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Prolactinomas, hypothyroidism, hyperthyroidism and pregnancy

Alper Gürlek and John A. H. Wass

PROLACTINOMAS

By definition, prolactinomas are prolactin (PRL)-secreting tumors of the pituitary which are almost invariably benign in nature. They are the most common form of pituitary tumor. Although microprolactinomas (diameter <1 cm) may be easily manageable by dopamine agonists, macroprolactinomas (diameter >10 mm) may be challenging in this respect because of compression and invasion of the surrounding vital structures, recurrence after surgery and resistance to medical treatment[1, 2].

Prolactinomas are more common in women than in men with a peak incidence in childbearing age[1]. It is, therefore, not unexpected that women with prolactinomas may either desire to become pregnant or find themselves pregnant with the tumor *in situ*.

Effect of pregnancy on prolactinoma growth

As gestation advances, estrogen-induced stimulation of PRL synthesis by lactotrophs causes an increase in PRL levels which reach a peak value of 150 ng/ml at term[3]. Prolactinomas tend to enlarge during pregnancy principally by two mechanisms: (1) loss of shrinkage effects of dopamine agonists after their withdrawal upon diagnosis of pregnancy; and (2) induction of tumor growth by estrogen secreted from the placenta[4].

Previous observations regarding prolactinoma growth during pregnancy have provided inconsistent results in terms of micro- and macroprolactinoma growth, with microprolactinoma risk of progression in size being lower than that of a macroprolactinoma. For example, only 11 out of 246 women with a microprolactinoma displayed asymptomatic tumor progression during pregnancy, and none necessitated surgical intervention owing to tumor growth[5]. Symptomatic enlargement of macroprolactiomas, on the other hand, reached 31% in a pooled analysis of patients from three different series of pregnant patients[5–7]. A surgical approach was required in 8.5% of these patients. Macroprolactinomas which have undergone surgical excision or irradiation before gestation also have a low tendency for further growth (5%), a feature which is comparable with microprolactinomas. Under such circumstances, it may be advisable for a patient with a macroprolactinoma to be operated or irradiated before planning of pregnancy.

Effect of dopamine agonists on fetal growth and development

A major concern regarding the management of a prolactinoma during pregnancy is the safety of use of dopamine agonist drugs. As mentioned

above, dopamine agonists are the drugs that are used to control the secretion and size of prolactinomas, as well as being effective in the achievement of fertility. Because fertility restoration is highly likely (90%) with use of such agents, most women have been exposed for 2–3 weeks when the diagnosis of pregnancy is eventually made. This issue makes the safety of these agents extremely important. As some prolactinomas grow during pregnancy, it would be advantageous to shrink the tumors by use of dopamine agonists which also would lead to alleviation of the compressive symptoms without the need for surgery.

The dopamine agonist drug bromocriptine has long been used in the medical treatment of prolactinomas, and much experience regarding its safe use during pregnancy exists. Krupp and Monka reported the results of a 4-month to 9-year follow-up of 988 children exposed *in utero* to bromocriptine, and concluded that the drug has no negative effect on physical development[8]. The incidence of spontaneous abortions, ectopic pregnancies and congenital malformations in pregnancies during which bromocriptine was used was comparable with that of the normal population[8]. Although discontinuation of this drug has long been advised when pregnancy is diagnosed, rapid elevations in prolactin and progression in tumor growth during the first trimester may be observed upon withdrawal[9]. Such progression may be unresponsive to bromocriptine reinstitution, and newer compounds like cabergoline may be required for treatment. Cabergoline is currently the most frequently used agent in prolactinoma treatment because of its greater tolerability and efficiency compared with bromocriptine[10]. Experience regarding its use in pregnant women with prolactinoma is, however, limited. In experimental models of pregnancy, cabergoline was not found to be teratogenic[11]. Analyses of cabergoline-induced gestations in humans revealed no increases in pregnancy-associated problems such as miscarriage and fetal malformations[12]. It is worth noting that cabergoline has a long duration of action keeping prolactin levels suppressed up to 4 months after its withdrawal[13]. The Pituitary Society therefore advocates withdrawal of cabergoline upon a missed menstrual cycle in patients with prolactinoma to make sure that the fetus does not become exposed during the critical first trimester[14].

Fewer, albeit more discouraging, data exist regarding the safe use of pergolide in pregnancy. Two major and three minor congenital malformations have been reported in 38 pregnancies of women taking pergolide[15]. Pergolide is associated with increased risk of spontaneous abortions, minor congenital malformations and intentional abortions, precluding its safe use in pregnant women[4]. As a result, it is not wise to recommend pergolide for restoring fertility in patients with prolactinoma who desire pregnancy.

