caucasians, HLA-D3 is present in approximately 50 percent of patients. The presence of both HLA-B8 and HLA-D3 indicates a fourfold increase in the risk of developing Graves' disease (Jonklaas, 2011).

1.2 Signs and symptoms

Common symptoms of hyperthyroidism may present as irritability, hyperactivity, altered mood, insomnia, fatigue, heat intolerance, increased sweating, palpitations, dyspnea, pruritis, weight loss with increased appetite, thirst and polyuria, increased stool frequency, oligomenorrhea or amenorrhea, and loss of libido. Hyperthyroidism signs may include fine tremor, hyperkinesis or hyperreflexia, warm, moist skin, palmar erythema, hair loss, muscle weakness and wasting, sinus hypertension, tachycardia, atrial fibrillation, and/or heart failure. When hyperthyroidism is left untreated, manifestations of Graves' disease may appear such as diffuse goiter, ophthalmopathy, retrobulbar pressure or pain, scleral injection, eyelid lag or retraction, exophthalmos, localized dermopathy, lymphoid hyperplasia, or thyroid acropachy. Conditions associated with Graves' disease may comprise of type 1 diabetes mellitus, Addison's disease, pernicious anemia, alopecia areata, vitiligo, myasthenia gravis, or celiac disease (Weetman, 2000).

1.3 Diagnosis

The American Association of Clinical Endocrinologists and the American Thyroid Association recommend reflect same (TSH) testing as an initial test for screening and evaluation of symptomatic disease (Bahn, 2011). Laboratory results in Graves' disease show an overall increase in both free triiodothyronine (FT_3) and free thyroxine (FT_4) with a disproportionate increase in triiodothyronine (T_3) to thyroxine (T_4). Values for serum T_3 and T_4 are elevated due to the saturation of thyroid binding globulin. However, levels for FT_3 and FT_4 are elevated to a greater extent than serum values. Reflect same (TSH) is suppressed to the undetectable range (Weetman, 2000; Jonklaas, 2011).

1.4 Treatment

Current treatments for Graves' disease include radioactive iodine, surgery, and antithyroid drugs such as propylthiouracil (PTU), methimazole, and carbimazole (a precursor molecule to methimazole not available in the US). Selection of the treatment modality varies greatly by geographic location with radioactive iodine being the treatment of choice in the United States and antithyroid drugs in most other countries (Weetman, 2000; Cooper, 2005; Jonklaas, 2011). In addition to geographic location, other aspects influence the selection of the most appropriate treatment such as: time to initial improvement, planning pregnancy, pregnancy or breastfeeding, size of the goiter, age of patient, likelihood of side effects, concurrent severe ophthalmopathy, interference with daily activities, and the likelihood of recurrence after treatment (Weetman, 2000).

1.4.1 Thioamides

Antithyroid drugs, thioamides, decrease thyroid hormone synthesis by inhibiting thyroid peroxidase catalyzed iodination of thyroglobulin and by inhibiting iodotyrosine coupling. Therefore, these drugs do not cure Graves' disease but only control hyperthyroidism. Propylthiouracil has an added mechanism of action by reducing the peripheral conversion of T_4 to T_3. The American Thyroid Association and the American Association of Clinical Endocrinologists recommend methimazole as the preferred antithyroid drug in any patient with Graves' disease except during the first trimester of pregnancy (Bahn, 2011).

The initial dosing of either thioamide is empirical. The American Thyroid Association recommends a starting dose of 10-40 mg of methimazole or 100-600 mg of PTU daily in nonpregnant women. The pharmacokinetics of the thiamides are distinct. Methimazole's onset of action is 12-18 hours with a duration of action of 36-72 hours. The peak plasma concentration of methimazole is reached within 1-2 hours of ingestion and the half-life is 4-6 hours after oral administration and has an oral bioavailability of 93% (Clark, 2006). Dosing depends on the severity of hyperthyroidism, 15 mg/day for mild up to 60 mg/day for severe hyperthyroidism. Based on the pharmacokinetics, the daily dose is divided into three doses, given every 8 hours. Methimazole is metabolized in the gastrointestinal system and first pass through the liver.

