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Pregnancy, postpartum and the thyroid: isn't it time to offer women optimal care?

V.J. Pop

Professor of Primary Care, Department of Medical Health Psychology, University of Tilburg, PO BOX 90153, 5000 LE Tilburg, the Netherlands.

Correspondence at: v.j.m.pop@uvt.nl

Abstract

In 2011, the American Thyroid association published guidelines concerning the attitude toward maternal thyroid (dys)function during pregnancy and postpartum. The American Association of Clinical Endocrinologists also recommend a case-finding approach although several studies has shown that up to 50% of women with thyroid dysfunction will be missed. Recently, it was shown that 0.6% of all pregnant women suffer from unknown overt hypothyroidism as a consequence of not screening: annually 1000 women in the Netherlands, 6000 in UK and over 24.000 in the US. Cost-effective studies have shown that screening of all pregnant women is beneficial.
This commentary criticizes the guidelines that (incorrectly) use RCT principles rather than following the more modern concepts of preventive medicine. Assessing a risk profile for an endocrine syndrome does not necessarily mean intervention per se. Informing women that they are at great risk for developing future thyroid dysfunction might help to reduce the tremendous patient and doctor delay of diagnosing hypothyroidism in pregnancy.

Key words: **guidelines, hypothyroidism, postpartum, pregnancy, prevention, risk profile, screening, thyroid function.**

In 2011, the American Thyroid association (ATA) published guidelines concerning the attitude toward maternal thyroid (dys)function during pregnancy and postpartum, an important topic in endocrinology, not only for the pregnant woman but even more for the developing foetus (Stagnaro-Green et al., 2011).

The American Association of Clinical Endocrinologists (AACCE) also recommend a case-finding approach (De Groot et al., 2012; Garber et al., 2012) although several studies have shown that up to 50% of women with thyroid dysfunction will be missed (Vaidy et al., 2007). These guidelines might be disappointing for the clinician, working in daily practice, for several reasons.

First, in my opinion, guidelines are especially meant for issues in medicine which are not fully scientifically proven (most often by randomized controlled trials or RCT's). Unfortunately the "terror" of evidence-based medicine as the exclusive standard to set-up guidelines seems also to be deeply rooted in thyroidology. As is quite often the case, the principles of evidence-based medicine are applied in the direction for which they were never developed: if a proposed strategy is not validated by a RCT then it should not be advocated. In my opinion this should be: if it has been proven by several RCT's that a strategy has no benefit, than it should not be applied. As a clinician, I prefer the attitude: "better safe than sorry", definitely to a woman who wants to become pregnant and whom we cannot advise: "wait until all the questions are answered by RCT proven evidence". Ideally, a prospective study should be performed in which 1000 TPO-Ab+ (thyroid peroxidase antibody) euthyroid women living in an iodine sufficient area at the age of 20 are randomly allocated into four groups, three groups receiving selenium or thyroxine or both for 10-20 years and one group receiving placebo, all with a follow-up of 30 years. End points are: possible obstetric problems, the neurodevelopmental outcome of (possible) offspring, the development during lifetime of full blown thyroid dysfunction, cardiovascular events, or diabetes-II…

It is obvious to the reader that such a trial will never be performed. But does this means today that it is nonsense to treat TPO-Ab+ women with family planning with thyroid hormone and or selenium?

The ATA guidelines are also rather selective: the principles of evidence-based medicine are not consequently applied! How can the authors state: there is no evidence for the benefit of T4 substitution in women with hypothyroxinemia or high TSH (sub-clinical hypothyroidism) on neurodevelopmental outcome of the offspring because RCT's are lacking (which I totally agree) while at the same time they state in their algorithm on postpartum thyroid dysfunction: assess thyroid function in those women who are tired or suffer from nervousness during the postpartum period? This refers to episodes in the postpartum who happen to almost every woman!! Can the authors refer to any RCT or prospective study in which the sensitivity, specificity and PPV of these symptoms on having thyroid dysfunction during the postpartum is demonstrated? Our group has shown in one study that symptoms during the postpartum period do not contribute at all to the prediction of postpartum thyroid dysfunction (ptd) (Kuijpens et al., 1998). How can the authors advice to assess thyroid function in pregnant women who are TPO-Ab + knowing at the same time that the only way to find out whether a woman is TPO-Ab+ is to screen? How can the panel advice a clinician that, when the FT4 during gestation is below the 5th percentile, action should be undertaken? Does a clinician have this information in common practice; does a clinician even know whether the (pregnant) woman lives in an iodine sufficient area (Vanderpump et al., 2011; Bath et al., 2013)?

Second, the new ATA guidelines are still based on the rather classical rules concerning the benefit of screening. In my view a more recent model in medicine should be applied: the assessment of *a risk profile* for the development of sub-optimal thyroid function, not only with regard to the woman but even more, in case of pregnancy, with regard to the developing foetus. Once a risk profile has been assessed it does not necessarily mean that an intervention is needed. Special follow-up strategies can be defined with no intervention at the time of screening but careful wait and see to help the patient to cope with a possible developing thyroid dysfunction in the future. But even applying the classical rules of benefit of screening has shown positive cost/effective analyses (Thung et al., 2009; Dosiou et al., 2012).