Quinagolide is also available for the medical management of prolactinoma. Similar to pergolide, its use also seems to be unsafe in pregnancy. In a review of 176 pregnancies during which quinagolide had been used for a median of 37 days, fetal outcomes were poor. Spontaneous abortion was reported in 24 cases, ectopic pregnancy in one, and stillbirth at the 31st week of gestation in an additional case[16]. Moreover, severe fetal malformations including spina bifida, cleft lip and Down syndrome were noted in the group who survived[16]. Under such circumstances, quinagolide therapy should not be instituted in women with a desire for pregnancy.

Recommendations for the treatment of prolactinomas in pregnancy

Microprolactinomas

No clinical trials have compared the outcomes of women with microprolactinomas who have been treated with dopamine agonists during pregnancy with those who have not, and

some experts choose to continue these agents during pregnancy. Nonetheless, a general sense exists toward discontinuation of dopamine agonists upon conception. The patient should then be informed about a small risk of tumor enlargement induced by pregnancy-associated hormonal changes. The patient must also be clearly and repeatedly informed that she should immediately notify her physician if any change in visual acuity or a defect in visual field should occur. Perimetric evaluation should occur on a bimonthly basis[17]. If the patient remains symptom free (no headache, no visual field problem), no intervention is required. After parturition, the patient may resume dopamine agonists if she does not intend to breastfeed. If, on the other hand, she wishes to do so, a magnetic resonance imaging (MRI) of the pituitary should be obtained to ensure there has been no progression in tumor size.

Conversely, the patient may have developed signs and symptoms suggestive of tumor progression as exemplified by new-onset headaches or visual field defects. In such instances, urgent pituitary imaging, preferably by MRI, is appropriate. It should be noted that PRL levels do not always rise in pregnant women with microprolactinomas as is the case in the non-pregnant women. PRL levels rise over the first 6–10 weeks after drug withdrawal and do not usually increase further after that period[9].

Since PRL rise does not accompany tumor growth[18], routine follow-up of PRL levels is not helpful as a means to detect changes in tumor size. In the event the tumor grows, the patient may be treated with dopamine agonists in an attempt to reduce the size. If this therapy is insufficient, transsphenoidal tumor removal (preferably in the second trimester), or early delivery in the third trimester may be proposed[4]. Figure 1 provides an algorithm for the management of microprolactinomas.

Macroprolactinomas

Treatment for pre-pregnant or pregnant women with macroprolactinomas is much more complex, being primarily based on the extent and size of the tumor. Since macroprolactinomas tend to be invasive, pregestational evaluation is crucial. If the tumor is restricted to the sellar region or shows a small infrasellar extension, then dopamine agonists may be used alone[4].

Patients with macroadenomas having undergone treatment with dopamine agonists should strongly be advised not to become pregnant until it is demonstrated that a significant shrinkage of the tumor within the sellar cavity has been achieved. Then the patient may more safely attempt pregnancy. After discussing the risk of progression with the patient, abortion may be considered as an option for large tumors showing no shrinkage with dopamine agonists. The responsive tumors in which there has been sufficient shrinkage may be handled in accordance with the principles mentioned above for microprolactinomas[4]. If abortion has been induced in an unresponsive patient, future pregnancy may be planned after debulking surgery is performed.

Macroprolactinomas with suprasellar extensions pose a serious risk of tumor enlargement with resultant chiasmal compression and other problems if dopamine agonists are used as sole therapy. In such instances, the most conservative approach would be to perform transsphenoidal surgery for tumor debulking. Afterwards, dopamine agonists must be reinstituted to normalize PRL levels which may interfere with ovulation. Since radiotherapy is considered harmful by increasing the risk of hypopituitarism, it is not generally recommended in an attempt to control tumor growth. Another option in such cases may be continuation of the dopamine agonist treatment throughout the gestational period[19]. Such an approach does not seem to pose a significant risk to fetal outcome[20]. If a woman