The peak plasma concentration of PTU is reached within 1-2 hours of ingestion and the elimination half-life is 1-2 hours. The oral bioavailability of PTU is 53-88% and the duration

of action is 12-24 hours. Again, dosing depends on the severity of hyperthyroidism but usually is 100-300 mg/day divided into 3 doses, every 8 hours.

The pharmacokinetics of PTU and methimazole in pregnant women are similar to non-pregnant women (Clark, 2006). However, the metabolism and excretion of these drugs are increased in pregnant women with hyperthyroidism, due to an increased metabolic state of pregnancy. Therefore, during pregnancy women may require a higher daily dose of antithyroid drug, such as PTU 300-450 mg per day or methimazole 30-40 mg per day.

Propylthiouracil is highly protein bound (80-85%) whereas, methimazole has neglible protein binding. It was thought PTU was less likely to cross the placenta compared to methimazole (Clark, 2006). To address the theory that PTU has less fetal transfer than methimazole, Mortimer et al. evaluated the maternal to fetal transfer in nine isolated human placental lobules perfused with low and high doses of PTU and methimazole (Mortimer, 1997). Placentas were collected from euthyroid women with no history of antithyroid drug ingestion. All placentas were delivered at term by cesarean. Both PTU and methimazole readily crossed the placenta achieving steady state concentrations in approximately two hours. Both drugs demonstrated similar transfer kinetics, were nonsaturable, and were unaffected by the addition of bovine albumin to the perfusate. The authors concluded that PTU and methimazole had similar placental transfer kinetics. Therefore the rationale that PTU has less fetal transfer than methimazole was not supported in this well established model of drug transfer across the human placenta (Mortimer, 1997). So although, methimazole has neglible protein binding, methimazole has similar placental transfer compared to PTU.

Because propylthiouracil has a shorter half-life, higher protein binding, and less drug concentration in breast milk, some providers view PTU as a safer option in breastfeeding. However, the American Academy of Pediatricians considers both compatible with breastfeeding (AAP, 2001). Nonetheless, methimazole has been found sufficient amounts in breastfed infants to cause thyroid dysfunction. Low doses of methimazole (<20 mg/day) have not been shown to be a serious risk to nursing infants (Cooper, 2009; Marx, 2009). Doses of propylthiouracil of less than 300 mg a day is recommended (Marx, 2009; Abalovich, 2007). It is recommended to have the mother take the antithyroid drug after breastfeeding (Marx, 2009). Monitoring the infant's thyroid function while the nursing mother is taking either antithyroid drug is advised.

One of the serious, rare side effects of thioamides is agranulocytosis, presenting with a fever, sore throat and an absolute granulocyte count of less than 500 per cubic millimeter. Thioamide-induced agranulocytosis has an incidence of 0.1-0.4% among the thioamides, is not dose related, and usually occurs within the first 90 days of therapy. If suspected, a complete blood count should be drawn and the medication should be immediately discontinued. Unfortunately, there is a significant likelihood of cross reaction among the thioamides so switching to another thioamide should not be an option. Routine white blood count monitoring has not been helpful in prevention because the thioamide-induced agranulocytosis occurs rapidly. However, a baseline assessment of the patient's white blood cell count is recommended prior to initiation of the thioamide.

Other side effects include leucopenia, thrombocytopenia, hepatitis, and vasculitis. Vasculitis has been reported more often with PTU and results in glomerulonephritis and diffuse alveolar hemorrhage (Kang, 2006). Methimazole has been reported to have a 33% chance of

cross reaction to PTU-induced vasculitis. More common side effects for both methimazole and PTU include fever, rash, arthritis, nausea, anorexia, and loss of taste or smell. (Weetman, 2000; Garcia-Mayor, 2010) The incidence of thioamide side effects is similar among pregnant and non-pregnant women. Side effects to methimazole are dose-related; PTU is less dose-related (Garcia-Mayor, 2010). Cross reactivity to thioamide-induced adverse events between the two agents may be as high as 50% (Garcia-Mayor, 2010).

