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# Maternal Hypothyroidism and Gastroschisis: The Case for Universal Maternal Thyroid Screening and Therapy in Early Pregnancy

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**ABSTRACT**

Maternal hypothyroidism has long been known to cause adverse effects on fetal and neonatal neurobehavioral development, and thus, thyroid function testing of at-risk pregnant women is commonplace. However, universal thyroid function screening has not been globally implemented primarily due to uncertainty about the embryo-fetal developmental effects of maternal subclinical hypothyroidism. In a recent Canadian population-based research study, hypothyroidism was associated with gastroschisis, a relatively rare but severe defect with midgut prolapse into the amniotic cavity in newborns. Given this new data, the substantial humanistic and financial cost associated with gastroschisis, and the relatively minor cost of thyroid function testing, we argue that the obstetrical standard of care should be updated to include universal screening with thyroid function testing of all women as early in pregnancy as possible.

**KEYWORDS**

Gastroschisis, hypothyroidism in pregnancy, thyroid screening in pregnancy

## INTRODUCTION

Public health and clinical perspectives on hypothyroidism in pregnancy as well as the controversy about reliance on criteria for screening thyroid function in pregnant women, are rooted in the historical awareness of myxedematous, neurological or mixed cretinism in infants, primarily driven by maternal dietary iodine deficiency (1). Subsequent considerations about testing and treating maternal hypothyroidism have largely been driven by the broader concern of potential compromises of normal neurological development in infants (2-4) and, more recently, consideration of cardiovascular developmental anomalies (5-7). Herein we argue that the recent demonstration of an association between maternal hypothyroidism and the risk of gastroschisis is an important additional basis on which to justify the detection and treatment of maternal hypothyroidism, as early as possible, meaning prior to pregnancy or as early in pregnancy as possible. We argue that the weight of evidence now supports moving the global standard of care to include universal pre-pregnancy or early prenatal screening of maternal thyroid function. While some investigations have failed to show that treatment of maternal prenatal hypothyroidism improves neurological outcomes in the offspring, the recent study regarding the risk of gastroschisis included the full range of hypothyroidism presentations and diagnoses. Thus, consistent universal detection of maternal hypothyroidism and appropriate treatment would provide the basis for assessing treatment effects for the several important neonatal outcomes, meaning neurological, cardiovascular, and gastroschisis-related risks.

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A recently published population-based research study identified significant risk factors for the development of gastroschisis. Liu et al. (8) found that babies conceived in the summer had a lower risk of developing gastroschisis, while maternal depression and hypothyroidism increased that risk. Causal mediation analysis demonstrated that hypothyroidism was the primary mediator of the gastroschisis risk associated with perinatal depression. This association with maternal depression merits thorough consideration in terms of maternal welfare. Beyond this, though, it is our perspective that the observation documenting the association of gastroschisis in offspring with antecedent maternal hypothyroidism is a call to action for prevention.

## EMBRYO-FETAL RISKS OF MATERNAL HYPOTHYROIDISM

The adverse effect of maternal hypothyroidism on fetal and neonatal development has long been known. As noted above, whereas hypothyroidism in mid to late pregnancy is associated with poor neurodevelopmental outcomes, maternal thyroid disorders during the early weeks of pregnancy are also associated with adverse effects, including cardiac and vascular diseases. Furthermore, a recent report by Sankoda et al. (9), showed that even isolated hypothyroxinemia or subclinical hypothyroidism in the first trimester had an increased risk of having small for gestational age (SGA) infants.

While the endogenous causes of hypothyroidism can vary, recent studies suggest a potential exogenous cause since widespread environmental thyrotoxicants may pose an additional risk in developmentally sensitive stages of pregnancy (10). Those exogenous thyrotoxicant exposures justify heightened concerns about the potential risk to fetuses due to diminished maternal thyroid function.

## THE LACK OF A GLOBAL STANDARD OF CARE FOR MATERNAL THYROID SCREENING

The protracted obstetrical debate about whether all gravidas or only those with a pertinent medical history or other risk factors for hypothyroidism should undergo thyroid function screening tests in pregnancy is ongoing. Multiple published reviews, studies, and guidelines present well-considered appraisals of the scientific, medical, public health and health economics literature that serve as suggestions for patterns of practice (11-17), subject to the appropriate use of clinical judgment of each practitioner for individual patients. While most such guidelines or recommendations favor the approach of testing thyroid function only in those women who have one or more risk factors for thyroid disease, there are some countries where the literature suggests that such screening is effectively universal (18-20).

