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### Maternal hypothyroxinaemia during (early) gestation

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*Published in:*

The Lancet: A Journal of British and Foreign Medicine, Surgery, Obstetrics, Physiology, Pathology, Pharmacology, Public Health and News

*Publication date:*

2005

*Document Version*

Publisher's PDF, also known as Version of record

[Link to publication in Tilburg University Research Portal](#)

*Citation for published version (APA):*

Pop, V. J. M., & Vulsma, T. (2005). Maternal hypothyroxinaemia during (early) gestation. *The Lancet: A Journal of British and Foreign Medicine, Surgery, Obstetrics, Physiology, Pathology, Pharmacology, Public Health and News*, 365(9471), 1604-1606.

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summer but the data are suggestive, and Japan may be one of the few cultures where further results on the relative success of living-related donors for islet transplantation could be garnered.

Some cautionary notes should be sounded. Insulin independence is now being reported with single organs from cadaveric donors.<sup>7</sup> More importantly, the report by Matsumoto and colleagues does not explore the issue of islet survival. Transplant programmes of type 1 islets from cadaveric donors have reported outcomes after long periods of insulin independence in the recipient—perhaps a year.<sup>2,7</sup> Islet survival after transplantation might not be indefinite—it is unclear whether late islet loss is because of rejection, failure of regeneration and repair in the extrapancreatic site, or recurrence of autoimmune diabetes. If islet loss is because of recurrence of autoimmune diabetes, the data from Matsumoto's patients will not be readily applicable to the population with type 1 disease. If islet loss is not because of recurrence, the benefits of temporary insulin independence for the patient must be weighed against the health risk to the surviving donor. Protection from severe hypoglycaemia in the Edmonton series of patients persists beyond insulin independence. Against that, the donor in Matsumoto's study had a significant operation and exposed herself to increased risk of diabetes, as a result of the loss of part of her own pancreas.<sup>8</sup>

It is estimated that up to 25% of patients with type 1 diabetes are susceptible to recurrent severe hypoglycaemia.<sup>9</sup> Of these patients, perhaps 15% cannot be substantially improved by proper manipulation of conventional therapy. For them, transplantation—be it of whole organ as the Americans recommend,<sup>10</sup> or islet transplantation as currently clinically available in Canada<sup>11</sup>—can and should be available. But to render islet transplantation an appropriate therapy for more

people with insulin-deficient diabetes, we need ways of improving islet recovery and survival after the transplantation, and much more specifically targeted immunosuppression. In societies in which transplantation of cadaveric organs is feasible, the use of living, related donors seems difficult to justify. Matsumoto's group is in a position to ethically explore whether such donors can safely provide more robust successes, and the diabetes world should watch their progress with great interest.

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## Maternal hypothyroxinaemia during (early) gestation

Brain development is strongly dependent on an adequate supply of thyroid hormone. Because the fetal thyroid cannot produce thyroxine until mid-gestation, the fetus is totally dependent on thyroxine that originates from the mother.<sup>1</sup> In other words, mental and motor skills in later life depend on the integrity of the

maternal thyroid and its regulatory system, and an adequate maternal supply of iodine (the unique and essential substrate for thyroid hormone) during gestation. However, there is no consensus about whether level of the maternal free thyroxine concentration or the maternal thyroid-stimulating

hormone (thyrotropin, TSH) during gestation should be the main determinant to verify adequacy of the thyroxine supply to the fetal brain.

Recently, Hossein Gharib and Martin Surks and their respective colleagues<sup>2,3</sup> gave their views about screening and treatment of subclinical thyroid dysfunction on statements made previously by an expert panel of the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society.<sup>4</sup> For the consequences of subclinical hypothyroidism (ie, increased TSH with free thyroxine within its reference range) during pregnancy, the clinicians' view<sup>2</sup> favours screening by TSH measurement during or even before gestation, while the evidence-based approach disagrees.<sup>3</sup> No comments were made about gestational hypothyroxinaemia (ie, free thyroxine below the 5th or 10th percentile with TSH within its reference range), although an association between this condition and impaired infant (neuro)development has repeatedly been shown.<sup>1</sup> A relation with attention deficit and hyperactivity disorders also has been suggested.<sup>5</sup> The expert panel defined (non-pregnant) reference ranges as 0.45–4.5 mIU/L for TSH and 10.3–25.7 pmol/L for free thyroxine.<sup>4</sup> However, a 20-year follow-up in the general population showed that TSH levels over 2.0 mIU/L increases the risk of future overt thyroid dysfunction, suggesting that above this level thyroid functioning is already compromised.<sup>6</sup>