2. Graves' disease in pregnancy

It is estimated that hyperthyroidism is present in approximately 0.1-0.2% of pregnancies (Miehle, 2003; Mestman, 2004; Galofre, 2009). Of those pregnancies, neonatal Graves' disease occurs in 1-5% of those babies (Fitzpatrick, 2010; Marx, 2008). Hyperthyroidism is the second most common endocrine disorder that occurs during pregnancy, following only diabetes mellitus (Mestman, 1998). Graves' disease is the most common cause of hyperthyroidism during pregnancy, accounting for 85-95% of the cases (Galofre, 2009; Ecker, 2000). Another cause of hyperthyroidism results from overstimulation of the thyroid gland via human chorionic gonadotropin (hCG). This syndrome, known as gestational transient thyrotoxicosis (GTT), occurs during the first half of gestation due to hyperemesis gravidarum and is less severe than hyperthyroidism due to Graves' disease (Glinoer, 2003).

2.1 Etiology

Thyroid function changes during pregnancy due to the elevated hCG, an increase in estrogen that increases circulating thyroid binding globulin levels which is the major transport protein for thyroid hormone, and a decrease in iodide due to increased renal clearance and losses due to the fetus and placenta (Marx, 2009). Before 12 weeks gestation, significant fetal brain development occurs through maternal thyroid hormones. After 12 weeks gestation, the fetal thyroid gland concentrates iodine and synthesizes thyroid hormone and continues fetal brain development (Morreale, 2000; Inoue, 2009; Abalovich, 2007).

2.2 Signs and symptoms

Pregnancy complicated by Graves' disease usually presents with symptoms appearing in the first trimester, improving in the second and third trimesters, and reappearing in the postpartum period (Mestman, 2004; Inoue, 2009). Significant fetal and maternal complications can occur if the condition is left untreated. Specifically, spontaneous abortion, preterm delivery, stillbirth, low birth weight, preeclampsia, heart failure, and thyroid storm are known complications (Mestman, 2004; Inoue, 2009; Marx, 2009). Low birth weight has been reported to occur nine times as often compared to pregnancies not complicated by hyperthyroidism (Millar, 1994). Neonatal hyperthyroidism, prematurity and intrauterine growth retardation may occur. A 5.6% incidence of fetal death or stillbirth and a 5% incidence of fetal and neonatal abnormalities have been reported (Hamburger, 1992). Unfortunately, fetal and neonatal risks associated with Graves' disease may be related to either the disease or the treatment of the disease. Since Graves' disease is mediated by antibodies that cross the placenta, the risk of immune-mediated hypothyroidism and hyperthyroidism may develop in the neonate (ACOG, 2002; Inoue, 2009). Women with Graves' disease have TSI and TBII that can stimulate or inhibit the fetal thyroid, causing fetal hyperthyroidism or hypothyroidism, respectively. There is no

clinical correlation between the levels of antibodies and disease severity (Rashid, 2007). Occasionally, the antibodies may change during pregnancy from stimulation to inhibition of the TSH receptor (Laurberg, 2009).

2.3 Diagnosis

The American Association of Clinical Endocrinologists and the American Thyroid Association recommends measuring TSH but also FT_4 or free thyroxine index (FTI) in symptomatic pregnant women. The FT_4 rises in the first trimester due to the high circulating levels of human chorionic gonadotropin. Rarely hyperthyroidism during pregnancy is due to an abnormally high level of FT_3 instead of high FT_4. The TSH receptor antibody tests, TSI and TBII, may be helpful since these antibodies have been associated with infants born with hypothyroidism. If a pregnant woman has a low TSH but a normal FT_4, subclinical hyperthyroidism is diagnosed and requires no treatment since treatment in this group has not been shown to improve pregnancy outcomes (Abalovich, 2007).