We are convinced that this new observation regarding the risk of gastroschisis provides significant additional evidence for the necessity of advancing the obstetrical standard-of-care to include,

1. universal screening of maternal thyroid function as part of preconception preparations for planned pregnancies and as early as possible in all other pregnancies; and
2. implementation of indicated thyroid hormone replacement therapy before planned pregnancies or as early as possible in all other pregnancies.

Our call to action on these two points regarding detecting and treating hypothyroidism in early pregnancy presents a rational prospect to reduce the risk of this severe developmental anomaly, with its devastating impact on infants, parents, and families and the attendant massive healthcare costs for each affected infant.

## NEW JUSTIFICATION FOR MATERNAL THYROID SCREENING

The three justifications for our advocacy to promptly make these changes in the obstetrical standard of practice are based on our assessments of the following:

First, we will appraise the humanistic consideration of the welfare of infants born with this developmental anomaly as well as the impact on their families. When advocating for increased or decreased screening for any medical condition, it is, of course, essential to weigh the monetary costs and benefits, accessibility, feasibility, etc., of the proposed change in care. However, along with these more practical concerns, we must also analyze how a change in screening practices could prevent or alleviate human suffering. In addition to the neurodevelopmental and cardiovascular risks, in the case of thyroid function testing to prevent gastroschisis, we contend that at an individual and population level, the potential reduction of suffering in newborns, their adult selves, their parents, and their families vastly outweighs the nonexistent to relatively minor suffering caused by universal thyroid function testing during early pregnancy.

To begin, let us specify the suffering caused in each case of gastroschisis. Gastroschisis is a serious congenital paraumbilical abdominal wall defect, usually right-sided, with mid-gut prolapse into the amniotic cavity (21) without a covering of a peritoneal sac. Although it can be challenging to gauge the pain or comfort experienced by newborns, it is logical to assume that having such a defect and the consequent inflammatory effects on the intestines or other abdominal organs would cause immense suffering. This suffering cannot be discounted or ignored simply because the patient experiencing the pain cannot communicate that they are in pain. Moving forward in a patient's life, children with gastroschisis often experience various symptoms and complications. The most common are growth failure (22), vomiting, and malabsorption (see https://averysangels.Org/long-term-issues/). It is also common for infants with gastroschisis to be readmitted to the hospital within the first year for bowel obstructions or abdominal distention/pain (23). Some children also experience an increased risk for cognitive problems (24) and low self-esteem due to

scarring (see https://averysangels.org/long-term-issues/). Finally, it is common for children to need multiple additional surgeries later in life to correct long-standing problems resulting from gastroschisis, and in complex cases, these surgical interventions can be as extensive as intestinal (25) or liver (26) transplantation.

Long-term outcomes of children with prompt surgical management of gastroschisis tend to be favorable. Most patients overcome neurodevelopmental (27) and growth delays (28) and can expect to live a healthy daily life. However, some common long-term symptoms remain, including gastroesophageal reflux disease (GERD), constipation, and chronic abdominal pain (29).

It must not be overlooked that alongside the suffering experienced by these young patients with gastroschisis, there is also immense distress experienced by the parents and families of these affected infants. These caregivers face deep emotional distress and significant financial consequences and often struggle with coordinating additional care for the child (For more, see The Global Gastroschisis Foundation at https://averysangels.org/averys-story/).

In contrast to gastroschisis, maternal thyroid function testing presents a practically nonexistent cost to human welfare. Thyroid function tests are measured via a blood draw with subsequent laboratory analysis. This sampling may require an additional venipuncture or might be obtained along with the other routine blood tests recommended for women in early pregnancy.