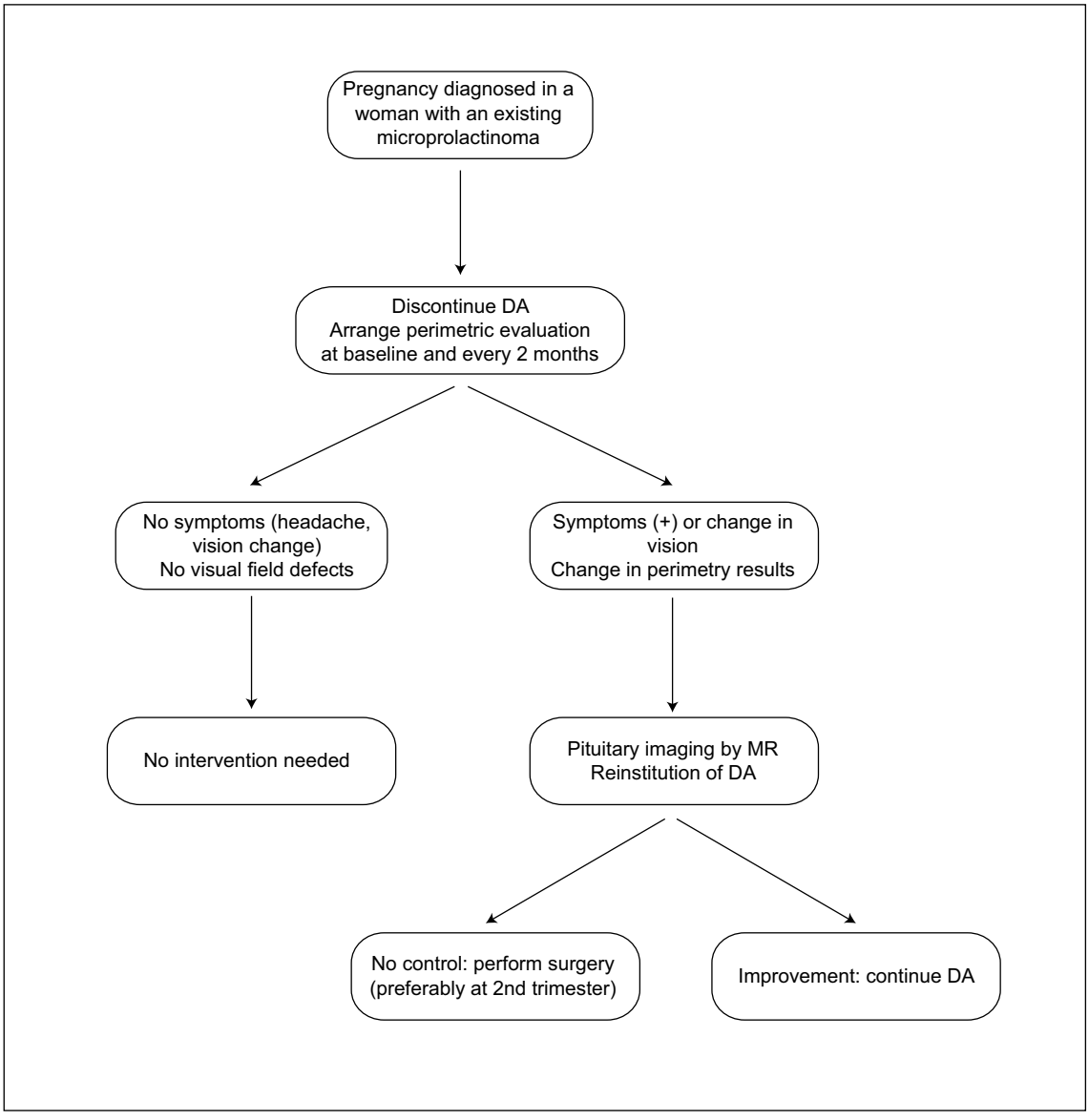

Figure 1 Management algorithm for microprolactinomas in pregnancy. Adapted from references 1 and 17. DA, dopamine agonist; MR,magnetic resonance

presents with a history of inadvertent dopamine agonist use in late pregnancy, therapeutic abortion should not be considered unless a fetal abnormality is present. In such cases, discontinuation of the drug and normal delivery may be recommended. Since any type of surgical procedure is accompanied by at least a 1.5–5-fold risk of fetal loss during pregnancy[21], the best initial approach in a patient with enlarged tumor would be initiation of medical therapy. Surgery should be reserved for failure of this conservative approach as exemplified by deterioration of visual field defects or no effect of dopamine agonists on tumor size. Figure 2 presents an algorithm for the management of macroprolactinomas.