2.4 Treatment

It has been shown that hyperthyroidism in a pregnant woman should be treated to lessen the fetal and neonatal risks. The highest complications were associated with the poorest control and the best control was associated with the least complications (Abalovich, 2007). Therefore, the goal of treatment is to achieve the high euthyroid or low hyperthyroid range (maternal FT_4 at or slightly higher than the upper limit of the normal nonpregnant reference range) and maintain this range throughout pregnancy in order to improve pregnancy outcomes (Chan, 2007). To accomplish this, antithyroid drugs are the preferred treatment during all stages of pregnancy. Radioactive iodine is contraindicated during pregnancy; inappropriate radioiodine administration given after 10-12 weeks destroys the fetal thyroid and results in neonatal hypothyroidism and cretinism (Gorman, 1999; Abalovich, 2007). Surgery is reserved for patients who require large doses of antithyroid drugs, or those who demonstrate poor medication adherence and continue to remain hyperthyroid (Cooper, 2005; Miehle &Paschke, 2003; Mestman, 2004; Mestman, 1998; Glinoer, 2003; Karabinas & Tolis, 1998; Masiukiewicz &Burrow, 1999; Atkins, Cohen & Phillips, 2000). If surgery is necessary, surgery is preferred during the second trimester to decrease the risk of spontaneous abortion (Galofre, 2009).

2.4.1 Thioamides

During pregnancy, women may require a higher daily dose of antithyroid drug. Propylthiouracil should be given 100-150 mg three times daily or methimazole 30-40 mg per day until the patient becomes euthyroid. Upon euthyroid, the dose may be reduced to the lowest amount to maintain the euthyroid state with serum T_4 at the upper end of normal and continued throughout pregnancy and labor. Improvement in FT_4 is usually seen in 4 weeks; whereas improvement in TSH occurs in 6-8 weeks (Galorfre, 2009). It is important not to overtreat because it may result in maternal or fetal hypothyroidsm (Casey, 2006). Therefore, monitoring is crucial; TSH and FT_4 every 2 weeks and then every 4-6 weeks when euthyroidism is achieved (Clark, 2006).

2.4.1.1 Teratogenicity

Historically, PTU has been the drug of choice when treating Graves' disease during pregnancy in the United States. Throughout the rest of the world, methimazole and carbimazole, are widely used to treat hyperthyroidism in pregnant women (Mandel, 2001; Dwarakanath, 1999). Methimazole has been linked to at least 25 reported cases of aplasia cutis, as well as at least 22 cases of esophageal or choanal atresia or a combination of both (Mestman, 2004; Mandel, 2001; Ferraris 2003; Hamburger, 1992; Van Dijke, 1987; Karlson, 2002; Seoud,2003; Kannan, 2008; Karg, 2004). Methimazole has been described as "methimazole embryopathy" in children exposed to methimazole during the first trimester of pregnancy, especially during the first 7 gestational weeks (Karlsson, 2002; Clementi, 1999). The embryopathy includes congenital anomalies such as choanal or esophageal atresia or aplasia cutis and developmental delay, hearing loss, and dysmorphic facial features (Chan, 2007).

An evaluation of 49,091 live births estimated the incidence of aplasia cutis in the general population to be 0.03% or 0.05% of congenital skin defects (Van Dijke, 1987). DiGianantonio and colleagues prospectively compared 241 women exposed to methimazole during pregnancy to 1,089 pregnant controls. No increased incidence of spontaneous or induced abortions or major congenital anomalies was reported in the methimazole cohort (DiGianantonio, 2001). Although a possible association between methimazole exposure during pregnancy and fetal congenital defects may exist, it has not been proven and may be secondary to hyperthyroidism (Briggs, 2011).

At least 7cases of congenital anomalies have been reported in newborns exposed to PTU. A causal relationship between PTU exposure and congenital anomalies has not been found (Briggs, 2011). The Israeli Teratology Information Service reported that the rate of major anomalies was comparable between PTU-exposed pregnancies and controls (Rosenfeld, 2009). At least 47 reports have been published describing PTU-related hepatic impairment in adults and children, approximately 0.1-0.5% in adults (Cooper, 1999; Cooper, 2009; Kontoleon, 2002; Patil-Sisodia, 2010). However, only one case has been reported of neonatal hepatitis secondary to transplacental propylthiouracil (Hayashida, 1990). Therapy with PTU should be discontinued since 25% of affected patients may progress to fulminant, fatal hepatic failure (Kontoleon, 2002; Patil-Sisodia, 2010). The incidence of PTU hepatic failure does not correlate to PTU dosage or duration or patient age (Patil-Sisodia, 2010).