As described above, even a single case of gastroschisis causes an immense amount of suffering. Unquestionably, reducing the frequency or severity of gastroschisis cases will serve the interests of young children, their adult selves, and their families. One necessary step towards reducing the incidence and severity of gastroschisis is universal thyroid function testing, which represents only a minor inconvenience to pregnant women. Given this stark contrast between the suffering caused by gastroschisis and that caused by maternal thyroid function testing, we conclude that from a humanistic perspective with reduction of suffering as our aim, universal thyroid screening for women as early in pregnancy as possible must be implemented in an attempt to reduce the incidence and severity of this terrible developmental defect.

Additionally, the maternal welfare benefits potentially include recognition and normalization of a commonly under-recognized endocrine disorder (hypothyroidism), but as reported in the study by Liu et al. (8), there is also the adverse mental health burden experienced by many young women. This cooccurrence of hypothyroidism and depression, particularly in women, was demonstrable in a recent large systematic review and meta-analysis (30), and some of these affected women may gain substantial relief of their depressive symptomatology by addressing their underlying metabolic disorder. Pregnant women who have cooccurrences of depression and hypothyroidism surely merit appropriate care for both of these diagnoses.

Finally, consideration of the added healthcare cost for performing an early as possible thyroid function screening tests in every pregnancy must be compared to the extremely expensive prospects of caring for a neonate affected by this developmental anomaly. Two decades ago, the surgical and hospitalization costs alone were estimated to be on the order of $125,000 (USD) (31). Hospitalizations of neonates with gastroschisis have been reported to average more than 40 days, much of which is in neonatal intensive care. Following discharge from the initial hospitalization, extensive costs that are not readily accessed via usual documentation in healthcare economics are those accrued over the ensuing months and years by the families as a consequence of having an affected child.

## WELL-ESTABLISHED ARGUMENT FOR UNIVERSAL MATERNAL THYROID SCREENING

Our current advocacy for universal thyroid screening in early pregnancy adds to the well-developed argument advanced by Taylor et al. in 2018 (17). Taylor et al. presented the arguments for and against universal thyroid screening in early pregnancy. To do so, the authors reviewed the criteria for screening and outlined how thyroid function testing fulfills these standards. They summarized the importance of thyroid hormones for fetal development and the significant adverse effects of thyroid dysfunction on infant neurodevelopmental outcomes. They also described the prevalence of thyroid dysfunction in women of childbearing age and how screening only high-risk patients tends to miss a majority of cases. However, in spite of the severity of thyroid dysfunction in pregnant women, they also explained the relative affordability and ease at which thyroid function can be tested and that there are well-established treatments for this disease. Additionally, they illustrated the cost-effective nature of universal thyroid function screening even if "… only overt hypothyroidism was assumed to have adverse obstetric effects."

The only criteria from the authors' list that was not satisfied was that "… there should be an agreed policy on whom to treat as patients." However, they noted that this was "… understandable given that thyroid dysfunction… is a continuum in which thresholds for intervention are uncertain." Adding that while guidelines recognize the need to treat overt thyroid disease, it is unclear when to step in and how to manage cases of "subclinical hypothyroidism, isolated hypothyroxinemia, and euthyroid autoimmunity." Currently, the standard set by the American Thyroid Association is to "definitely treat women with TSH [thyroid stimulating hormone] > 10 mU/L or antibody-positive women with TSH > 4.0 mU/L." Taylor et al. note that this guidance is logical given that women above these thresholds likely have thyroid disease and will eventually experience thyroid failure. However, there is less guidance provided on whether to treat women below these thresholds, and this leaves the door open for physicians and their patients to make case-specific decisions on what care to provide. This aspect of clinical decision-making certainly merits additional investigation and open discourse, given that there is no convincing evidence that neurodevelopmental outcomes are improv-

ed by treating maternal subclinical hypothyroidism (32). Additionally, it appears that current practices may lead to overdiagnosis and overtreatment (33). This unintended consequence must also be assessed and addressed since thyroid hormone excess is also a risk factor for obstetrical and fetal complications, including increased risk of fetal loss, fetal growth restriction, preterm birth, and low birth weight. Overcorrection of thyroid status must also be avoided throughout pregnancy.

