During the last decades ideas related to the transfer of thyroid hormones (TH), T4 and T3, and their possible role in fetal brain development have changed: TH do reach developing embryonic tissues both before and after onset of fetal thyroid function (FTF), both in non-mammalian and mammalian species. In man, T4 has been shown in first-trimester embryonic cavities, with free T4 (FT4) concentrations reaching levels similar to those circulating in adults. T3 and its nuclear receptors, partially occupied by T3, are also found before FTF, especially in the brain.

The mother is the only source of TH for the developing embryo and fetus before FTF; after its onset, the source is both fetal and maternal, as the latter continues until birth, and has important protective effects for fetal brain development in cases of fetal thyroid failure. Both epidemiological studies in areas of severe iodine deficiency (ID) and experimental data show that maternal T4 and T3 are not equivalent for fetal brain development, with T4 playing the major role. Thus, neurological cretins are born to severely iodine deficient (ID) mothers, who are hypothyroxinemic, despite the fact that their circulating T3 is normal. The rat fetal brain depends almost exclusively on the local production of T3 from T4 for its intracellular supply of T3, explaining the damaging effects of hypothyroxinemia, even when circulating T3 is normal.

Although there is a general consensus that TH are necessary for a normal development of the fetal brain during the second half of pregnancy, the idea that they may be also quite important before onset of FTF has not received the same generalized acceptance, especially with regard to the first trimester of pregnancy. However, recent experiments have shown that an inadequate supply of maternal T4 early in rat pregnancy results in an irreversible alteration of cell migration during cortical histogenesis, and during development of the hippocampus. In man these events take place before mid-gestation.

On the basis of epidemiological and experimental studies which we have recently reviewed (JCEM 85:3975-3987, 2000) we propose that:
— Irreversible brain damage is most severe when both maternal and fetal T4 production are impaired and left untreated from early pregnancy, such as occurs in ID, in cases of maternal TSH-receptor blocking auto-antibodies, of pit-1 deficiency, etc. Treatment with T4 at birth might prevent further damage, but would not revert alterations in brain structures which were TH-sensitive in utero.
— First-trimester maternal hypothyroxinemia alone, whether or not it is accompanied by an increased serum TSH, may also result in neurodevelopmental defects, which might be prevented by timely treatment of the mothers. The most widespread cause of maternal hypothyroxinemia is mild and moderate ID, still prevailing in much of Europe.
— Congenital hypothyroidism (CH) alone does not result in major irreversible neurodevelopmental abnormalities, as evidenced by the good results of prompt detection and postnatal treatment. This is attributed to the protective effects of a normal maternal T4, combined with an appropriate response of cerebral type II iodothyronine deiodinase (5’D-II).
— Infants born prematurely represent a group at risk, the more so the earlier their birth: their immature thyroid gland might not be able to meet their TH requirements, which were being largely met in utero until birth by the continuing maternal TH transfer. Previous maternal ID, or an inadequate iodine supply after birth, would further increase the frequency of neonatal hypothyroxinemia, and of the negative developmental impairments associated with it.
— The number of infants born from mothers with first-trimester hypothyroxinemia, or born prematurely, who are at risk for neurodevelopmental defects (with I.Q <85 and/or disabling cerebral palsy) is much greater than...
that of neonates with CH, for whom successful screening programs exist.
— It appears urgent to implement measures for the prevention of brain damage resulting from maternal hypothyroxinemia. Considering that this condition is not necessarily accompanied by an increase in circulating TSH, or by clinical signs and symptoms of hypothyroidism, most cases will not be reported to the thyroidologist or endocrinologist for evaluation and possible treatment interventions, and will thus remain undetected unless mass screening of all pregnant women is implemented, preferably at booking.
— Mass screening of pregnant women for increased TSH and thyroid antibody positivity have already been proposed, mostly for the benefit of the woman herself. In our opinion, their benefit for her progeny would be significantly increased if the screening algorithm included the early detection of hypothyroxinemia.
— Even before such programs become available, doctors and health care personnel can already contribute quite positively to the prevention of neurodevelopmental defects caused by an iodine intake that is inadequate for the pregnant and lactating woman, considering that this is still the most frequent cause of maternal hypothyroxinemia worldwide. Urgent measure are:
1) Promote the enforcement in their respective countries of USI: Universal Salt Iodination, namely, iodination of all salt used for human and animal nutrition, including the salt used in food industries. Once women have had an adequate iodine intake from early in life, it is likely that their thyroid stores of TH will be able to meet the increased requirements during pregnancy and lactation.
2) Include iodine supplementation, as KI tablets (where available), or in vitamin-mineral mixtures, in the routine care of pregnant women from the onset of pregnancy, starting before pregnancy whenever possible. This has already been achieved successfully with folates, and the iodine supplements are at least as important for the unborn child.
3) These efforts should aim at urinary concentrations during pregnancy and lactation of 180 µg l/ L or 220 µ l/ g creatinine, or higher.