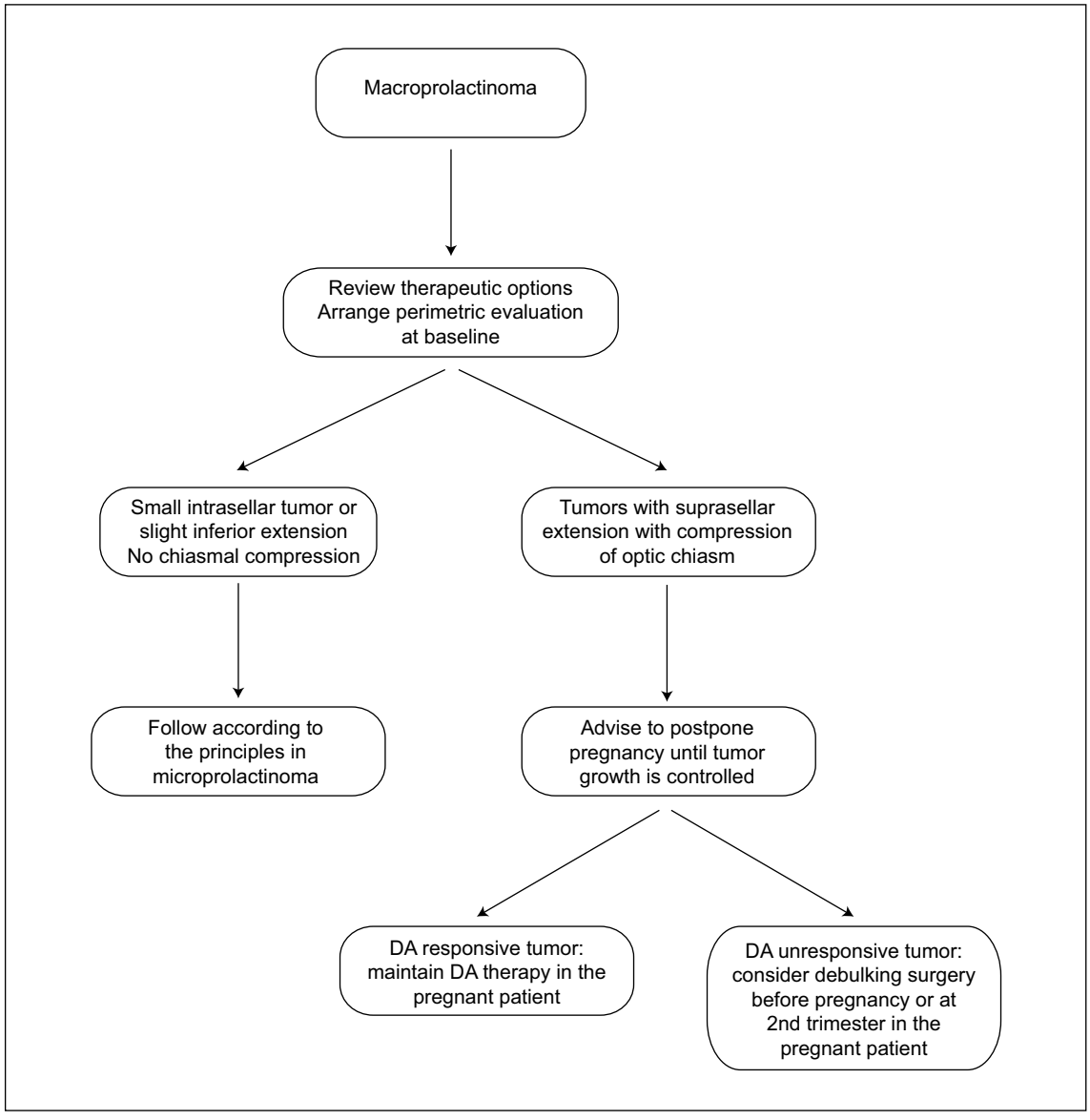

Figure 2 Management algorithm for macroprolactinomas. Adapted from references 1 and 17. DA, dopamine agonist

HYPOTHYROIDISM

After diabetes, thyroid disease is the second most common disorder affecting women of reproductive age. Pregnancy alters the clinical presentation of thyroid diseases, and also modifies thyroid function tests[22]. In normal pregnancies, a fall in thyroid-stimulating hormone (TSH) concentrations and increase in serum free thyroxine (T4) concentrations occur during early weeks. This effect is primarily mediated by the TSH-like activity of placental-derived human chorionic gonadotropin[23]. Conversely, in the late stages of pregnancy, a significant decrease is observed in free T4 levels[23]. These physiological changes may

challenge the interpretation of thyroid function tests in hypothyroid and hyperthyroid pregnant women. For example, hypothyroidism may be masked by the aforementioned changes in free T4 and TSH levels in early pregnancy.