In the view of assessing a risk profile of sub-optimal thyroid function during a critical period I propose some alternatives, based on the following assumptions:

- Thyroid dysfunction is by far the most common endocrine disorder in women affecting at least 2-6% of women in their fertile period (13-55 years of age).
- An immune compromised thyroid, as reflected by elevated levels of TPO-Ab, affects (according to ethnic and geographical characteristics) at least one out of ten women. There is no discussion about the fact that these women are at high risk (compared to TPO-Ab negative women) to develop future thyroid dysfunction. Moreover, there is growing consensus that these women are at risk for mood disorder, especially bi-polar depression which affect 1-2% of all women.
- Signs and symptoms of thyroid dysfunction (except for the rare full blown hypo- and hyper-thyroidism cases) are so a-specific that there are no guidelines for a clinician when to think on the existence of a thyroid function problem, especially in the group of pregnant and postpartum women. In this light it would be interesting to investigate the average time delay (patient- and doctor related) between the first signs and symptoms of hypothyroidism and its final diagnosis. A careful lifetime history in a woman with a diagnosis of Hashimoto diagnosed in their forties often reveals that the first signs and symptoms were childbearing related. Our group recently showed that in a large sample of pregnant women up to 0.62% had unknown severe hypothyroidism which should – according to the same ATA guidelines – immediately been treated. These figures suggested that in the Netherlands, because we are not screening, annually up to 1000 women with full blown hypothyroidism (with severe consequences for pregnancy and the foetus) are missed, in UK up to 6000 and in the US up to 25.000 women.
- However, there exist clearly defined groups of women who are *at risk* for thyroid dysfunction, such as postpartum women.
- Although living with unrecognized hypo-thyroidism is never comfortable for a woman, there are groups of women who are *especially vulnerable* when sub-optimal thyroid function is not recognized: pregnant and postpartum women.
- This vulnerability is substantially increased during pregnancy and early postpartum in areas *with suboptimal iodine intake*, a phenomenon which is unknown not only to all women but also to most clinicians, not restricted to the developing countries but also in Western society, for example in the UK, as has recently been demonstrated (Vaidya et al., 2007).
- Several meta-analyses have shown unequivocally that women with elevated TSH (without any

symptom) are at risk for developing *future cardiovascular events* (CVE), although the underlying mechanism is not known (Gencer et al., 2013).
- It is well established that women with AITD are at tremendous increased risk for *other auto-immune diseases* (Effraimidis and Wiersinga, 2014).

In the Netherlands at the new millennium (at last), in Primary Care, prevention strategies have received growing interest by the Government, but most of all by the increasing awareness of the patient and the health insurance companies (when I pay your health care does my client get the best care with regard to costs/benefit ratio?). In UK, GP's are rewarded once they show to be actively involved in prevention programs of their patients (such as cardiovascular risk management). Nowadays, a patient is more and more involved in making a decision to set up his or her own risk profile with regard to all kinds of diseases. I think the time has come that a woman at fertile age should be advised to know her risk profile for developing thyroid function problems with possible consequences not only for herself but also for a developing foetus or newborn in case of family planning.

In all adult women thyroid function should be assessed for the simple reason that they are females: they have a 7-10 times higher risk than men to suffer from thyroid dysfunction with a life prevalence varying according to age of 2-6%. But one of the most expensive parts of population screening is the logistics that have to be organized in case of screening: how do you reach your target population? To what costs? How is the collected information communicated etc. There is however one moment during a woman's life where all these costs are already paid and the logistics are well organized: the standardized blood assessment at 8-12 weeks gestation (although this attitude excludes women without family planning) followed by regular visits to a community midwife or obstetrician. The only thing that is needed is one more tube to assess TSH, FT4 and TPO-Ab, all very reasonable cheap assessments. Several studies have shown a positive cost-effective analysis of this attitude (Thung et al., 2009; Dosiou et al., 2012). Implementing thyroid screening during pregnancy for example for one decade will give us a tremendous quantity of information which eventually may result in the conclusion that screening makes no sense. Apart from the findings of the last decades there are preliminary data showing that high TSH might be related to breech position, low FT4 to abnormal cephalic position, both important causes of obstetric problems. Breech in turn has been related to autism. Hypothyroxinemia during gestation to ADHD. Screening of thyroid function of large samples of pregnant women for one decade will elucidate more on these issues.

A. Recommended strategy for all pregnant ("healthy") women.

Assess TSH, FT4 and TPO-Ab as early as possible during gestation, not only because at this stage the immune down-regulation is not that strong and most of the TPO-Ab + women will be picked-up but also at this stage the FT4 assessment is still reliable and correlates inversely with the TSH (despite the HCG). Moreover, if a possible intervention with T4 could benefit (if ever) the developing nervous system of the foetus, it should be started as soon as possible.

