INTERNAL MEDICINE GRAND ROUNDS:

January 13th, 2012

THE CARE OF A PREGNANT PATIENT WITH THYROID DISEASE:

THE CONTROVERSIES

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A controversy in art...

On the cover: Jan van Eyck, *Arnolfini Portrait*. Oil, 1434. National Gallery, London.

While it is known that the painting represents Giovanni Arnolfini, a wealthy cloth merchant and his wife Giovanna Cenami, there are a lot of controversies about this painting. Some refer to it as the Wedding Portrait. Others argue that the picture already has too much of marital intimacy to be a representation of a wedding vows.

Although viewers' eyes are certainly drawn to Giovanna's prominent dress folds at the abdomen level, it is unclear that it signifies that she is actually pregnant. Similar representations have been rendered to virgin saints in works of the period and some argue that the lifted dress edge symbolizes purity. The gravid appearance, as well as a little statue of St Margaret, a patron saint of childbirth, fruit on the table and Giovanna's bare-footedness all hint at Giovanna's childbearing potential. It is not known however, whether they mean that Giovanna was with child at the time when the portrait was painted. It is conceivable that they simply suggest her fecundity, an important and valued trait for a woman of her era. It may be that this painting is a representation of her as a virtuous wife, who hoped for a pregnancy.

From historical documents we know that the couple died childless, but it is unknown whether Giovanna had ever been pregnancies. There are even speculations that Giovanna died prior to the completion of the work and that the painting represents a woman who might have died during childbirth.

Sources:
http://en.wikipedia.org/wiki/Arnolfini_Portrait,
SUNNY Oneonata website: article written by an arts history faculty member
http://www.oneonta.edu/faculty/farberas/arth/arth214_folder/van_eyck/arnolfini.html
LaGrange college website: Author Flemming Gardner
http://www.lagrange.edu/resources/pdf/citations08/GIOVANNIARNOLFINIANDHISBRIDE.pdf

Thyroid hormone physiology and normal pregnancy

Pregnancy is a time of many profound changes in hormonal milieu. The mother's body provides not only nutrients but also all the hormones necessary for the normal development of the fetus. When this fails the results are disastrous for the fetus.

One of such physiologic changes early in the first trimester of pregnancy is the need for increased production of thyroid hormone. This is driven by multiple factors, the most important one being significant the increase in thyroid binding globulin(TBG), which is a result of increased estrogen levels inducing hepatic production. In addition there is increased sialylation of TBG, which results in their decreased clearance (1). Furthermore, there is also an increase in maternal plasma volume, which has a dilutional effect. As a result of this TBG increase, there is an overall increase in total thyroxine and total triiodothyronine level, since majority of T4 (99.96%) and T3 (99.6%) are bound. This increase plateaus around 12-14 weeks of pregnancy.

There is also a small increase in free T4 level during the first part of pregnancy. The reason for a need of such an increase is unknown, It is believed, however, to be mediated by HCG, which bears homology with TSH, as do their receptors (4). Although HCG has a week thyrotropic activity during the first trimester, it is present in very high concentrations. Studies have shown an inverse relationship between HCG and TSH, which likely is a result of HCG suppressing TSH (5). In addition a decreased coupling between free T4, free T3 and TBG during pregnancy has been observed.

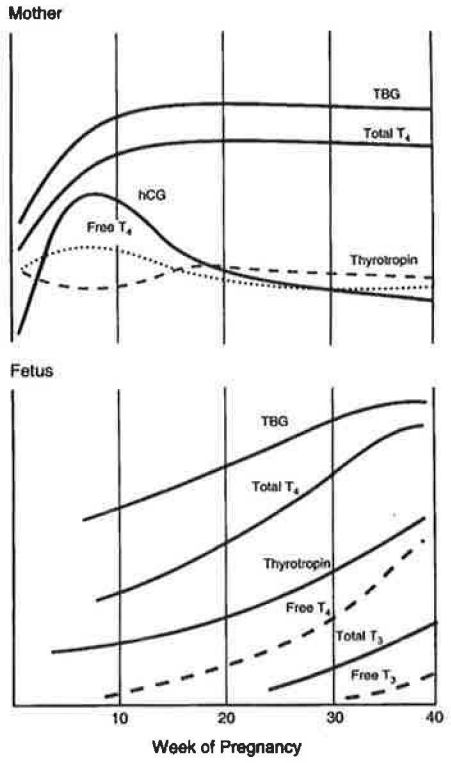
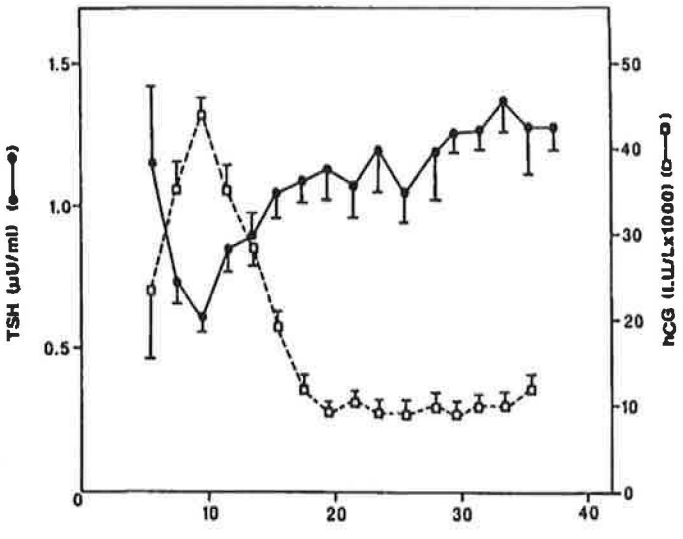


Figure 1. Relative Changes in Maternal and Fetal Thyroid Function during Pregnancy.

