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ARTICLE TITLE

Hypothyroidism in Pregnancy

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No conflicts of interest to disclose

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KEYWORDS

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4-8 keywords to enhance online search results

KEY POINTS

- Hypothyroidism is common in women of child-bearing age and commonly associated with adverse obstetric and offspring outcomes.
- Pregnancy places substantial additional demands on the thyroid axis and women who have normal thyroid function prior to pregnancy may have insufficient reserve for pregnancy especially those with auto-immune thyroid disease
- Levothyroxine is the treatment for hypothyroidism; in women established on levothyroxine prior to pregnancy doses will need increasing.
- Screening for thyroid disease in pregnancy is being undertaken in some countries although this is a major debate in thyroidology at present.

3 to 5 bullet points of approximately 25 words each that summarize the main ideas of your article. Key points appear at the very beginning of your article in print and online.

SYNOPSIS

Brief summary of your article (100 to 150 words; no references or figures/tables). The synopsis appears only in the table of contents, and is often used by indexing services such as PubMed.

Thyroid hormone is essential for pregnancy and ensuring foetal development. Pregnancy also places substantial demands on the thyroid axis. Overt hypothyroidism is associated with substantial adverse obstetric and offspring outcomes and requires treatment. Borderline thyroid dysfunction (subclinical hypothyroidism and isolated hypothyroxinemia) are common in women and are associated with adverse obstetric and offspring outcomes although benefits of screening for and treating borderline thyroid function are less clear. Many women are established on thyroid hormone replacement prior to pregnancy and doses will need increasing during pregnancy. Care needs to be taken to prevent over-replacement as this may offset benefits observed for IQ and may increase the risk of ADHD symptoms. Universal thyroid screening in pregnancy is now being undertaken in several countries although it remains a matter of intense debate

Introduction

Adequate thyroid hormone is essential for maintaining a pregnancy and optimal fetal development[1]. During the first half of pregnancy, the fetus is entirely dependent on maternal thyroid hormone. Thyroid disorders, particularly low thyroid function are common in women of childbearing age and are frequently encountered in antenatal clinics. It is well established that overt hypothyroidism results in substantially higher risks of adverse pregnancy and offspring outcomes and all endocrine and obstetric societies recommend treating this. Iodine is essential for thyroid hormone production so adequacy here is vital during pregnancy and in women of reproductive age. There is now increasing evidence that even borderline thyroid function and thyroid auto-immunity are also associated with adverse outcomes raising the possibility that universal thyroid screening in pregnancy should be considered[2]. Furthermore, pregnancy places additional demands on the thyroid axis, so women with adequate thyroid hormone prior to pregnancy may fail to meet the additional demands of pregnancy.

Clinically thyroid function is assessed by measuring the pituitary hormone - thyroid stimulating hormone (TSH) and thyroid hormone levels. The complex inverse relationship between TSH and thyroid hormone results in small changes in thyroid hormone levels causing larger changes in TSH. It is essential to measure thyroid hormone levels as well as TSH in order to differentiate between overt and subclinical thyroid disease.

Iodine status and thyroid function

Iodine is essential for the synthesis of thyroid hormones[3]. The recommended daily iodine intake in pregnancy has recently been increased to 250 μg/day which implies a urinary iodine excretion of 150– 250 μg/day as being adequate[4,5]. Iodine deficiency during pregnancy is associated with maternal goitre and results eventually in a reduced circulating maternal thyroxine concentration. These effects are preventable by iodine supplementation[6] and benefits of this are observed only in both areas of severe iodine deficiency (24-h urinary iodine less than 50 μg) and also in areas of mild to moderate deficiency[7]. Children born to mothers with profound iodine deficiency show impaired neuro-intellectual development, sometimes to the extreme of cretinism in severely deficient states. These effects can be reduced by iodine administration before and even during gestation and this should be performed in areas of moderate to severe iodine deficiency[3]. It is noteworthy that even mild-moderate iodine deficiency in pregnant women is associated with adverse maternal effects including goitre[8] and lower IQ in offspring[9]. Although a recent trial did not show benefit on iodine supplementation during pregnancy in areas of mild iodine deficiency[10] further studies are required. Assessment of iodine status is challenging and urinary iodine remains an imperfect marker of iodine status serum thyroglobulin may become a useful biomarker of iodine status. Endocrine disruptors such as perchlorate, may exacerbate iodine deficiency and may also have a deleterious effect on offspring neurodevelopment[11,12].

