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Endocrine emergencies in pregnancy

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Endocrine emergencies in pregnancy are rare and are more likely to occur in the absence of good obstetric care. Serious thyroid and diabetes related events in pregnancy are more common because of their higher prevalence in the normal population. Pituitary complications in pregnancy are now relatively rare. A high index of suspicion is needed for early diagnosis, and medical treatment is directed primarily at maintaining maternal hemodynamic stability. A close liaison between an endocrinologist, maternal-fetal specialist and intensivist is critical in optimising both maternal and fetal outcomes.

Endocrine emergencies in pregnancy

Acute thyroid complications in pregnancy

During pregnancy, the hypothalamic-pituitary-thyroid axis undergoes significant adaptation to accommodate the growing fetus. There is an increased demand for thyroid hormone during pregnancy and the normal thyroid gland is able to hypertrophy and meet this demand. Any maternal thyroid gland abnormality or insufficiency can potentially influence the pregnancy outcomes for mother and fetus at all stages of pregnancy. Poor control of thyroid hormone is associated with miscarriages, pregnancy-induced hypertension, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm, and maternal congestive heart failure. More recent evidence also suggests that even very mild maternal hypothyroidism may result in intellectual deficiency in the offspring in later years [1]. Thus a close monitoring of the thyroid hormone levels and precise titration of the thyroid medications are essential to achieve desirable outcomes in women with thyroid abnormalities.

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Maternal hyperthyroidism, either pregestational or diagnosed during gestation presents a challenge to health care professionals. Graves disease is the commonest cause of hyperthyroidism during pregnancy. Hyperthyroidism during pregnancy will need to be managed with 4 to 5 weekly visits with monitoring of serum levels of free T4 and TSH. These levels will have norms that change with the stage of pregnancy. Poorly controlled or untreated hyperthyroidism can potentially develop into thyroid storm with high maternal and fetal mortality.

Drug treatment complications in pregnancy

Propylthiouracil (PTU) is recommended as the drug of choice in pregnancy [2]. However, a recent Cochrane review has found no randomised study on drug treatment of hyperthyroidism in pregnancy [3].

Although rare, the known complications of skin allergy, liver damage and the more serious agranulocytosis have all been reported with the use of PTU in pregnancy [4]. If there is skin allergy (usually a severe itch) or liver complications to PTU, then carbimazole should be used instead. If there is agranulocytosis, then oral medication should be stopped. Thyroidectomy is the treatment of choice, as radioiodine is contraindicated in pregnancy.

Thyroid storm

Thyroid storm during pregnancy is very rare, and may occur with untreated or inadequately treated thyrotoxicosis during pregnancy. It may be masked by the physiological erythema and tachycardia of pregnancy, and may manifest as cardiac failure, especially at parturition. The exact pathophysiology is not well understood, but the labor process induces high emotional and physical stress, and in some the need of a Caesarean section may exacerbate adrenergic activity [5,6]. Early recognition and initiation of appropriate therapy is important. There may be presence of high fever, disproportionate tachycardia and agitation or confusion. The diagnosis of thyroid storm is a clinical one, taking together the constellation of clinical symptoms and signs, and exclusion of infection and other causes. The elevated level of circulating thyroid hormone values is helpful but is not distinguishable from those seen in patients with uncomplicated hyperthyroidism. A scoring system using precise clinical criteria has been developed to facilitate the identification of thyroid storm [7].

The treatment of thyroid storm does not differ from non-pregnant women, and should be managed by a team consisting of an endocrinologist and maternal-fetal specialist in an intensive care unit. The management is directed at a rapid inhibition of thyroid hormone synthesis and its peripheral conversion, aggressive management of the systemic disturbances and identification and treatment of the precipitating cause [8]. Aggressive treatment of the cardiac failure is essential with diuretics. Glucocorticoids are also essential: dexamethasone, 8 mg/day can be administered and blocks the deiodination of T4 to T3 (while assisting also with fetal lung maturation). PTU is the preferred anti-thyroid medication as it can additionally block the peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3). PTU can be administered orally, by nasogastric tube, and in the event that the oral route is contraindicated, rectally. PTU is given at a dose of 200–250 mg every 6 hours. Iodide can be administered 1 hour after PTU to inhibit the release of preformed thyroid hormone. Iodide can be given orally (Lugol's solution or saturated solution of potassium iodide, 4–8 drops every 6–8 hours; radiographic contrast media: iopanoic acid or sodium ipodate – 2 gm loading dose followed by 1 gm daily) or intravenously (sodium iodide 1 gm in 250–500 mL normal saline, infused twice daily).