Fig 1. Left: adapted from Burrow et al. (3)

Fig 2. Below: Inverse relationship between TSH and HCG (2).



Importance of maternal thyroid hormone for normal fetal physiology

Thyroid hormone is necessary for proper development of the fetal nervous system, which already takes place within the first month after conception. At that time, the embryo is totally dependent on the mother for the presence of thyroid hormone which crosses through the placenta. Fetal thyroid finally develops at 10-12 weeks of gestation, but it is not capable of substantial thyroxine production until about 18-20 weeks of gestation.

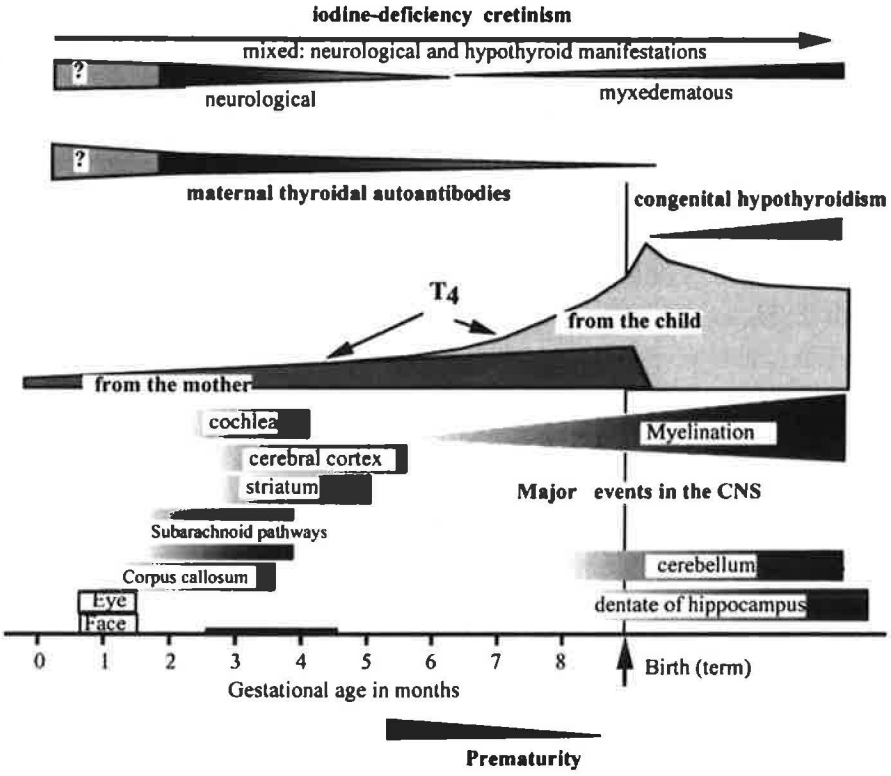


Fig 3. Approximate timing of major insults to the brain resulting from hypothyroxinemia, superimposed on major neurodevelopmental events (6).

Maternal thyroid hormone continues to supplement fetal thyroid production significantly until term. Evidence for it comes from children born with congenital absence of thyroid: their cord blood samples contained about only about 20-50% of thyroid hormone level present in cord blood of normal newborns (7). We also know that there is a positive correlation between other maternal thyroid parameters such as maternal and cord blood TSH and cord blood of newborns (8).

Laboratory assessment of thyroid function tests in pregnancy

Measuring thyroid function tests in pregnancy presents a number of problems. For one, the physiologic changes result in altered normal range from that of non-pregnant patients. Many laboratories do not routinely provide physicians with a pregnancy-specific ranges for thyroid function test. The newest guidelines recommend that physicians use TSH range that is both trimester and lab specific. (9) This is crucial, given that there is an enormous variation among the analyzers and methods. This is well exemplified in pathology quality assurance literature, where the same sample of TSH analyzed on different equipment and with different methods, can give results ranging from 6.75 to 14.457 mIU/L, while in the same time having a quite good coefficient of variability for that specific analyzer. (10) See Fig 4. Aware that laboratories often do not provide trimester and method specific ranges to physician, the American Thyroid Association attempted to give physicians guidance for TSH ranges to be used during pregnancy, when such ares not available from the laboratory. These are as follows:

First trimester, 0.1–2.5 mIU/L
Second trimester, 0.2–3.0 mIU/L
Third trimester, 0.3–3.0 mIU/L

The ATA does not have much confidence in the recommendation to use these range, giving it grade I (insufficient evidence to recommend for or against.) Fig 4. (below) will make it clear why this is so.

