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Maternal Hypothyroidism and Pregnancy Loss: Awaiting Firm Recommendations on Testing and Treatment

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Since up to 75% of fertilized ova and at least 15% of clinically-recognized pregnancies do not survive to birth, spontaneous loss is the most common complication of human pregnancy. The majority of pregnancy losses occur prior to clinical detection. Set against this startlingly high background, spontaneous loss of two pregnancies occurs in approximately 1% of pregnancies and loss of three or more pregnancies in 1 in 300 couples. Although isolated fetal aneuploidy is certainly etiologic in many pre-clinical and clinical losses, other causes have been suggested. In the last 15 years, there has been an increasing interest in the role of thyroid dysfunction and in thyroid autoimmunity in patients with pregnancy wastage and many clinicians have instituted thyroid-related testing and treatment protocols based on this growing body of literature. It is important to re-examine the evidence for these interventions and to consider risk: benefit balances in acting on the existing literature.

The physiologic and metabolic demands of pregnancy require increased production of thyroid hormone from the maternal gland and the positive linear relationship reported between maternal TSH levels and pregnancy loss [1] suggests that inadequate response to these demands may be problematic. It might follow that thyroid hormone supplementation for those women who may suffer adverse alterations in thyroid function during pregnancy may help to avert pregnancy loss. Several questions immediately arise, including: 1) Which women should be screened and 2) At what TSH levels should supplementation be recommended. This topic was systematically reviewed within the past 12 months and the meta-analysis presented indicated that use of levothyroxine to treat clinical hypothyroidism significantly decreased pregnancy loss rates (RR: 0.19; CI: 0.08-0.39) [2]. The same study could not definitively determine whether treatment of subclinical hypothyroidism improves pregnancy maintenance [2]. Note that the investigators in this study collected well over 7000 relevant articles for consideration but only 11 could be included in their meta-analysis. Like much of the other literature in the pregnancy loss field, there is a dearth of well-designed investigations on this topic. The same Dutch group published another meta-analysis about a year prior that addressed the effects of subclinical hypothyroidism on pregnancy maintenance and found a positive association with perinatal mortality (OR 2.7; 95% CI: 1.6-4.7) [3]. They also extended this investigation to include an assessment of the effects of thyroid auto antibodies on adverse pregnancy outcomes and found a positive relationship between the presence of anti-Thyroglobulin (anti-TG) and anti-Thyroidperoxidase (anti-TPO) antibodies and isolated (OR 3.7; 95% CI: 1.8-7.6) and recurrent (OR 2.3; 95% CI: 1.5-3.5) pregnancy loss [3]. This latter study did not address treatment paradigms, but again only a very small proportion of the existing literature was appropriate for inclusion in their meta-analysis (38 of 14,208 articles).

Several reports can be found among those screened and included in these meta-analyses that have received a significant amount of attention in isolation. For instance, a 1990 study from Stagnaro-Green linked the presence of elevated levels of anti-Tg or of anti-TPO antibodies to repeated pregnancy loss [4]. Although many authors have subsequently shown similar positive correlations, most do not see a separate link with antibody titers, bringing into question the mechanism(s) responsible for these correlations. Included among the hypotheses to explain this association are: 1) anti-thyroid antibodies are more commonly found in older women and the correlation is actually just a reflection of the association of age with pregnancy loss, 2) women with antithyroid antibodies are more likely to have generalized autoimmunity, which, in itself is associated with poor pregnancy outcomes, and 3) antithyroid antibodies themselves have adverse effects on oocytes, embryos and/or the endometrium. Of the studies included in the Dutch meta-analyses [2,3] that addressed screening for and treatment of thyroid disorders to prevent pregnancy loss, only two were randomized control trials and both came from the same study group in Italy. In 2006, Negro et al. [5] studied 984 pregnant women, among which 115 were anti-TPO antibody positive. The 115 antibody positive women were divided into two groups: 58 receive levothyroxine preconceptionally and 57 did not. The remaining 869 women acted as controls. Those women positive for anti-TPO antibodies who received supplementation had pregnancy loss rates similar to those who were antibody negative and which were significantly lower than those who were antibody positive but untreated (RR for loss 1.75; CI: 1.13-2.25 in the untreated group). In 2010, in a study of 4562 women, the same group of investigators reported that women with TSH levels between 2.5 mIU/ml and 5.0 mIU/ml (considered "normal" in most clinical laboratories) had higher rates of early pregnancy loss than those with levels below 2.5 mIU but still within the normal clinical range even when they screened negative for antithyroid antibodies [6]. In the same year, De Vivo et al. [7] reported on a study that included 216 screened pregnant women among which 26 were positive for antithyroid antibodies and 8 had subclinical hypothyroidism. The authors found that subclinical hypothyroidism and the presence of antithyroid antibodies were each independently associated with pregnancy loss and that many of these losses occurred at very early gestational ages. This study was retrospective and was not included in either of the Dutch meta-analyses. Still, several groups have responded to these and earlier similar reports by looking for interventions that may improve outcomes and a 2010 Cochrane review of such potential interventions [8] concluded that it may be useful to treat women with subclinical hypothyroidism that are also antithyroid antibody positive with exogenous thyroid hormone in an attempt to improve pregnancy outcomes.

In response to these and other supporting reports, many groups, including our own [9], have begun screening women with a history of pregnancy loss, particularly repeated pregnancy losses, with

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preconceptional serum TSH, anti-TPO and anti-TG antibody levels. Those with subclinical hypothyroidism and antibody positivity are offered preconceptional levothyroxine therapy and thyroid function is followed closely during pregnancy to allow for appropriate adjustments in therapy to maintain TSH levels in the 0.5-2.5 mIU/ml range.

While these interventions may be useful, and there are no indications that such supplementation is harmful if patients remain euthyroid, widescale adoption of this approach has certain and dramatic economic ramifications. More importantly, the approach has yet to be appropriately studied outside of southern Europe and the only randomized controlled trials available addressed anti-TPO but not at anti-Tg antibody levels. We continue to lack large-scale, multicenter, double-blinded, randomized, placebo-controlled clinical trials that give us clear guidance in this area. Fortunately, at least one such trial, centered in the Netherlands is currently enrolling patients. Again, this trial appears to limit study to those with anti-TPO antibodies, which are more common than anti-Tg antibodies, but are not solely responsible for thyroid autoimmunity and dysfunction in women of reproductive age. Still, we eagerly anticipate the completion of this trial and publication of its results to allow more informed and financially responsible care for women with this common and complex condition.

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