All the thyroid parameters should be assessed in the background (if possible) of knowing the iodine status of the area where she lives. As a matter of fact it is unethical nowadays to advise women about becoming pregnant, not knowing the iodine status of the area where she lives. If there is suboptimal iodine intake, advice iodine supplements according to WHO.

Strategy 1. If a woman has TPO-Ab > 100 IU/l (with TSH < 2.5 mIU/L) it should be concluded that this woman is immune compromised and has an increased risk for poor obstetric outcome (not necessarily related to the thyroid but more likely because there might be a problem with the general down-sizing of the immune response to protect the foetal allograft).

- Think about the possibility of selenium substitution up to 100-200 microgram. No harm has been shown so far and many pregnant women already use supplements during pregnancy which contain up to 60-100 microgram of selenium.
- Realize that she is at risk for developing thyroid dysfunction (although less likely during gestation) and her thyroid function should be assessed again after 4 weeks and – when TSH < 2.5 mIU/L – should be checked every trimester in order to follow thyroid functioning.
- She will be at risk for ptd and her thyroid function should be checked every 8 weeks starting 8 weeks postpartum until the first postpartum nine months.
- She will be at risk for developing thyroid dysfunction during lifetime. Thyroid function should be checked annually or explain her that whenever during lifetime she is facing an episode

of all kind of vague symptoms she should check her thyroid function immediately.
- Whenever she develops a depressive episode in life, check the presence of bi-polar disorder.
- She is at increased risk to develop other auto-immune diseases.

Strategy 2. If TSH is > 4 mIU/L, irrespective of TPO-status

- Repeat the assessment within 4 weeks.
- If the TSH remains high, discuss T4 replacement therapy. However, explain the patient that this might benefit the obstetric outcome but – although it will not harm the foetus – we currently do not know to what extent the extra amount of T4 will reach the foetus. It is well known that the placenta Deiodase-III degrades high amounts of T4 that comes from the mother. Check her thyroid function every 4 weeks until 32-34 weeks gestation.
- Discuss the same issues as described in Strategy 1.
- Look after other cardiovascular risk factors and let her thyroid function be checked annually after childbearing.

Strategy 3. If she is TPO-Ab negative with normal TSH but FT4 below the outside pregnancy reference range (still reliable at 8 to 12 weeks gestation) she has hypothyroxinemia: think at sub-optimal iodine intake and advice iodine supplementation. If T4 substitution is started, see the comments in Strategy 2.

B. Recommended strategy for all pregnant women on thyroid hormone replacement therapy.

1. Always check the reason why she is hypothyroid: be aware of former Graves' patients who have been treated by radioactive Iodine and became hypothyroid. If so, check the TSH receptor antibodies. When positive, check for increased foetal heart rate and for growth Intra-uterine retardation by ultrasound as a preliminary sign of possible foetal hyperthyroidism.
2. Remember a large retrospective epidemiological study showing in over 15.000 women followed during gestation that sub-clinical hyperthyroidism during gestation was not related to any obstetric problem (Casey et al., 2005). If a clinician wants to have an FT4 level > 12 pmol/l at 12 weeks and > 10 pmol/l during further gestation at the costs of an undetectable low TSH: fine, no harm has been demonstrated (assuming a non-pregnant reference range between 10-24 pmol/l).

C. Recommended strategy for all postpartum women:

1. If no problems were found at screening always check thyroid function in any woman who does not have a normal recovery after childbearing until 9 to 12 months postpartum (including mood problems). Do not relate all kind of symptoms to breastfeeding, feeding at night, a "difficult" baby. According to ethnic differences one out of 12-16 women will suffer from ptd.

2. If the risk profile assessed during gestation is positive:

- Check thyroid function every 8 weeks during the first nine postpartum months.
- Explain that, although she might have become pregnant without any problem, she is at risk for future fertility problems because of possible asymptomatic increased TSH levels which might interfere with ovulation.
- Assess a cardiovascular risk profile as part of cardiovascular risk management when TSH stay above 4 mIU/L and discuss starting of T4 replacement.
- Be aware of an increased risk for other auto-immune diseases when she complains about joint pain, has a disturbed glucose tolerance e.g.

One more final comment: The fact that several studies have found a statistically significant IQ delay in children, at the age of one, or two, or five years, of mothers with high TSH or low FT4 during gestation, does not give any insight into the clinical relevance of (neuro) development of these children *on the long term*. The ATA expert panel states that the only intervention study performed so far did not show any benefit, which is correct. But they advice, that we should wait until future trials show more results. However, is it not more logical to advice that we should evaluate what the clinical relevance is of a delay at early age in relation to (neuro) development in adolescence? We know from clinical experience that many children with mild delay problems at pre-school age have improved almost to normal once they get older and (neuro-behavioral) physiotherapy has been started. And if the first 6-10 weeks are crucial for the development of the foetal CNS are we not always too late when starting with T4 substitution during gestation at 12-16 weeks? Is the only appropriate way not a preconception visit in which the risk profile is evaluated and women at risk are advised to start an intervention before they become pregnant?

In conclusion, offering pregnant women a more sophisticated approach of risk profiling of thyroid

dysfunction seems to be a more advisable attitude towards optimal care of pregnant women.

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