METHOD	NO. LABS	MEAN	S.D.	C.V.
ABBOTT ARCHITECT i	178	9.899	0.501	5.1
ABBOTT AXSYM	25	9.836	1.432	14.6
BECKMAN ACCESS/2 3RD	178	11.239	0.610	5.4
BECKMAN ACCESS/2 FAST TSH	99	10.449	0.660	6.3
BECKMAN UNICEL DXI 3RD	222	11.237	0.736	6.5
BECKMAN UNICEL DXI FAST TSH	89	10.367	0.630	6.1
ROCHE e411/ELECSYS	65	11.417	0.378	3.3
ROCHE e600 SER/E170	307	11.404	0.256	2.2
SIEMENS ADV CNTR/XP	219	13.214	1.289	9.8
SIEMENS ADV CNTR/XP TSH3U	50	12.208	0.385	3.2
SIEMENS ADVIA CENTR 3G	89	12.046	0.435	3.6
SIEMENS ADVIA CENTR CP	24	12.383	0.815	6.6
SIEMENS DIMENSION EXL	54	7.111	0.277	3.9
SIEMENS DIMENSION HM	143	10.881	0.874	8.0
SIEMENS DIMENSION VISTA	148	6.753	0.213	3.1
SIEMENS IMMULITE 1000	22	11.616	0.862	7.4
SIEMENS IMMULITE 2000	53	11.148	0.778	7.0
SIEMENS IMMULITE 2500	12	11.128	0.599	5.4
SIEMENS IMMULT 2K/2500 3G	12	10.908	1.041	9.5
TOSOH ST AIA-PACK	28	13.457	0.802	6.0
VITROS 3600,5600,ECI/ECIQ	266	12.145	0.840	6.9

Fig 4. Range of TSH results obtained via different analyzers (10). Our lab uses Roche e600

Measuring T4 presents even greater problem during pregnancy. The usual and widely available method of measuring free T4 is by immunoassay. Unfortunately this method is quite unreliable in pregnant women. This is because serum of pregnant women has much higher concentration of thyroid binding globulins, non-esterified fatty acids and significantly lower levels of albumin, which can result in falsely lower results of free T4. In addition, pregnant women have a higher number of non-specific heterophile antibodies, which can further interfere with the assay (11).

The next best method is to try to separate free T4 prior to measuring it. This is achieved by allowing free T4 to equilibrate across a dialysis, which does not permit proteins. This is a much more reliable method of measuring thyroid hormone in patients with serum protein abnormalities as well as in pregnancy. It is available as a send-out lab to the Mayo clinic at our institution as well as in some commercial laboratories.

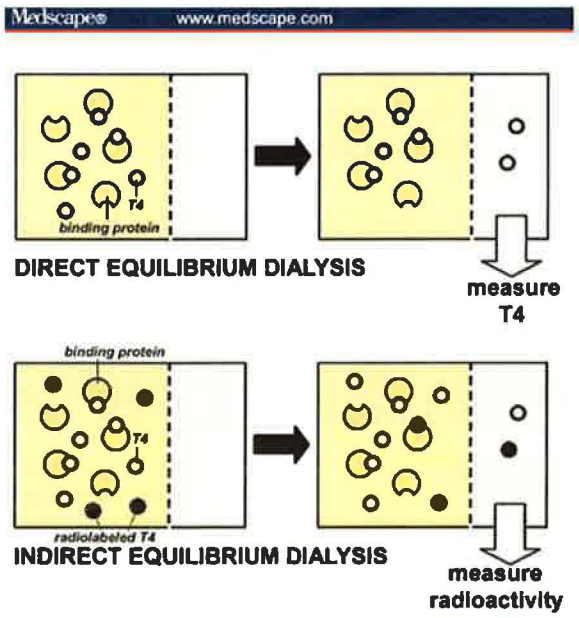


Fig. 5. Free T4 by direct and indirect equilibrium dialysis. Usually the direct method is used, given that it avoids using radioactive material (12).

The gold standard of analyzing free T4 in pregnant women is by liquid chromatography and tandem mass spectrometry (LC/MS). ATA states that this is the method of choice when testing pregnant women, and gives this recommendation a grade "A." Unfortunately due to the fact that the equipment is costly, and the method labor intensive LC/MS is not widely available at this time, even as a send-out lab (11, 12).

Overt hypothyroidism

Hypothyroidism is a very common problem in women. The current definition of overt hypothyroidism as specified in the ATA guidelines is high TSH associated with low free T4 or TSH >10 mIU/L. 3.1% of American women were found to have hypothyroidism (13).

Since hypothyroidism is more prevalent in women, it follows that we would encounter this condition during pregnancy. 1-2% of all pregnant women are treated with levothyroxine during pregnancy (3), while the rate of overt untreated hypothyroidism during pregnancy is 0.3–0.5%.

This number is so low because hypothyroidism often results in subfertility and increased rate of miscarriages, noted as up to 60 by some authors (14-16). There is no doubt, however, that pregnancies that do progress are at risk for multiple overt negative outcomes for both the mother and the baby. Among reported perinatal complications associated with overt hypothyroidism are pregnancy-induced hypertension, which occurs in 0-44%, placental abruption in 0-19%, anemia 0-31% and post partum hemorrhage present in 0-19%. There is also an increase risk of cesarean sections (17). Fetal distress and perinatal death increase from 0.9% to 8.1% up to 12% in some studies (14-16). Preterm birth occurs in 9.3% vs 3.4% of unaffected populations and up to 31% in some populations. Low birth weight is reported to occur in 22% vs 6.8% of unaffected population (14).