The United States Food and Drug Administration classifies PTU and methimazole as Category D because of the potential for fetal hypothyroidism, rather than the potential teratogenicity. The American College of Obstetricians and Gynecologists (ACOG) recommends that either PTU or methimazole may be used to treat pregnant women with hyperthyroidism.

The "block and replace" regimen that adds levothyroxine with an antithyroid drug is not recommended in pregnant women (Marx, 2009). It was originally thought that the placental transfer of levothyroxine would prevent fetal hypothyroidism. Levothyroxine and methimazole administered concomitantly to pregnant women with Graves' disease has shown to reduce the incidence of postpartum hyperthyroidism (Hashizume, 1992). However, the necessary dose of the antithyroid drug is much higher when given with levothyroxine that fetal goiter and fetal hypothyroidism may still occur. Furthermore, the risk of fetal hypothyroidism is increased because the antithyroid medications but not levothyroxine cross the placenta (Rosenfeld, 2009).

2.4.1.2 Clinical trials

Clinical studies support that fetal thyroid function outcomes are similar between the two drugs (Mortimer, 1997; Marchant, 1977; Momotani, 1997). A retrospective chart review of 135 patients with a history or diagnosis of hyperthyroidism at a high risk obstetrics clinic over a 16 year time period (1974 to 1990) compared the use of PTU and methimazole to treat hyperthyroidism during pregnancy (Wing, 1994). Of the 135 patients, 99 (73.3%) received PTU and 36 (26.7%) received methimazole. Selection of the treatment agent was based solely on physician preference. Six of the patients received both PTU and methimazole and were therefore excluded from analysis.

Diagnosis of hyperthyroidism was based on history, physical exam, thyroid-stimulating hormone, free thyroxine index, and free triiodothyronine index. The time required to normalize free FT_4 levels and the incidence of congenital malformations or fetal hypothyroidism were evaluated. Maternal and fetal outcomes were obtained via retrospective chart review from clinic, labor, delivery, and postpartum records. Baseline characteristics for the two treatment groups were similar with respect to age, ethnicity, and parity.

Maternal results showed that gestational age had no effect on the time to free FT_4 normalization. The median time to normalization was 7 weeks for the methimazole-treated group and 8 weeks for the PTU-treated group ($p=0.34$). The Cox proportional hazard compared the time of normalization between the two groups after adjusting for the initial measurements with no statistical difference between the PTU-treated group and the methimazole-treated group ($p=0.52$). Of the 135 pregnancies, four infants (3%) were born with congenital anomalies to mothers treated with either PTU or methimazole. Of these four infants, three (3%) of the fetal anomalies occurred in the 99 women who were treated with PTU and one (2.7%) occurred in the 36 women treated with methimazole. Fetal anomalies reported were ventricular septal defect, patent ductus arteriosus, and severe pulmonic stenosis in the infants of the PTU-treated mothers, and congenital inguinal hernia in the infant of the methimazole-treated mother. No cases of aplasia cutis were reported in either group. Congenital hypothyroidism occurred in one infant of a PTU-treated mother. The authors concluded that the incidence of congenital anomalies were consistent with the national average of 2% to 5% in the general population. The authors concluded that both PTU and methimazole were equally safe and effective in the treatment of hyperthyroidism during pregnancy (Wing, 1994). Potential limitations to the study were mostly due to the retrospective design; unrandomized, unblinded, and non-placebo controlled. Selection bias in medication may have occurred as the choice of medication was based on physician preference. Also, small sample size resulted in inadequate power to evaluate the equivalence of the two medications.

Momotani et al. evaluated the effect of maternal ingestion of PTU and methimazole on fetal thyroid status using cord sera at delivery (Momotani, 1997). The authors identified 249 pregnant women with Graves' disease who received either PTU or methimazole during their pregnancy. Of these 249 women, 77 (30.9%) had received at least four weeks of therapy, 34 (44.2%) with PTU and 43 (55.8%) with methimazole. Controls consisted of 32 healthy women with no history of thyroid disease and who delivered at term.