Impact of pregnancy on the maternal thyroid status

Pregnancy places substantial demands on the maternal thyroid axis these are summarized in **Table 1 and Figure 1**. The fetal thyroid is not functional until 18-20 weeks gestation so additional maternal thyroid hormone is required to meet this demand. Additionally there is increased thyroxine binding globulin and increased thyroid hormone degradation by placental type 3 deiodinase[13] which also increases demands. There is also increased urinary iodine excretion during pregnancy. Urinary iodine excretion in pregnancy is maximal in the first trimester followed by a decline in the second and third trimesters. It is increasingly recognized that countries may have iodine sufficiency in the general population, but be insufficient for pregnancy[14]. As a result some countries can be iodine sufficient in the general adult population, but inadequate for pregnant women, the UK and Russia are notable examples of this[15]. This iodine deficiency can result in increased risk of maternal goitre as well as hypothyroidism. The pregnancy

hormone beta hCG does stimulate the thyroid to produce thyroid hormone which will assist with meeting the increased demands on the thyroid axis in pregnancy. Recent data suggests that TPO antibody positive women may have an impaired thyroidal response to hCG[16]. This may explain why women with thyroid auto-immunity with positive thyroid peroxidase antibodies (TPO) have increased risk of adverse obstetric outcomes which can be independent of thyroid status.

Assessment of thyroid status during pregnancy

It is important to recognize that assessment of thyroid function in pregnancy is more complex than the general adult population. The above physiological changes in pregnancy have a substantial effect on the interpretation of thyroid function tests in pregnancy and result in a downward shift of TSH reference intervals. A pragmatic upper limit of 2.5 mU/L was previously advocated for TSH but recent data now shows this threshold to be too low [17]. One approach suggested in the current guidelines of the American Thyroid Association (ATA) is to set the pregnancy reference range at 0.5 mU/L and 0.4 mU/L below the upper and lower non-pregnant reference range respectively, reflecting the anticipated magnitude of the TSH drop [18].

Current ATA guidelines advocate the use of pregnancy specific, local population-based reference ranges where possible;[18] however it is well recognized that such data are not widely available. Assessment of thyroid function in pregnancy is also best done according to pregnancy specific reference-ranges calculated in a population of pregnant women free of key factors that interfere with thyroid function including women with known thyroid disease (including thyroid auto-immunity), use of thyroid altering medication, known iodine deficiency and high hCG states (twin pregnancies or IVF conception). However, it is also well established that normal thyroid status changes over pregnancy and accurate classification of thyroid function in pregnant women requires the use of gestational-age specific reference ranges[19]. There is also growing evidence that specific reference ranges may be considered based on ethnicity[20], BMI[21] and parity[21].

With respect to FT4, the most commonly used immunoassays are prone to biases in pregnancy due to changes in thyroid binding globulin and albumin concentrations[18,22]. Total T4 is a more predictable alternative as it typically rises by 50% of baseline values attaining peak levels by 16 weeks gestation [18]. However Total T4 is less clearly associated with adverse outcomes so many clinicians prefer the use of FT4. More robust methods such as equilibrium dialysis, liquid chromatography-tandem mass spectrometry (LC-MS/MS), or FT4 index calculations are cumbersome to perform and not routinely used [18].

Classification and epidemiology of thyroid abnormalities

Overt hypothyroidism in pregnancy is defined as a TSH level above the pregnancy specific reference range and a low level of FT4. Although women established on levothyroxine make -up around 1% of pregnancies, newly diagnosed overt hypothyroidism occurs in approximately 0.2-0.6% of pregnant women[17,23] . Treatment is mandatory as it is associated with profound adverse obstetric and offspring development outcomes. The milder forms of low thyroid dysfunction are subclinical hypothyroidism (TSH above the population's pregnancy reference range, but normal FT4) and isolated hypothyroxinemia (IH) (Normal TSH with FT4 in the lowest 2.5% of the reference range) and these are more common. Subclinical hypothyroidism with an elevated TSH and normal FT4 concentrations—can occur in up to 18% of pregnancies depending on the precise definition and TSH assay used. Observational studies have indicated that subclinical hypothyroidism is associated with adverse pregnancy outcomes, but not offspring neuro development. In contrast IH is associated with adverse outcomes with regard to offspring IQ and behavior, but less consistent associations have been observed for pregnancy outcomes.