Treatment of hypothyroidism in pregnancy

Experts as well as professional societies agree that thyroid function should be normalized (to <2.5IU/L or trimester specific) in women with hypothyroidism in order to improve outcomes for both babies and mothers. This information comes from observational studies (18.) It is also well known by now that thyroid hormone requirements increase during the first half of pregnancy (19).

The best strategy to treat patients at this point has not been fully untested. Alexander et al proposed that increasing therapy by 2 extra tablets a week will provide adequate replacement in a majority of patients (20). In his NEJM study, he found that pregnant patients requirements on average a dose that is 49% higher than before pregnancy, and that the majority of his patients needed this increase in dose by 16 weeks. There was however a significant variation among the participants in the dose increase (10-80%) required to maintain pre-pregnancy TSH level. As a result a THERAPY trial was completed, which tested if two vs three tablet increase was the best option (21). The outcome was better for two tablets.

There is some disagreement about recommending a flat 2 dose tablet increase for everybody. Some experts argue that "one-size-fits-all" approach does not take into consideration the pathology of the disease when treating hypothyroidism in pregnancy (22). Further testing dose increase in pregnant women, Loh et al found that while Hashimoto thyroiditis patients required on

average 92.5 +/- 32.0 micrograms of levothyroxine, patients after radioiodine ablation required 140.4 +/- 62.4 micrograms and post surgical hypothyroidism patients required 153.2 +/- 30.3 micrograms. In this study the adjustment was necessary all the way until the 3rd trimester (23).

There is also some disagreement about frequency of blood draws necessary in order to adjust the dose appropriately. Guidelines recommend that labs be drawn every 4 weeks during the first half and at least once in the second half of pregnancy. Some experts believe that this interval is not frequent enough and that blood should be drawn every 2 weeks to avoid overtreating and undertreating pregnant patients (23). Several studies are ongoing to address this question in the future.

Subclinical Hypothyroidism

Subclinical hypothyroidism is a much more controversial subject. There are again many studies which quote various rates of complications, but overall the rate of the complications appears to be lesser than that in over hypothyroidism. The two of the three largest studies of this problem have been done in the United states. The first one was done by the FASTER consortium and was conducted at 15 centers throughout the United States. After enrolling 10,990 patients, 240 patients were identified during the first trimester and 2.2% (243) during the second trimester. There was no difference in obstetrical outcome between the optimal thyroid level group and subclinical hypothyroidism group (24).

A Finnish study of 5805 women showed no increased perinatal risk associated with subclinical hypothyroidism. It did however point out to increased risk of future thyroid disease in the mothers [RR 3.3 (1.6–6.9)] (25).

On the other hand, a study conducted at Parkland by Casey et al in a population of 17,298 pregnant women screened at 20 weeks showed a significant risk for placental abruption with RR 3.0 (95% CI 1.1-8.2). Preterm birth (<34 weeks) was also more common with RR 1.8 (95% CI 1.1-2.9). Other negative perinatal outcomes associated with prematurity were also more common in children of mothers with subclinical hypothyroidism. This included admission to the neonatal intensive care unit and respiratory distress (RR 1.8, 95% CI 1.1–2.9 and 1.0–3.3.) Overall rates of subclinical hypothyroidism were very similar to those found in the FASTER trial: 2.3% (404 women) (26).

Neurologic outcome in children of mothers with subclinical hypothyroidism

A significant report that is often quoted as evidence that subclinical hypothyroidism can affect offspring's IQ appeared in NEJM in 1999. Haddow and colleagues reported on children of

mothers with normal free T4, but elevated TSH (mean TSH was 13.2±0.3), who underwent neuropsychiatric evaluation at the age of 7-9 years. The main shortcoming of the study was that it really did not study the patients we now call subclinically hypothyroid. It lumped together women who were overtly hypothyroid with women who where undertreated to a subclinical hypothyroidism level. As a result it showed that untreated and partially treated women had children with lower IQs, although this was not true statistically significant (p=0.06). Also, greater number of children with low IQs were in the untreated group, while the undertreated group had a trend towards having greater number of children with IQ <85 (27).

On the other hand a Dutch trial which included a cohort of 3139 children and their mothers did not find a decrease in performance on neuropsychological testing in children of women with subclinical hypothyroidism (28). Likewise, a recent study performed in Teheran of a cohort of 44 children and controls of undertreated hypothyroid mothers and well as mothers with gestational subclinical hypothyroidism showed no difference in IQ outcomes (29).

Treatment of subclinical hypothyroidism

ATA encourages treatment of pregnant women with subclinical hypothyroidism in presence of anti TPO antibodies. This is based on evidence from Italy, which showed that women with anti-TPO antibodies had higher TSH than women without antibodies and that treating them decreases the rates of miscarriage and pre-term delivery. (30)

In the absence of antibodies there are no trials to guide us and therefore ATA is unable to make recommendations. There are however, studies on the way, which should be completed within the next few years.