Serum samples from mother and fetus were assayed for free FT_4 and TSH. No statistical difference was observed in mean fetal free FT_4 or fetal TSH between the PTU and methimazole treated groups. Low fetal free FT_4 was seen in 6% of the PTU group and 7% of the methimazole group. High fetal TSH rates were 21% in the PTU group and 14% in the methimazole group. The relationship between maternal dose and fetal thyroid status was not significant; low doses of PTU were associated with high TSH in 21% of infants and low doses of methimazole were associated with high TSH in 14% of infants. The authors concluded that the two agents were similar regarding the effects on fetal thyroid status, and the selection of PTU over methimazole to treat hyperthyroidism during pregnancy was not justified (Momotani, 1997). The trial appeared to be well designed and utilized a direct measure of fetal thyroid status at birth. Potential bias may have existed as medication selection was based solely on provider preference. The selection process was not explained regarding how pregnant women with Graves' disease and those who served as controls were identified.

Azizi et al. evaluated the methimazole's effect on intellectual development of children whose mothers received methimazole during pregnancy but not during lactation (Azizi, 2002). The authors identified 23 children, ages 3 to 11 years, of mothers who were treated with methimazole during pregnancy and 30 children, ages 3 to 11 years, of mothers who were not treated with methimazole during pregnancy. All mothers delivered at term and there were no congenital malformations in either group. Methimazole-exposed mothers received methimazole doses up to 20 mg per day. All neonates were euthyroid at the time of delivery.

No difference between the methimazole-treated group and the control in serum T_3, T_4, or TSH concentrations was observed. Physical characteristics such as weight and height were similar in both groups. A psychologist blinded to methimazole exposure used the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) to detect a difference in verbal and performance IQ between the two groups. No difference in verbal or performance IQ between the two groups of children was shown. Total IQ for the methimazole-treated group was 117±11; IQ for the control group was 113±14. The authors concluded that no detrimental effects on the physical or intellectual development occurred in those children exposed to methimazole during pregnancy (Azizi, 2002). The main strength of this study was the single blinded psychologist evaluation of child intellect using the WPPSI exam. Unfortunately, the WPPSI is an intelligence test designed for children ages 2 years 6 months to 7 years 3 months and the study population included children 3-11 years of age. Other limitations to this study were a small sample size and low exposure dose of methimazole.

3. Conclusion

The selection of PTU over methimazole as the drug of choice to treat Graves' disease during pregnancy should not be based on misleading statements in the literature that PTU has less placental transfer than methimazole, that PTU leads to less fetal hypothyroidism, or that exposure to methimazole during pregnancy leads to a decreased intellectual function in children. The United States Food and Drug Administration classifies both PTU and methimazole as a Category D because of the potential for fetal hypothyroidism, rather than potential teratogenicity. The ACOG recommends that either PTU or methimazole may be

used to treat pregnant women with hyperthyroidism. However, the Endocrine Society recommends PTU as a first line drug, especially during the first trimester (Abalovich, 2007). Clinical data shows that PTU and methimazole are equally efficacious in pregnant women with hyperthyroidism (Wing, 1994; Momotani, 1997). However, the possible association between methimazole and fetal anomalies such as aplasia cutis, esophageal atresia, and choanal atresia may present methimazole a less desirable first line treatment option than PTU. Although a causal relationship between methimazole and these fetal anomalies has not been established in clinical trials, the possibility of a relationship still exists. Therefore, in the absence of a compelling indication for the use of methimazole, PTU should still be considered as the first line agent in the treatment of Graves' disease during pregnancy. However, methimazole should be considered a viable second choice if the patient is intolerant to PTU, has an allergic reaction to PTU, or fails to become euthyroid on PTU.

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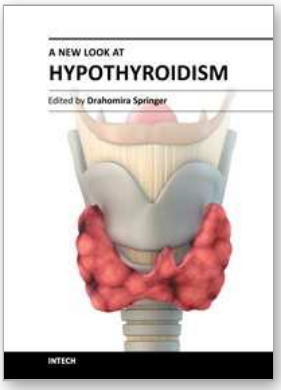

A New Look at Hypothyroidism

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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