Overt hypothyroidism

Overt hypothyroidism has been repeatedly associated with substantial adverse impacts on obstetric outcomes and fetal neuro development. Adverse obstetric outcomes include fetal loss, premature delivery, low birthweight and pre-eclampisa[23,24]. A large case-control study demonstrated that overt hypothyroidism resulted in a 7-point lower IQ than women with normal thyroid function[25]. It is worth noting, that women with adequately treated hypothyroidism have no higher risk of pregnancy complications, unlike those with untreated hypothyroidism indicating that thyroid status is a clearly reversible risk factor for adverse obstetric outcomes.

Subclinical hypothyroidism

Numerous studies have identified that subclinical hypothyroidism is associated with adverse pregnancy similar to overt hypothyroidism but as to be expected risk effects are more marginal. From meta-analyses subclinical hypothyroidism the following outcomes were all statistically significant for adverse outcomes with (95%CI) provided. The odds of adverse outcomes are as follows - miscarriage (1.90 - 2.01) preterm delivery (1.20 – 1.81) growth restriction (1.54 – 3.36) pre-eclampsia (1.30 – 2.24) and gestational diabetes (1.28 – 4.33)[26]. One problem has been with these analyses is that many studies have defined subclinical hypothyroidism differently. What is clear is that subclinical hypothyroidism does not appear to be associated with adverse neuro-behavioral outcomes in the offspring.

Isolated hypothyroxinemia

IH was originally considered to be a pregnancy-specific disease, reflecting a state of mild iodine deficiency. However, this has now been called into question as it also occurs in iodine sufficient areas. Other risk factors for IH include iron status, BMI and placental angiogenic factors[1]. IH has been associated with impaired offspring developmental outcomes [27] and has also been associated with offspring verbal delay[28] autism[29] and ADHD[30] . In contrast to subclinical hypothyroidism it has not been consistently associated with adverse obstetric outcomes.

Thyroid auto-immunity

Anti-thyroid peroxidase antibodies are found in around 10% of otherwise normal pregnant women. They are a marker of thyroid auto-immunity and the main risk factor for thyroid dysfunction in pregnancy and in the postpartum period. Even in euthyroid women TPOAb positivity is associated with premature delivery and fetal loss although the exact mechanism remains unclear[31,32] . One randomized controlled trial has shown that levothyroxine administration reduced the risk of fetal loss and premature delivery in euthyroid TPOAb-positive women[33]. A later study failed to replicate the benefits for fetal loss but did find a reduction in pre-term delivery[34]. Women who are TPOAb positive are at an increased risk of thyroid-related adverse pregnancy outcomes, its interaction with higher TSH levels means it is likely that this risk is substantially increased in individuals who also have elevated TSH levels or those in the higher end of the normal range. As highlighted earlier women who are TPOAb positive have an impaired thyroidal response to beta hCG compared to women who are TPOAb negative this may explain its association with adverse obstetric outcomes and synergistic impact with higher TSH levels.

Trials of Treatment with levothyroxine

All endocrine and obstetric societies recommend treating *overt hypothyroidism* in pregnancy although there have been no recent trials in this area, but to have a control group here would be unethical. To date three large randomized controlled trials have investigated the effects of screening for and treating borderline low thyroid function in pregnancy: these are the controlled antenatal thyroid screening (CATS) study [35], a study by Casey *et al.*[36] and a recent study by Nazarpour *et al* [34]. These trials are summarized in **Table 2**. The Nazarpour trial focused on preterm delivery and identified that levothyroxine may reduce the risk of preterm delivery in individuals with TSH