Isolated hypothyroxinemia

Another entity in the hazy world of obstetric thyrology is hypothyroxinemia. It is defined as free T4 below the lower 5th or 10th percentile of normal in the absence of elevated TSH.

Casey and colleagues in the Dallas area study reported no negative outcome in their population, and attributed the abnormal free T4 levels to problems with the assay (31). On the other hand, the FASTER trial showed that hypothyroxinemia was associated with preterm labor (adjusted odds ratio of 1.62; 95% CI 1.00 –2.62) and macrosomia (aOR - 1.97; 95% CI 1.37–2.83), when it occurred in the first trimester. In the second trimester, hypothyroxinemia was associated with gestational diabetes (aOR 1.7; 95% CI 1.02–2.84). In association with positive anti TPO and anti thyroglobulin antibodies, there was an increased risk for preterm premature rupture of

membranes(24). Negative obstetric outcomes were also recently confirmed by a group from China (iodine sufficient area) (32).

It is unclear if hypothyroxinemia results in impaired neurologic development in children. A 1999 study of 220 healthy children of TPO-, I- sufficient Dutch mothers found that fT4 <10th % at 12 weeks correlated with increased risk of impaired psychomotor development at 10 months : RR 5.8 (95% CI: 1·3–12·6), but there was no such correlation when maternal free T4 was low at 32 wks (33). In a follow up study, Pop and colleagues confirmed that children whose mothers were hypothyroxinemic during the first trimester and had lower scores on neurocognitive and motor tests. Their tests normalized however, if their mother's free T4 entered normal ranges during 24-32 weeks of gestation (34). Recently, others also confirmed that while hypothyroxinemia can negatively impact neurocognitive developement of children when it occurs during the first trimester, maternal early 3rd trimester hypothyroxinemia has no impact (35).

Treatment of isolated hypothyroxinemia

Given conflicting data on whether hypothyroxinemia results in maternal or pediatric complications, the ATA took a stand against routine treatment of pregnant women with this condition. This may however still change as more trials are performed. At this point, some experts suggest that this is a condition of relative iodine insufficiency and encourage adequate supplementation through iodine-containing prenatal vitamins or other forms of therapy (potassium iodine) (37). The recommended dose is additional 150 µg a day in an iodine-sufficient region, to achieve a total of 250 µg intake.

Autoimmune thyroid disease

Thyroid autoantibodies are found in 5–18% of women in the childbearing age. There is however no concensus in literature as to what is definded as a having autoimmune thyroid disease. While everybody agrees that anti-TPO antibodies are required for this diagnosis, there are some differences as to what is the cut off of positivity: with >50 IU/ml being a common threshold. Also, some groups report additional tests such as anti-thyroglobulin antibodies and anti-microsomal antibodies.

Although not all studies are consistent, autoimmune thyroid disease has been linked to multiple negative outcomes. These negative outcomes include miscarriages, subfertility, premature rupture of membranes, placental abruption, preterm delivery and fetal respiratory distress (37-42).

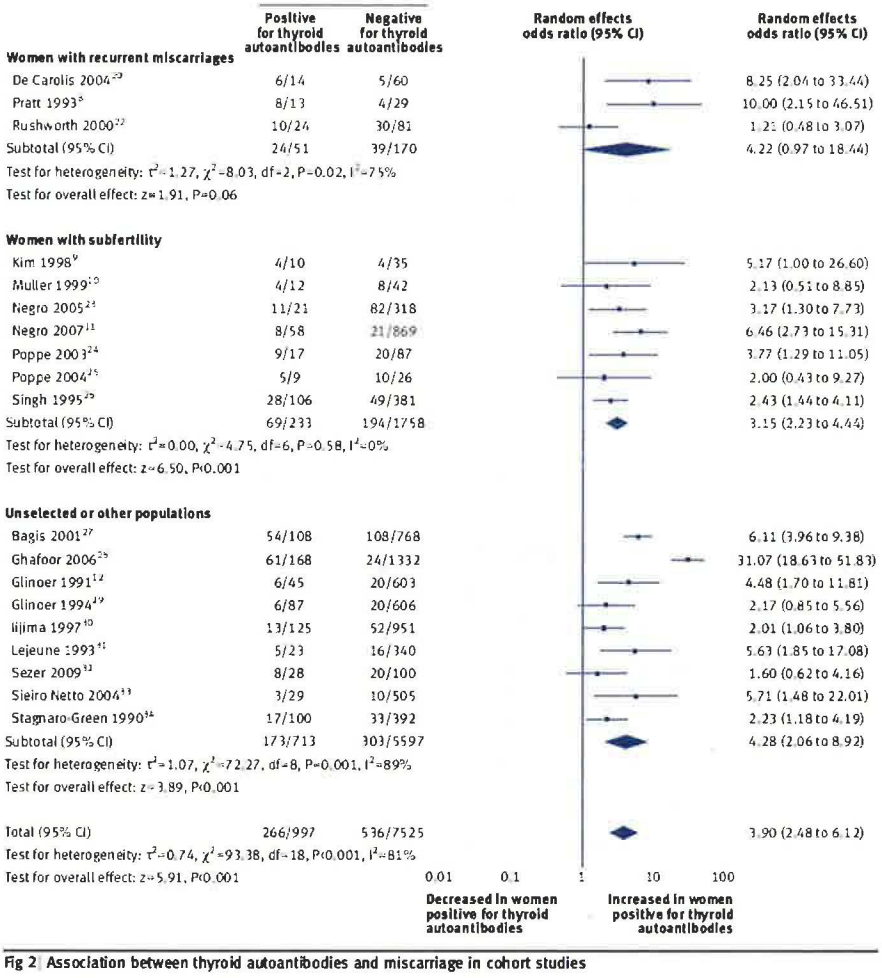


Fig 2 | Association between thyroid autoantibodies and miscarriage in cohort studies

Fig. 6. Metaanalysis o f studies reporting miscarriage or subfertility associated with anti-TPO antibodies (42).