The prevalence of autoimmune thyroiditis in Western developed countries in women of childbearing age ranges between 5 and 15%[24]. The prevalence of overt and subclinical hypothyroidism in this same age group is 0.3–0.5% and 2–3%, respectively[24], with similar values during pregnancy[25]. The main cause of hypothyroidism during pregnancy is autoimmune thyroiditis, particularly in iodine-sufficient areas[26]. In underdeveloped parts of the world, however, the commonest cause is iodine deficiency[26]. Severe iodine deficiency causes endemic cretinism characterized by mental and motor retardation, and deafness[23]. Other less common causes include radioiodine ablation and surgical removal of the thyroid gland[23]. Iron compounds are commonly used in pregnant women, and their interference with intestinal T4 absorption may also worsen hypothyroidism during pregnancy[23]. To avoid this problem, iron compounds should be given at least 4 hours after T4 has been administered 1 hour before breakfast.

The impact of pregnancy on hypothyroidism

Patients with autoimmune thyroiditis are prone to developing subclinical or clinical hypothyroidism with advancing gestation. This occurs primarily due to a lack of capability on the part of the affected thyroid gland to increase its secretory reserve to overcome the increased thyroid hormone demands. Subclinical hypothyroidism also tends to evolve into clinically overt disease by the same mechanism[27].

The impact of hypothyroid state on pregnancy and its outcome

Autoimmune thyroid disease is more common in infertile compared with fertile women[28,29]. Although hypothyroidism may be implicated in infertility, thyroid autoimmunity *per se* is not associated with impaired fetal implantation[28,29]. The success rate of *in vitro* fertilization procedures is lower in patients with untreated hypothyroidism, but not in those with autoimmune thyroiditis and normal thyroid function[28,29]. It is reasonable to advocate appropriate treatment of hypothyroidism and normalization of thyroid function in women with a desire for pregnancy. This process is also valid for patients who cannot spontaneously conceive and require assisted fertilization. How often this occurs in IVF clinics worldwide is unknown.

Obstetric complications associated with subclinical and overt hypothyroidism include miscarriage, anemia, pre-eclampsia, placental abruption and preterm delivery[30,31]. The incidence of postpartum hemorrhage and risk of newborn acute respiratory distress syndrome is also increased in untreated hypothyroidism[30]. In a prospective randomized trial, early intervention with thyroid hormones at 5–10 weeks after conception significantly reduced the risk for miscarriage and preterm delivery compared with untreated control subjects[32]. These results underline the importance of early treatment of hypothyroid patients when pregnancy is diagnosed.

Apart from the aforementioned obstetric complications, untreated hypothyroidism may also be implicated in impaired fetal neurodevelopment, particularly when hypothyroidism is present in early pregnancy[27]. Even mild deficiencies may be associated with reduced cognitive and intellectual function in the offspring[33]. The fact that neural developmental

defects are related with the duration and severity of the hypothyroidism supports the need for the patient to begin thyroxine replacement immediately upon detection of hypothyroidism. Even isolated hypothyroxinemia without concomitant TSH elevation in the early gestational period may lead to a lower psychodevelopmental index in the newborn[34]. Fortunately, most newborns recover spontaneously and there is insufficient evidence to advocate treatment of this condition in newborns[34]. An important issue to be addressed is whether therapeutic abortion should be induced in a pregnant woman during late pregnancy whose severe hypothyroidism has previously remained undiscovered and untreated. The appropriate approach at this stage is debatable, and most obstetricians would hesitate to terminate the pregnancy. Whatever is decided, parents should be carefully notified about the potential brain damage caused by prolonged hypothyroidism.

Treatment of hypothyroidism

Before conception, patients with known hypothyroidism should be assessed for TSH level. The TSH value should be less than 2.5 mU/l[35,36]. In patients with euthyroid autoimmune disease, this TSH cut-off may also be used, although there is no direct evidence in favor of this approach[27]. Once pregnant, the patient should be advised to increase her thyroxine dose by at least 30% to avoid inadequate fetal thyroid hormone delivery during the critical period of organogenesis and brain development[37]. The amount of this increase may also be based on the underlying cause of hypothyroidism. Patients with Hashimoto's thyroiditis require less dose augmentation than do those who have undergone surgical or radio-ablation of the thyroid gland[38].