levels > 4.0 mU/l (RR: 0.38; 95% CI: 0.15 to 0.98; p= 0.04)[34]. Offspring IQ was not assessed in this study. The two other large randomized controlled trials CATS[35] and the study by Casey et al[37] studied the effects of screening and treating borderline low thyroid function in pregnancy on offspring IQ and pregnancy outcomes. Neither study showed any beneficial effects of treatment on offspring IQ[35,37]. Reasons for failure to establish benefit aside from no treatment benefit, include the relatively late initiation of treatment (particularly in the Casey study) and early age of IQ assessment (particularly in the CATS study). It is worth highlighting that neurological development is crucial in the first 12 weeks of pregnancy. Follow on analysis of the CATS study revealed no apparent benefit of treatment at age 9 although this was only performed in a subset also showed no treatment benefit. Work in the follow-up CATS study also identified levothyroxine over-treatment may increase the risk of autism symptoms[38]. More recent analysis using data linkage and the majority of the CATS cohort (to include those with normal thyroid function) identified that levothyroxine treatment significantly reduced the risk of miscarriage/still birth[38]. Similarly, another prospective study did identify that levothyroxine reduced the risk of miscarriage and pre-term birth[33]. However no benefit was observed with levothyroxine on obstetric outcomes in the Casey study although again this may be due to the relatively late initiation of treatment[37].

Treatment of established hypothyroidism in pregnancy

Approximately 1% of pregnant women are established on levothyroxine prior to pregnancy. In women established on levothyroxine prior to pregnancy, initial control in pregnancy is often sub-optimal [39] and may be associated with increased odds of foetal loss[39], and optimization should ideally occur prior to conception[40]. Women of child-bearing age on levothyroxine should be reminded to increase their pre-conception dose of levothyroxine by 30-50% as soon as pregnancy is confirmed. One approach is to take double their usual levothyroxine dose on 2 days of the week [41]. It is worth noting, that dose increases are often higher in post-surgical or post-ablative hypothyroidism. Women on levothyroxine should also be aware of important drug interactions with iron supplements and proton pump inhibitors in particular which can impair levothyroxine absorption. Other drugs to be aware of increase which increase levothyroxine clearance include carbamazepine, rifampicin and valproate. If overt hypothyroidism is diagnosed for the first time in pregnancy, we recommend starting a weight-based dose of 2mcg/kg a day.

Close monitoring of thyroid function is essential in pregnancy we recommend to check thyroid function early in the first trimester and every 4-6 weeks thereafter. One should ideally aim for a TSH < 2.5mU/l in the first trimester and < 3 mU/l in later pregnancy. One should aim to ensure that the FT4 level is not too high and aim for the upper half of the reference range. There is some evidence that over-replacement with levothyroxine may increase ADHD symptoms and the relationship of FT4 and IQ is "U shaped" with both low -normal and high-normal FT4 are associated with lower IQ [42]. After delivery we suggest returning levothyroxine to pre-conception dose and to recheck thyroid function at 6 weeks post-partum.

Screening for and treating low thyroid function in pregnancy

Universal thyroid screening in pregnancy remains contentious[2]. It is noteworthy that screening for and treating low thyroid function meets almost all the screening criteria laid down by Wilson and Jungner[43]. In particular it is an important asymptomatic health problem, with an accepted treatment and a suitable diagnostic test. It is also economically viable [44]. However, at present it is still unclear what TSH threshold should be used for treatment in pregnancy and whether there should be a differential threshold based on TPO status. The criterion 8 "there should be an agreed policy on who to treat" is therefore not met. However, as there is widespread variation in clinical practice at present, this should not necessarily prevent the introduction of universal thyroid screening and indeed regular audit and review may establish more definitive treatment thresholds. Current ATA guidance takes into account the potential for interaction by TPO antibody status in its guidance, but did not recommended for or against

universal thyroid screening[18]. This has not prevented some countries including Spain China and Poland from implementing universal thyroid screening. It is however accepted that targeted screening should be performed in those women at high risk for thyroid disease[18,45] . Women deemed at high risk for thyroid disease in pregnancy include those with previous thyroid disease, a visible goitre, symptoms suggestive of hypo or hyperthyroidism, those with a family history of thyroid disease, those with a history of type 1 diabetes or other auto-immune conditions including positive thyroid antibodies, and women with a previous history of infertility, fetal loss or infertility. However this targeted approach would miss approximately one third of women with significant thyroid dysfunction[46]. This high risk screening approach has been further called into question as universal thyroid screening is pregnancy appears to cost-effective; screening solely for overt hypothyroidism also had a cost-effectiveness ratio of $6,776/QALY (quality adjusted life-year)[44] which is favorable compared to gestational diabetes mellitus screening ($12,078/QALY) and is substantially below the $50,000/QALY figure used in the United States as a criterion for screening decisions. This work also indicated universal screening appears to be more cost-effective than targeted screening.