There is also at least one report linking maternal anti-TPO positivity with poorer performance on neuropsychologic testing (36).

At this time there is not enough data to support the recommendation of treating anti-TPO positive women with levothyroxine in the absence of thyroid dysfunction, but close monitoring of TFTs during pregnancy is warranted and recommended.

Universal screening

Universal screening is a hotly debated topic in endocrine and obstetrical literature. Up to date American College of Obstetrics and Gynecology advises that universal screening is not supported by sufficient evidence and advises to screen women who are symptomatic and have conditions associated with thyroid disease, such as for example diabetes (43).

American Association of Clinical Endocrinologists (AACE) takes a very different stand in a very controversial document, which some may argue was misleadingly named "Consensus Statement: Subclinical thyroid dysfunction, A joint statement on management from the American Association of clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society." AACE promotes the idea of universal screening for thyroid dysfunction among women in early pregnancy or those considering pregnancy. While AACE acknowledges the position from ACOG is based on evidence, it endorses universal screening of women who are pregnant or contemplating pregnancy. They explain their position by the following statement:

> "*...Because the potential harm of early detection and treatment appears to be so minor and preventable, it seems prudent to err on the side of early detection and treatment until there are sufficient data to definitively address these issues*" (44).

Endocrine society takes a middle position. It agrees with ACOG and does not endorse universal screening. But it also encourages aggressive case finding. It is much more explicit about which conditions are in the at risk group. The list of risk factors warranting an evaluation with TSH includes personal history of hyperthyroid or hypothyroid disease, post-partum thyroiditis, goiter, thyroid lobectomy, family history of thyroid disease, known history of thyroid antibodies, symptoms or clinical signs suggestive of thyroid underfunction or overfunction, including anemia, elevated cholesterol, and hyponatremia, type I diabetes, other autoimmune disorders, infertility, previous therapeutic head or neck irradiation, history of miscarriage or preterm delivery (45).

While eliciting symptoms and signs of hyperthyroidism is easy, identifying hypothyroidism during first trimester is especially difficult. This is because of significant overlap between symptoms of hypothyroidism and pregnancy, which can include fatigue, weight gain and constipation. In addition some patients with hypothyroidism can be asymptomatic. The new 2011 ATA guidelines have gone a step further. It has listed the same risk factors as those proposed by the Endocrine Society, but also added morbid obesity (body mass index 40 kg/m^2), since it has been associated with higher prevalence of hypothyroidism. In a recent publication, SCH was present in 13.7% of the morbidly obese cohort, while overt hypothyroidism affected 19.5%. Also, since risk of hypothyroidism increases with age, ATA advised to screen women who are 30 years of age or older. Prior treatment with amiodarone, lithium as well as exposure to iodinated radiological contrast agents within prior 6 weeks are among the new risk factors added. Overall however, ATA has concluded that there is insufficient evidence to recommend "for or against" screening.

But how effective is our case finding? There are a handful of trials that have tried to answer this question. In his study of British women, Vaidya et al found that while being classified as "high risk" does correlate with higher prevalence of elevated TSH (6.8 vs 1%), 30% of all women with elevated TSH had no known risk of the disease (46). Similar findings were published by Horacek et al, who reported that 55% of their patients, who met criteria for treatment were in a low risk group and would have been missed. Their screening however, included anti-TPO antibodies and treatment

criteria extended to sonographically-confirmed thyroiditis in the presence of anti-TPO antibodies (47).

A larger study, which attempted to answer the question of whether there is a significant benefit to universal screening was done by Negro and Stagnaro-Green. In this study 4562, Italian women were stratified to universal screening vs case finding. Each of these groups were further divided as high vs low risk. High risk women were screen and treated in both groups. In the universal screening group low risk women were screened as well and treated when appropriate. In case finding group patients' blood was drawn and analysed after they delivered. There was no difference in outcomes between universal screening and case finding groups. Secondary analysis, revealed however an interesting observation. There were twice as many negative obstetric/perinatal outcomes in the low risk case-finding group as in every other subset of patients (48).