## THYROID SCREENING LABORATORY MEDICINE CHALLENGES AND PROGRESS

Taylor et al. (17) described two practical needs that must be met before universal thyroid function screening can be actualized. The first of these is to establish pregnancy-specific thyroid hormone reference ranges from pregnant women who do not have thyroid disease. The importance of establishing these references is to make it possible to identify thyroid dysfunction in contrast to normal pregnancy-induced changes in thyroid function. Additionally, these reference ranges would help prevent over-diagnosis. The second need described by Taylor et al. is to create a universally agreed upon set of "criteria and unified nomenclature for diagnosing thyroid conditions in pregnancy." It is also necessary for obstetricians and endo-crinologists to be better trained on how to interpret abnormal thyroid function tests, for standard care plans to be established, and for resources to be made widely available for treating thyroid dysfunction.

Subsequent publications have, at least in part, addressed the need to establish generalizable laboratory reference standards for use in pregnancy and development and consistently apply diagnostic and therapeutic algorithms for use in obstetrical care. First, for establishing generalizable laboratory reference standards, in 2022, Osinga et al. reported on TSH and free thyroxine (fT4) reference intervals in pregnancy (34). They noted that the interpretation of thyroid function tests during pregnancy had lacked the generalizability of reference intervals due to differences in laboratory methodologies. They evaluated 102 studies and identified 48 deemed helpful for clinical applications. From their systematic review and meta-analysis, they were able to provide an overview with available reference intervals to be useable in clinical care when population and assay similarity are considered.

Second, to provide one example that illustrates how one major medical center has addressed the need to develop and use a thyroid testing algorithm in pregnancy, we refer to the publication by Woodworth and Schuler (35) as used at the University of Kentucky Medical Center in Lexington, KY. In their clinical chemistry laboratory, pregnant patients who are deemed to be at high risk of thyroid disease are those women with a personal or family history of thyroid disease, clinical signs and/or symptoms of thyroid disease, presence of goiter on physical exam, >30 years age, high body mass index, type 1 diabetes or presence of other autoimmune disorders, thyroid peroxidase antibody positive, previous head or neck irradiation, history of preterm birth, miscarriage, infertility, or the patient is from an iodine-deficient region. Woodworth and Schuler also commented as follows:

*"In the absence of universal screening recommendations, laboratories should outline carefully defined screening parameters to guide clinicians in determining when it is appropriate to screen for thyroid dysfunction in pregnancy. After identifying high-risk patients, screening for thyroid dysfunction in pregnancy should begin with a TSH measurement, followed by assessment of fT4 if TSH is abnormal using TSRIs. If overt thyroid disease is identified, assessment of thyroid antibody status should also be evaluated as this knowledge helps direct care particularly in the postpartum period… Given the dependence of the developing fetus on maternal thyroid function, particularly early in pregnancy, as well as the severity of outcomes in untreated thyroid disease, appropriate screening should take place as early as possible such that the proper treatment course can be administered. If a patient's thyroid antibody status is known to be positive, or if a patient has an autoimmune disease, thyroid screening should take place before conception if possible and be monitored appropriately throughout pregnancy."*

## THE UPDATED ARGUMENT FOR UNIVERSAL MATERNAL THYROID SCREENING

The strategy of targeted thyroid screening of women in early pregnancy has recently been challenged from a failure of implementation point-of-view. There are two current reports documenting that in practice, there is poor compliance with reliance on the clinical guidelines that recommend a risk-based screening strategy. In both a recent publication from Denmark (36) and a presentation at the May 2023 Annual Meeting of the American College of Obstetrics and Gynecology (ACOG), Dong and Lott (37) presented the findings of their US retrospective study showing that less than half of the pregnant patients who met the criteria for thyroid screening by the criteria of either the ACOG or the American Thyroid Association (ATA) were actually screened by their clinician. These latter investigators also reported that the patients who met the criteria and did receive screening had higher live birth rates and lower miscarriage rates than those who met the criteria but were not screened. Both of these reports imply that in routine clinical practice, clinicians find it difficult to comply with the current targeted screening guidelines of various professional organizations.