Management of hyperpyrexia, treatment of precipitating factors and control of hyperadrenergic activity should be instituted simultaneously. Propranolol should be administered orally (40–80 mg every 6–8 hours) or intravenously (0.5–1 mg over 10 minutes, followed by 1–3 mg every few hours). The short-acting β_1-selective antagonist, esmolol can also be used intravenously (0.25–0.5 μg/kg loading dose, followed by an infusion of 0.05–0.1 μg/kg/min). The use of β-blocker is essential to survival from thyroid storm but need close monitoring. Plasma exchange has been tried in rare instances where aggressive conventional therapy fails to bring about discernible clinical improvement [9].

Careful monitoring of the fetus is also critical. However, prompt delivery of the fetus is currently not recommended during thyroid storm, unless indicated [10]. If the fetus is exposed to recent high-dose

maternal thionamides (e.g. PTU), close monitoring of the newborn thyroid status is important as thionamides may cross the placenta and inhibit fetal thyroid hormone synthesis and secretion.

Acute diabetic complications in pregnancy

Pregnancy in women with type 1 diabetes is associated with a higher risk of maternal and perinatal complications than in the non-diabetic population [11]. Studies have shown that increasing levels of first-trimester glycosylated haemoglobin (HbA1C) starting from values slightly below 7% show a dose-dependent association with the risk of adverse pregnancy outcome [12]. The Diabetes Control and Complications Trial showed that timely institution of intensive therapy was associated with rates of spontaneous abortion and congenital malformation similar to those in the non-diabetic population [13]. However, several studies reported that near optimal glycaemic control did not obviate these complications considerably [11]. In addition, specificity and sensitivity of HbA1C was relatively low in predicting adverse outcome in the individual pregnancy, making HbA1C measurements a less useful and reliable tool in diabetic pregnancies [12].

The incidence of diabetic ketoacidosis (DKA) during pregnancy ranges between 2 to 3%, and carries a 10–20% risk of fetal death [14]. The majority of DKA occur in the second and third trimesters of pregnancy. During second and third trimester, there is a significant decrease in the maternal insulin sensitivity which renders the need to increase the insulin requirement by an average of 50% [14]. Other precipitating factors include infection, non-compliance to insulin therapy, insulin pump failure, and the use of sympathomimetic drugs or corticosteroids. DKA during pregnancy may occur at lower glycaemic levels or even at euglycaemic state due to enhanced ketogenesis, in particular towards the end of gestation [15]. In addition, pregnant women have a respiratory alkalosis from increased alveolar ventilation. The development of respiratory alkalosis is followed by a compensatory decrease in serum bicarbonate concentration which reduces the capacity to buffer hydrogen ions [16]. Women with type 1 diabetes with unexplained hyperglycaemia (blood glucose $>$11.1 mmol/L) during pregnancy should alert their physician immediately to exclude DKA. In oriental women (predominantly) recent reports of 'fulminant diabetes' have been described. This is an abrupt and rapidly developing severe diabetes during pregnancy or within 2 weeks of delivery [17]. Fulminant diabetes mellitus often rapidly progresses to DKA and is characterized by absence of diabetes-related autoantibodies and a very low C-peptide level during presentation. The pathophysiology of fulminant diabetes is still not clear, but accumulating evidence suggest acute viral related immune destruction of the pancreatic β-cells [18].