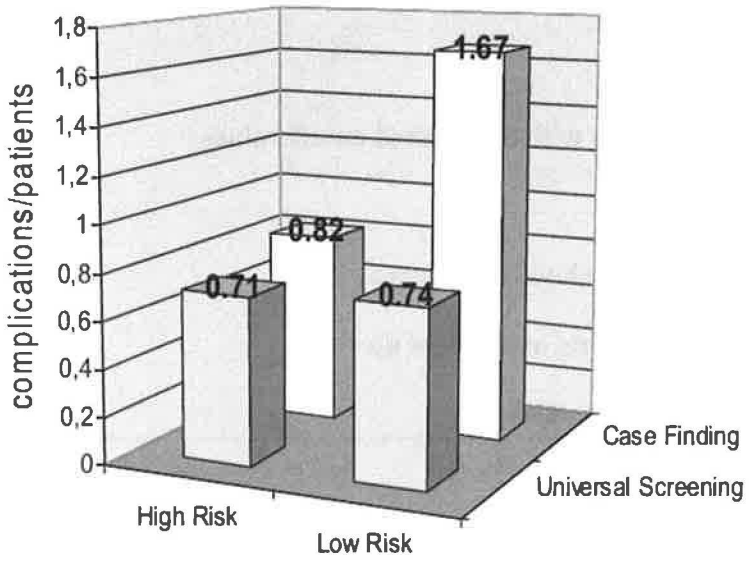


Fig 7. Increased risk of complications in low risk case finding group (48)

This translated into screening 36 low risk women in order to identify one who needed therapy, screening 40 to prevent a single negative outcome, and screening 60 to prevent one patient from experiencing any adverse outcomes.

Another much bigger trial is on the way in Wales. CATS (Controlled Antenatal Thyroid Screening is not published yet and focuses on IQ scores of children affected by maternal thyroid dysfunction. Preliminary data reveals no difference in IQ between 3 year old children of treated and untreated mothers, but a subgroup analysis identifies a difference in the number of children with IQ below 85: 9.5% in screening group vs. 15.6% in controls. (49)

So with such evidence so far, the question follows: how expensive would it be to screen? To date two studies have attempted to answer this question. Dosiou et al found that universal screening would actually save $102 per pregnancy and increase quality-adjusted life expectancy by

5.84 days relative to no screening. Screening with anti-TPO antibodies increased quality-adjusted life expectancy by 5.11 days and was cost-effective for an incremental cost-effectiveness ratio ICER) of $15 182 per QALY (50). Another study produced similar results, while focusing solely on cost attributed to subclinical hypothyroidism. Again, screening 100,000 pregnant women resulted in $8,356,383 saved and 589.3 QALYs gained. When subclinical hypothyroidism prevalence is reduced by treatment to 0.25%, screening remains cost-effective at $21,664/QALY gained (51).

In order for a test to be a good candidate for universal screening, a certain set of pre-requisits must be met. (See Table 1)

Table 1: Justification for screening test (52).

(1)Well-defined disorder with known incidence/prevalence.
(2) Medically important disorder.
(3) Screening test simple and safe with established cutoff values.
(4) Effective treatment available.
(5) Cost of test relative to benefit should be known.
(6) Adequate logistics for the testing and follow up.
(7) Patient and management acceptability.

Thyroid testing during pregnancy fulfills these criteria. While at this point we are still lacking data from randomized controlled trials proving benefit, data from secondary analysis from Negro and Lazarus is very encouraging that treatment of subclinical hypothyroidism does improve outcome (48,49). It is worthwhile to consider that while we do not have solid data to support universal screening, we do not have any data that proves that lack of screening is beneficial to our patients. As such, medicine is still an art with plenty of room for a judgment call on part of the physician, with consultation with the patient.

Special "Thanks" to Dr Jose Enrique Garcia, for his help in editing of this manuscript as well as his continuous support.

REFERENCES

1. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab. 1987;65(4):689.

2. Glinoer D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejeune B 1990 Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 71:276–287

3. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994; 331(16):1072–8.

4. Yoshimura M, Hershman JM 1995 Thyrotropic action of human chorionic gonadotropin. Thyroid 5:425–434

5. Hershman JM. The Role of Human Chorionic Gonadotropin as a Thyroid Stimulator in Normal Pregnancy. J Clin Endocrinol Metab. 2008 Sep; 93(9):3305-6.

6. de Escobar GM, Obregon MJ, del Rey FE. Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia? J Clin Endocrinol Metab 85: 3975–3987, 2000.

7. Vulsma T, Gons MH, de Vijlder JJ. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med. 1989;321(1):13.

8. Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SMPF, Jaddoe VVW, Albert Hofman, Herbert Hooijkaas, Eric A. P. Steegers, Henning Tiemeier, Bongers-Schokking JJ, and Visser TJ. Maternal Early Pregnancy and Newborn Thyroid Hormone Parameters: The Generation R Study J Clin Endocrinol Metab, February 2012, 97(2) on line ahead of print.

9. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum 2011 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 21:1081–1125.

10. Collage of American Pathologists Participants Summary (K-B 2011) Publication.

11. Soldin OP, Soldin SJ. Thyroid hormone testing by tandem mass spectrometry. Clin Biochem 2011;44:89–94

12. Faix JD. Harmonizing Hormones -- Standardization of Endocrine Testing: A Report From the 2006 Annual AACC Meeting.

13. Aoki Y, BelinRM, Clickner R, et al. SerumTSH and total T4 in the United States population and their association with participant characteristics: National Health and NutritionExaminationSurvey (NHANES1999-2002). Thyroid2007;17(12):1211–23.

