

Recurrent pregnancy loss in patients with thyroid dysfunction

Debanjali Sarkar

Department of Obstetrics & Gynaecology, MGM Medical College, Bihar, India

ABSTRACT

Purpose of the Review: Thyroid disturbances are common in women during their reproductive years. Thyroid dysfunction interferes with human reproductive physiology, reduces the likelihood of pregnancy and adversely affects pregnancy outcome, thus becoming relevant in the algorithm of reproductive dysfunction. This review highlights the “gap” in knowledge regarding the contribution of thyroid dysfunction in reproduction. **Literature Reviewed:** Following implantation, the maintenance of the pregnancy is dependent on a multitude of endocrinological events that will eventually aid in the successful growth and development of the fetus. It is estimated that approximately 8-12% of all pregnancy losses are the result of endocrine factors. Autoimmune thyroid disease is present in around 4% of young females and up to 15% are at risk because they are thyroid antibody-positive. There is a strong relationship between thyroid immunity on one hand and infertility, miscarriage, and thyroid disturbances in pregnancy and postpartum, on the other hand. Even minimal hypothyroidism can increase rates of miscarriage and fetal death and may also have adverse effects on later cognitive development of the offspring. Hyperthyroidism during pregnancy may also have adverse consequences. **Summary:** Pregnant women with subclinical hypothyroidism or thyroid antibodies have an increased risk of complications, especially pre-eclampsia, perinatal mortality, and miscarriage. Universal screening for thyroid hormone abnormalities is not routinely recommended at present, but thyroid function must be examined in female with fetal loss or menstrual disturbances. Practitioners providing health care for women should be alert to thyroid disorders as an underlying etiology for recurrent pregnancy loss.

Key words: Recurrent pregnancy, thyroid autoimmunity, thyroid disorder

Thyroid hormone is well known to be essential for development of many tissues, including the brain and heart. The potential role of thyroid hormone in the development of reproductive tissues that might impact fertility is not clear.^[1] Thyroid dysfunction is quite prevalent and affects many organs, including the male and female gonads. It interferes with human reproductive physiology, reduces the likelihood of pregnancy and adversely affects pregnancy outcome, thus becoming relevant in the algorithm of reproductive dysfunction.^[1] Thyroid dysfunction and thyroid autoimmunity are prevalent among women at reproductive age and are associated with adverse

pregnancy outcomes. Subclinical hypothyroidism may be associated with ovulatory dysfunction and adverse pregnancy outcome.^[1] Even minimal hypothyroidism can increase rates of miscarriage and fetal death and may also have adverse effects on later cognitive development of the offspring. Pregnancy affects thyroid economy with significant changes in iodine metabolism, serum thyroid binding proteins, and the development of maternal goiter, especially in iodine-deficient areas. The thyroid gland and gonadal axes interact continuously before and during pregnancy. Hypothyroidism influences ovarian function by decreasing levels of sex-hormone-binding globulin and increasing the secretion of prolactin.^[1]

Pregnancy is also accompanied by immunologic changes, mainly characterized by a shift from a T helper-1 lymphocyte to a T helper-2 lymphocyte state. Thyroid autoimmunity increases the miscarriage rate, and thyroxine treatment does not seem to protect. Thyroid peroxidase antibodies are present in 10% of women at 14 weeks' gestation,

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DOI:
10.4103/2230-8210.104088

Corresponding Author: Dr. Debanjali Sarkar, 162/163, Shastri N.N Ganguly Road, Howrah - 4, Bihar, India. E-mail: drds13@gmail.com

and are associated with (i) an increased pregnancy failure (i.e., abortion), (ii) an increased incidence of gestational thyroid dysfunction, and (iii) a predisposition to postpartum thyroiditis.^[2] During the first trimester, however, pregnant women with autoimmune thyroiditis (AITD) carry a significantly increased risk for miscarriage compared to women without AITD, even if euthyroidism.^[3] Presence of thyroid autoimmunity does not interfere with normal embryo implantation, but the risk of early miscarriage is substantially raised. Autoimmune thyroid disease is present in around 4% of young females, and up to 15% are at risk because they are thyroid antibody-positive.^[3] There is a strong relationship between thyroid immunity and infertility, miscarriage, and thyroid disturbances in pregnancy and postpartum. In the current review, we elaborate on the pathogenesis that underlies infertility and increased pregnancy loss among women with autoimmune thyroid disease. Such mechanisms include thyroid auto antibodies that exert their effect in a thyrotropin (TSH)-dependent but also in a TSH-independent manner. Lack of vitamin D was suggested as a predisposing factor to autoimmune diseases, and was shown to be reduced in patients with thyroid autoimmunity.^[4] In turn, its deficiency is also linked to infertility and pregnancy loss, suggesting a potential interplay with thyroid autoimmunity in the context of infertility. In addition, thyroid autoantibodies were also suggested to alter fertility by targeting zona pellucida, human chorionic gonadotropin receptors and other placental antigens. Spontaneous pregnancy loss is a common clinical problem. With the use of sensitive human chorionic gonadotropin (hCG) assays, it has been shown that 31% of pregnancies end in a miscarriage, with two-third of the losses occurring before clinical detection.^[3] It is postulated that the presence of thyroid auto antibodies reflects a generalized activation of the immune system and a generally heightened autoimmune reactivity against the fetoplacental unit. Most but not all studies have shown a significant association between the presence of thyroid antibodies and a higher miscarriage rate. However, patients with high titers of thyroid autoantibodies do not show a higher rate of miscarriages compared with patients with low titers. The mechanisms involved still remains unclear.^[5]

Universal screening for thyroid hormone abnormalities is not routinely recommended at present. Preconception or early pregnancy screening for thyroid dysfunction has been proposed but is not widely accepted. However, measurement of thyroid function and auto antibodies should certainly be considered in those who are at high risk of thyroid disease and in those whose pregnancy is otherwise high risk.^[1] In women at reproductive age,

hypothyroidism can be reversed by thyroxine therapy to improve fertility and avoid the need for use of assisted reproduction technologies. Accordingly, TSH determination is warranted for all women planning pregnancy or those already pregnant.^[1] Women with thyroid dysfunction at early gestation stages should be treated with l-thyroxine to avoid pregnancy complications. Whether thyroid hormones should be given prior to or during pregnancy in euthyroid women with AITD remains controversial.^[5] To date, there is a lack of well-designed randomized clinical trials to elucidate this controversy. Subclinical and overt forms of hypothyroidism are associated with increased risk of pregnancy-related morbidity, for which thyroxine therapy can be beneficial. Suboptimal iodine status affects a large proportion of the world's population, and pregnancy further depletes iodine stores.^[4] There is controversy surrounding the degree to which iodine should be supplemented and the duration of supplementation. The practicing clinician needs to be aware of the thyroid changes which accompany pregnancy.^[5] Future research, within the setting of clinical trials, should focus on the potential health gain of identification, and effect of treatment, of thyroid disease on pregnancy outcome. Furthermore, it was recently shown that thyroxine administration to pregnant women with positive thyroid auto antibodies and a history of recurrent abortions may improve the final outcome. Regarding prevention of miscarriage, there are few studies showing that thyroxine treatment may be effective in reducing the number of miscarriages when given during the early stages of pregnancy.^[1] Further studies are required with a greater number of women in order to reach definitive conclusions. At present, routine screening and treatment of autoimmune thyroid disease in euthyroid pregnant women is not warranted.

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Cite this article as: Sarkar D. Recurrent pregnancy loss in patients with thyroid dysfunction. *Indian J Endocr Metab* 2012;16:S350-1.

Source of Support: Nil, **Conflict of Interest:** None declared