We again refer to the comments of Taylor et al. (17), who summarized their view of the appropriateness of universal maternal thyroid disease screening in pregnancy as follows:

*"The ultimate aim of maternal thyroid disease screening in pregnancy is to optimize feto-maternal outcomes. Thus, therapeutic intervention when indicated should be implemented as early as possible in the course of fetal development. Accordingly, universal screening should ideally be performed once pregnancy is suspected or pre-conception if pregnancy is planned. A pragmatic algorithm is to measure TSH and then reflex FT4 and TPOAb [thyroid peroxidase*

*antibodies] if TSH is outside of the relevant reference range. This will be challenging to achieve but with thoughtful planning can be integrated into routine community health services… Universal thyroid screening in pregnancy fulfills most criteria for a beneficial and cost-effective screening programme and holds promise for improving fetal and maternal outcomes. However, areas of uncertainty remain especially with regards to the significance of borderline biochemical abnormalities and whether correction of such abnormalities can improve out-comes. A consensus is unlikely to be reached without further controlled trials, and such trials should aspire to recruit women preconception or as early as possible in pregnancy. In the interim regular audit of existing screening programmes will be crucial in gaining insights into the practicalities of universal thyroid screening in pregnancy. For centers undertaking universal or high-risk screening integrating thyroid auto-immunity into decision-making is essential."*

We not only concur with Taylor et al. but think that a) the association of first-trimester hypothyroidism with an increased risk of having small for gestational age (SGA) infants (9) and b) the recent observation of the association of hypothyroidism with the risk of gastroschisis (8), provide the additional weight of evidence to necessitate making the global obstetrical standard of care to now include as early as possible universal thyroid screening in pregnancy. We think that the proposed mode by which hypothyroidism can be teratogenic in gastroschisis is simple and its plausibility is well-supported by past publications. That argument is summarized as follows:

*"Based on the findings of our study, we propose the following hypothetical mechanistic pathway by which maternal hypothyroidism could be a key causal factor in the occurrence of many cases of gastroschisis. Thyroid hormone is essential for normal embryonic and fetal development. Maternal thyroid hormone is important for the well-being of the embryo/fetus throughout pregnancy but is the sole source prior to the onset of thyroid hormone synthesis and secretion by the fetal thyroid tissue beginning at approximately 16 weeks of pregnancy* (10). *Prior to that time, multiple major embryonic events unfold and are solely dependent upon that maternal source of thyroid hormone. While it is well-known that normal neurocognitive development depends upon normal thyroid exposure of developing neural tissues* (38)*, it is also well-understood that the process of angiogenesis, including developmental neovascularization, is also thyroid hormone-dependent* (39). *Specifically, the alphaVbeta3 integrin is a key mediator of angiogenesis in adult tissues, tumors, and during development and is directly regulated by a non-genomic thyroid hormone receptor within alpha-Vbeta3 integrin* (40, 41). *Accordingly, absent or reduced thyroid hormone signaling compromises angiogenesis. Since vascular insufficiency or compromise of the relevant abdominal wall vessels is one of the favored hypothetical mechanisms by which gastroschisis occurs, reduced or absent angiogenesis could be a key factor in the occurrence of gastroschisis. In brief, maternal thyroid hormone is the sole source for the embryo, and maternal thyroid hormone acts locally on the plasma membrane receptor located within alphaVbeta3 integrin to stimulate angiogenesis in the embryo. If maternal thyroid hormone supplied to the embryo is modestly, moderately or severely reduced, the angiogenesis that is essential for normal development of the abdominal wall of the embryo/ fetus would be compromised."*

In summary, beyond the usual concerns surrounding the prevention of adverse neural developmental effects of maternal hypothyroidism on the fetus and the evidence for increased risks of cardiovascular disorders and SGA, we are convinced that the demonstrated association of gastroschisis risk with maternal hypothyroidism provides the additional incremental weight of evidence to move the obstetrical standard of care to include universal early as possible screening and earliest possible initiation of therapy for maternal hypothyroidism when indicated.

While we certainly do not expect this single intervention to obviate all cases of gastroschisis, this systematic approach for the detection and treatment of maternal hypothyroidism will reduce the risk of gastroschisis and potentially reduce the severity of some of the residual cases that do occur. Nonetheless, the prospect of reducing the occurrence of gastroschisis and better assuring reduction of risk for adverse fetal neural development presents a strong argument for the assertive changes we herein endorse.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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