14. LaFranchi SH, Haddow JE, and Hollowell JG. Is Thyroid Inadequacy During Gestation a Risk Factor for Adverse Pregnancy and Developmental Outcomes? THYROID. Volume 15, Number 1, 2005.

15. Mandel. SJ Mandel. Thyroid disease in pregnancy: treating two patients. Presented at Endocrine Society Science Writers' Conference. 2011.

16. Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. Obstet Gynecol. 1988 Jul;72(1):108-12

17. Idris I, Srinivasan R, Simm A, and Page RC. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome," Clinical Endocrinology, vol. 63, no. 5, pp. 560–565, 2005.

18. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O 2002 Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 12:63–68.

19. Mandel SJ, Larsen PR, Seely EW, Brent GA 1990 Increased need for thyroxine during pregnancy in women with primary hypothyroidism. N Engl J Med 323:91–96.

20. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004;351(3):241–9.

21. Yassa L, Marqusee E, Fawcett R, et al. Thyroid Hormone Early Adjustment in Pregnancy (the THERAPY) trial. J Clin Endocrinol Metab 2010;95:3234–41.

22. Burman KD. Controversies Surrounding Pregnancy, Maternal Thyroid Status, and Fetal Outcome. Thyroid. April 2009, 19(4): 323-326.

23. Loh JA, Wartofsky L, Jonklaas J, Burman KD 2009 The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. Thyroid 19:269–275.

24. Cleary-Goldman J,MaloneFD, Lambert- Messerlian G, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol. 2008;112:85–92.

25. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Jarvelin MR, Suvanto E 2010 Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab 95:1084–1094.

26. Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol. 2005; 105:239–245.

27. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555.

28. Ghassabian A, Bongers-Schokking JJ, de Rijke YB, van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC, Visser TJ, Verhulst FC, Tiemeier H. Maternal Thyroid Autoimmunity During Pregnancy and the Risk of Attention Deficit/Hyperactivity Problems in Children. The Generation R Study. Thyroid. 2011 Dec 16. Epub ahead of print.

29. Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, Azizi F. Subclinical hypothyroidism in pregnancy: intellectual development of offspring. Thyroid. 2011 Oct;21(10):1143-7

30. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H 2006 Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 91:2587–2591.

31. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol. 2007 May; 109(5):1129-35.

32. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, Xu YH, Tao FB. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. J Clin Endocrinol Metab. 2011 Oct;96(10):3234-41. Epub 2011 Aug 10.

33. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf). 1999 Feb;50(2):149-55.

34. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ 2003 Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 59:282–288.

35. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. Clin Endocrinol (Oxf). 2010 Jun; 72(6):825-9.

36. Moleti M, Trimarchi F, Vermiglio F. Doubts and Concerns about Isolated Maternal Hypothyroxinemia. J Thyroid Res. 2011;2011:463029. Epub 2011 Jun 15.

37. Stagnaro-Green A. Maternal thyroid disease and preterm delivery. J Clin Endocrinol Metab, January 2009, 94(1):21–25

38. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. J Clin Endocrinol Metab. 2011 Jun;96(6):E920-4.

39. Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto E. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. J Clin Endocrinol Metab. 2010 Mar;95(3):1084-94. Epub 2010 Jan 15.

40. Haddow JE, Cleary-Goldman J, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD, Porter TF, Nyberg DA, Bernstein PS, D'Alton ME; First- and Second-Trimester Risk of Aneuploidy (FaSTER) Research Consortium. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. Obstet Gynecol. 2010 Jul;116(1):58-62.

41. Abbassi-Ghanavati M, Casey BM, Spong CY, McIntire DD, Halvorson LM, Cunningham FG. Pregnancy outcomes in women with thyroid peroxidase antibodies. Obstet Gynecol. 2010 Aug;116(2 Pt 1):381-6.

42. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ. 2011 May 9;342:d2616.

43. Committee Opinion #381, "'Subclinical Hypothyroidism in Pregnancy," is published in the October 2007 issue of Obstetrics & Gynecology.

44. Gharib H, Tuttle RM, Baskin HJ, et al. CONSENSUS STATEMENT: Subclinical Thyroid Dysfunction: A Joint Statement on Management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. J Clin Endocrinol Metab, January 2005, 90(1):581–585

45. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, Mandel SJ, Stagnaro-Green A 2007 Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 92(8 Suppl):S1–47

46. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R 2007 Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 92:203–207. 306.

47. Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Svilias I, Cepkova J, Mc Grath C, Maly J 2010 Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. Eur J Endocrinol 163:645–650.

48. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A 2010 Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 95:1699–1707.

49. Lazarus, J. et al. Controlled Antenatal Thyroid Screening. Unpublished data, presented at 14th International Thyroid Congress in Paris. 2010.

50. Dosiou C, Sanders GD, Araki SS, Crapo LM 2008 Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis. Eur J Endocrinol 158:841–851.

51. Thung SF, Funai EF, Grobman WA 2009 The cost effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am J Obstet Gynecol 200:267.e1–267.e7.

52. Wald N and Law M, "Medical screening in Oxford textbook of medicine," in Oxford Textbook of Medicine, D. A. Warrell, T. M. Cox, and J. D. Firth, Eds., vol. 1, pp. 94–108, Oxford University Press, New York, NY, USA, 5th edition, 2010.