Conclusion

Despite the dramatic recent advances in our knowledge of thyroid physiology in pregnancy and the consequences of its variation, further research is still required. Delete need In particular prospective trials of *early* screening of thyroid function in pregnancy with both obstetric and developmental outcomes assessed. Continued advocacy of iodine sufficiency in pregnancy and assessment of endocrine disruptors are also needed. In current practice monitoring of thyroid function in early pregnancy needs urgent optimization.

Table 1 Physiological changes that influence thyroid function in pregnancy

Physiological change	Effect on thyroid function test results	Impact on interpretation of thyroid function tests
↑ Thyroxine binding globulin	↑ Serum Total T3 and T4 concentrations	Total thyroid hormone levels may be misleading -need to rely on free thyroid hormone levels
↑ human chorionic gonadotrophin secretion	↑ Free T4 and ↓ TSH	High human chorionic gonadotrophin levels may result in gestational thyrotoxicosis. This usually only requires symptomatic treatment but needs to be distinguished from pathological thyroid disease. Response possibly impaired in TPO antibody positive women
↑ Iodine excretion	↓ Thyroid hormone production in iodine deficient areas	Need to be mindful of iodine deficiency and ensure optimal intake ideally prior to conception
↑ Plasma volume	↑ T3 and T4 pool size	
Increased Type 3 5-deiodinase (inner ring deiodination) activity from the placental	↑ T3 and T4 degradation	May explain in part the increasing thyroid demand in pregnancy
Thyroid enlargement (in some women)	Increased thyroglobulin	Small goitres are common in pregnancy, but may be a sign of low thyroid function so merits thyroid function testing

Adapted from the Oxford Textbook of Diabetes and Endocrinology, Chapter 9.1 General considerations relating to thyroid disease in pregnancy by Peter N Taylor, LDKE Premawardhana, John H Lazarus

Table 2

	CATS	Casey	Nazarpour
Year	2012	2017	2018
Countries in trial	UK, Italy	USA	Iran
Number with low thyroid function randomised	794	677	366
Placebo-controlled	No	Yes	No
Gestational age at recruitment (weeks)	Median (IQR) Screening 12.3 (11.6 - 13.6) Controls 12,3 (11.6 – 13.5)	Mean (SD) Screening 16.6 (3.0) Controls 16.7 (3.0)	Mean (SD) Screening 11.4 (4.1) Controls 12.2 (4.3)
Baseline TSH mU/l	Median (IQR) Screening UK 3.8 (1.5-4.7) Screening Italy 3.1 (1.3-4.0) Controls UK 3.2 (1.2 – 4.2) Controls Italy 2,4 (1.3-3.9)	Mean (95%CI) Screening 4.5 (4.4-4.7) Control 4.3 (4.2 -4.5)	Median (IQR) Screening 3.8 (2.8-4.8)
Outcomes assessed	IQ age 3, IQ age 9 Obstetric outcomes (analysed later and only in UK participants)	Pregnancy outcomes, offspring IQ and behaviour	Preterm delivery
Benefit of levothyroxine	No benefit with regard to IQ. Potential reduction in foetal loss.	No benefits observed with regard to pregnancy outcomes and offspring IQ	May reduce pre-term delivery at TSH levels > 4.0 mU/l