As patients may be diagnosed initially during pregnancy, routine assessment of thyroid function at the first antenatal visit seems mandatory to not overlook the condition. As stated above, the TSH level should be normalized as quickly as possible by giving more than daily maintenance doses. The patient should be seen after 4–5 weeks of treatment, and on a 6-weekly basis thereafter. Dose titration should assist in achieving target TSH levels (<2.5 mU/l at first trimester and <3 mU/l thereafter). A wide range of thyroxine doses may be required to achieve this goal (25–325 μg/day)[39]. After parturition, doses can be reduced for most women over a few weeks[39]. The thyroid status should be closely monitored as autoimmune thyroiditis increases the risk of development of postpartum thyroiditis.

HYPERTHYROIDISM

The prevalence of hyperthyroidism in pregnancies is 0.2%[23]. As many of the typical symptoms of hyperthyroidism (nervousness, tremors, tachycardia, weight loss, excessive sweating) are also compatible with the normal physiological changes of pregnancy, identification of patients with new-onset hyperthyroidism may be problematic. As noted above, pregnancy is associated with changes in thyroid function tests, so that free T4 levels and free T4 index are normally elevated and TSH level is depressed in early pregnancy. Since resin triiodothyronine (T3) uptake is normally decreased in pregnant women, its increase may indicate the presence of underlying hyperthyroidism.

As is the case in the non-gestational period, Graves' disease is the most common cause of thyrotoxicosis during pregnancy. The autoantibodies directed against TSH receptors have the ability to cross the placental barrier and bind to fetal follicular epithelial cells. The result is neonatal Graves' disease causing hyperthyroidism and thyroid enlargement. Apart from Graves' disease, gestational trophoblastic disease, toxic multinodular or uninodular goiter, viral thyroiditis and pituitary TSH-secreting

tumor may also cause hyperthyroidism during pregnancy[23].

Impact of hyperthyroidism on pregnancy outcome

The importance of timely diagnosis and treatment of hyperthyroidism complicating pregnancy is related to its association with seriously adverse pregnancy outcomes such as stillbirth, preterm delivery, pre-eclampsia and intrauterine growth retardation[40]. If present at conception, untreated hyperthyroidism may lead to spontaneous abortion. It is wise to bring the patient to euthyroid status before planning of pregnancy. Another important aspect of hyperthyroidism is that radionuclide studies should not be ordered in an attempt to make the differential diagnosis of thyrotoxicosis due to the risk of destruction of fetal thyroid epithelial cells[41].

Impact of pregnancy on the course of Graves' disease

Graves' disease generally improves in the second and third trimesters of pregnancy allowing reduction in the dosage and even discontinuation of antithyroid medication[42]. The disease may show reactivation during the postpartum period[42].

Treatment of hyperthyroidism

Women with Graves' disease may be treated by antithyroid drugs during pregnancy. For this purpose, propylthiouracil is superior to metimazole because of lower rates of transplacental passage. At high doses, however, both may pass the placenta and affect fetal thyroidal function[35,42]. Another advantage of propylthiouracil comes from its ability to block the conversion of T4 to T3 by inhibiting deiodinase. This helps to get a quicker and more pronounced suppression of thyrotoxicosis. A slightly elevated T4 level should be allowed to ensure that the fetus receives adequate amounts of thyroid hormones to avoid hypothyroidism[42]. Propylthiouracil may be given 100–150 mg t.i.d. initially; the patient then should be seen after 2–4 weeks for reassessment of thyroid function tests[23]. At that stage, the dosage may be titrated for maintenance. The beta blocker drug propranolol should be used with great caution to control adrenergic symptoms[23]. In the event that the symptoms are not adequately controlled in severe cases, thyroidectomy should be considered, preferably during the second trimester[23]. Radioiodine treatment is contraindicated due to risk of fetal thyroid destruction, and definite therapy should be postponed until after parturition[23].

CONCLUDING REMARKS

Women with microprolactinomas should receive preconceptional counseling to increase fertility by medical treatment with dopamine agonists. Current practice is to withdraw these agents upon diagnosis of pregnancy. It is preferable that macroadenomas be cured before conception, since they tend to grow during pregnancy causing significant visual problems. Patients with prolactinomas should consult with an endocrinologist and neurosurgeon for medical and surgical treatments, respectively. Since untreated hypothyroidism may decrease fertility, early detection is warranted and the patient should be treated and followed appropriately by an endocrinologist. Untreated hyperthyroidism at the time of conception is associated with increased risk of spontaneous abortion. To avoid this unwanted complication, it is mandatory that the patient consult with an endocrinologist in order to achieve a euthyroid state when pregnancy is planned.

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