Which reference ranges should be used throughout pregnancy? Because the placental hormone chorionic gonadotropin (HCG) is a weak thyroid stimulator, first-trimester maternal TSH values should be interpreted cautiously. When iodine supply is insufficient, changes in thyroid hormone concentrations might occur without changes in TSH.<sup>1</sup> Finally, it should be remembered that maternal TSH is unable to pass the placenta throughout pregnancy, which questions the implications of elevated maternal TSH levels for the fetus when simultaneous maternal levels of free thyroxine are still above the cut-off for hypothyroxinaemia. The 10th percentile level for free thyroxine of 11–12 pmol/L in early gestation decreases to 9–10 pmol/L in late gestation.<sup>7</sup> Women with subclinical hypothyroidism during gestation often have free thyroxine concentrations above these cut-offs. We still do not know why levels of free thyroxine gradually decrease with increasing term. However, we have to keep in mind that assessments of free thyroxine



are sensitive to aberrant concentrations of thyroid-hormone binding protein, such as the elevated concentrations of thyroxine-binding globulin during pregnancy.<sup>8</sup> Also, iodine intake influences free thyroxine levels. During the past decade, it has been hypothesised that women living in iodine sufficient or repleted areas are still at risk of iodine deficiency when they become pregnant, because then their iodine requirements almost double.<sup>9</sup> There is no discussion about the major negative effect both on pregnancy and neonatal outcome in areas with severe iodine deficiency. However, a recent meta-analysis of six European placebo-controlled studies, in which pregnant women living in areas with marginally sufficient iodine intake and supplemented with various doses of iodine, showed that there was hardly any effect on their thyroid hormone levels during gestation.<sup>10</sup> So, the assumption of a direct relation in these areas between iodine intake and maternal levels of free thyroxine might be too simple. What is urgently needed are valid gestational reference ranges for serum TSH and free thyroxine, especially in women whose thyroids are not

compromised by autoimmune diseases (as reflected by the absence of circulating thyroid antibodies) and with a definitely proven sufficient intake of iodine.<sup>8</sup>

“Dear colleague, I am a physician from the US. I am pregnant now for 12 weeks, and my free thyroxine was 11 pmol/L. Would you be in favour of an abortion in order not to have a child with impaired neurodevelopment?” Over the past 12 months, we have received over a dozen e-mails from all over the world with similar questions. Even endocrinologists have asked for advice because they did not agree with gynaecologists who recommended their pregnant patients consider abortion because of hypothyroxinaemia during early gestation.

Children of pregnant women with subclinical hypothyroidism can benefit from thyroxine treatment during gestation.<sup>11</sup> Moreover, a 2-year follow-up of children born to women with hypothyroxinaemia during early gestation showed no (neuro)developmental delay in the children whose mothers presented with (spontaneously) increasing levels of free thyroxine after the first trimester.<sup>7</sup> Placebo-controlled intervention studies in pregnant women with subclinical hypothyroidism or hypothyroxinaemia are needed to evaluate the effect of thyroxine administration on the (neuro)-development of the offspring. Careful monitoring of iodine intake during gestation, lactation, and the first 2–3 years of life will be needed.

As Surks and colleagues state,<sup>3</sup> the crux of the evidence-based approach is that “the physician will do no harm”. How can a clinician deal with this issue against the background that until now we do not know which determinant of thyroid function (free thyroxine or TSH) is most appropriate for screening purposes, which reference ranges should be used, which condition (hypothyroxinaemia or subclinical hypothyroidism) has the worse outcome and for whom (fetus vs mother), and what the confounding role is of individual iodine supplementation in populations with suboptimum iodine intake? Obviously, there is no evidence-based argument to advise hypothyroxinaemic women to have an abortion, but how do we deal with the risk of impaired neurodevelopment? The explained variance of impaired neurodevelopment due to hypothyroxinaemia is reported as 5–18% (which means that by far the majority of variance is not attributable to maternal level of free thyroxine). Nevertheless it would be best, for women with low levels of free thyroxine (<12 pmol/L) during

early gestation, even without elevated TSH, to supply thyroxine to keep their free thyroxine in the middle or upper range.

For clinicians, even the more scientifically rigorous members of the above-mentioned expert panel recommend treatment with thyroxine for pregnant women with subclinical hypothyroidism. Although there are no intervention trials published to support this recommendation, these experts argued that the potential benefit-risk ratio justifies this approach: the chances of harm when appropriately managed (including monthly monitoring of the maternal thyroid function) are minimum.<sup>4</sup> On the basis of the same arguments, we believe that also correcting isolated low levels of free thyroxine by supplementation with thyroxine would be good advice about how to deal with gestational hypothyroxinaemia.

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We declare that we have no conflict of interest.

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