Figure 1 Effects of Pregnancy on thyroid function

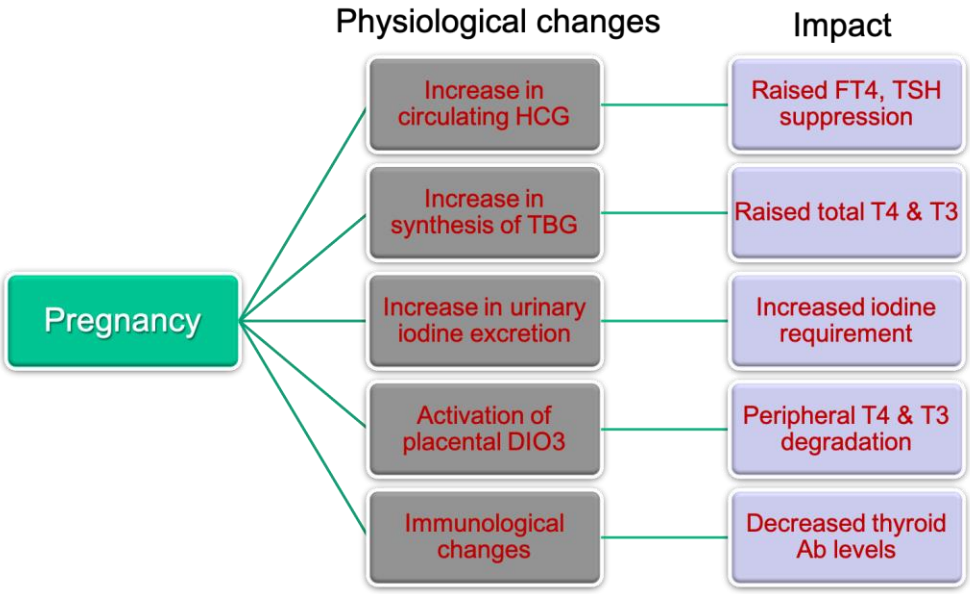
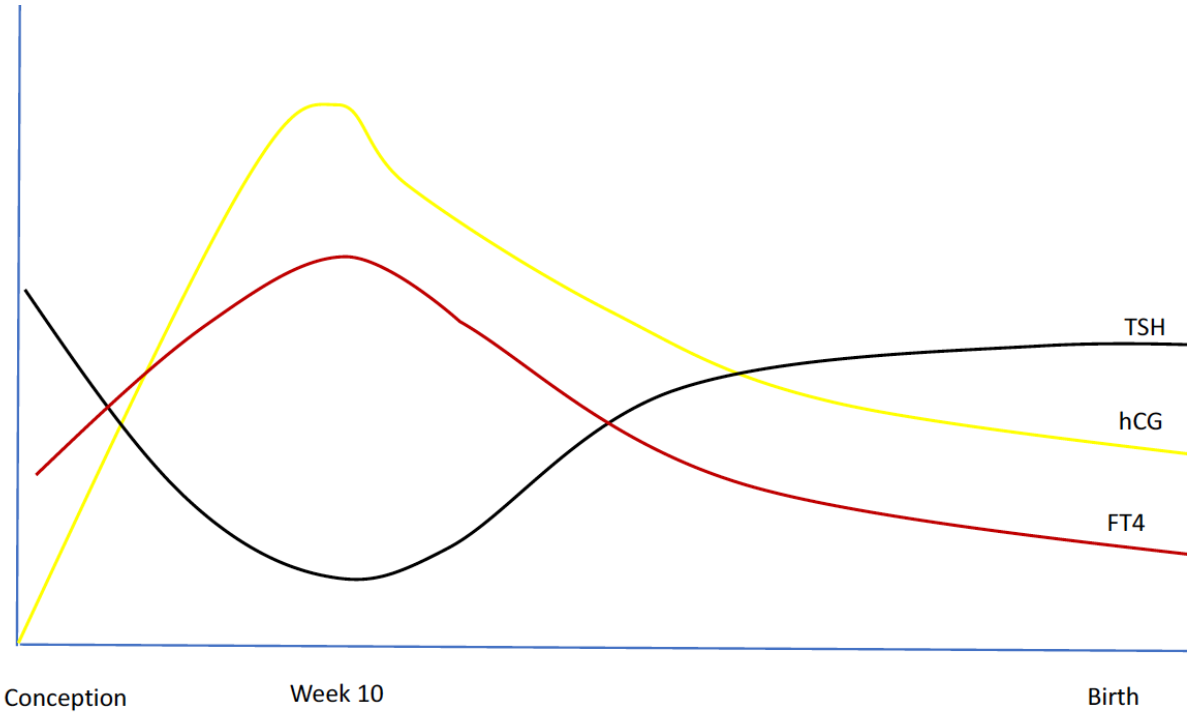


Figure 2 TSH FT4 and hCG levels over pregnancy.



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