The acute management of DKA during pregnancy is similar to that of non-pregnant and has been reviewed elsewhere [19,20]. Briefly, DKA should be treated in a high dependency unit under combined medical and obstetric care. Treatment includes aggressive volume replacement, insulin infusion, careful attention to electrolytes, and a search for and correction of precipitating factors. About 1–1.5 L of isotonic saline (0.9% NaCl) is given during the 1st hour. Subsequent choice for fluid replacement depends on the state of hydration, serum electrolyte levels, and urinary output. Potassium supplementation is usually added when renal function is adequate. Continuous infusion of regular insulin therapy is necessary to reduce ketogenesis. A fixed-rate intravenous insulin infusion calculated on 0.1 units/kg is recommended, aims for (i) reduction of the blood ketone concentration by at least 0.5 mmol/L/hr; (ii) in the absence of blood ketone monitoring, the venous bicarbonate should rise by 3 mmol/L/hr and capillary blood glucose fall by 3 mmol/L/hr [21]. If these targets are not achieved, the rate of the insulin infusion should be increased. If the initial blood glucose level is low ($<$14 mmol/L) or when the blood glucose falls below 14 mmol/L, infusion of dextrose (5% or 10%) solution should commence simultaneously in order to avoid hypoglycaemia. Ketonemia typically takes longer to clear than hyperglycaemia, and direct measurement of serum β-hydroxybutyrate may be helpful. Regular (recommended 2 to 4 hourly) monitoring of serum electrolytes, glucose, urea, creatinine, and venous pH should be performed to assess the efficacy of treatment. Bicarbonate and phosphate replacement is only indicated in specific situations and thus should be individualized.

Continuous fetal monitoring is of paramount importance. Some degree of fetal distress may be present as placental transfer of ketoacids may cause fetus to become acidotic. However, fetal distress improves with stabilization of maternal hyperglycaemia and acidosis, thus immediate fetus delivery is reserved for persistence fetal compromise after maternal resuscitation [19].

Although there is an increasing number of women with type 2 diabetes mellitus who now becoming pregnant, the incidence of hyperosmolar hyperglycaemic nonketotic syndrome in pregnancy is rare. The increase tendency of enhanced ketogenesis and lower buffer capacity for acidosis during pregnancy predispose them to ketoacidosis.

Acute pituitary complications in pregnancy

Prolactinoma

Prolactinoma is characterized by autonomous production of prolactin due to a pituitary micro- or macroadenoma. Excessive prolactin is a very common cause of subfertility in women of child bearing age. A dopamine agonist (bromocriptine or cabergoline) is the treatment of choice, and with adequate treatment this medication can inhibit prolactin secretion, cause tumor shrinkage and normalize circulating prolactin levels. However, managing prolactinomas during pregnancy poses a unique challenge. During pregnancy, estrogens levels increase progressively to peak in the third trimester. The stimulatory effect of estrogens can potentially increase the size of prolactinoma during pregnancy, leading to pituitary mass effect, irreversible visual loss and potential apoplexy. Thus, all women with prolactinomas should be counseled appropriately on the risk of tumor enlargement before attempting pregnancy [22].

In patients with microprolactinoma, the recommendation is that the dopamine agonist should be discontinued upon confirmation of pregnancy since the risk of the risk of tumor expansion is low [23,24]. On the contrary, the risk of tumor expansion may be significant for macroprolactinomas. The risk of tumor enlargement during pregnancy has been reported to be as high as 35% in women with macroprolactinomas [25]. For this reason, pregnancy should be deferred in women with macroprolactinomas where risk of tumor progression and visual loss is appreciably high. Periodic prolactin monitoring is of limited value during pregnancy due to the wide variation in levels during pregnancy. Visual field testing is mandatory, and pituitary imaging with MRI is needed in patients who develop symptoms of increased intracranial pressure and visual abnormalities.

If there is evidence of tumor enlargement, dopamine agonist therapy (i.e. bromocriptine or cabergoline) should be resumed immediately and continued throughout pregnancy. While there are no controlled studies, the evidence does not suggest any increased rates of abortion or congenital malformations with bromocriptine [26]. Experience with cabergoline during pregnancy is more limited [27], but again there has been little evidence to indicate any difference from bromocriptine. Prepregnancy transphenoidal debulking or radiation therapy of a macroprolactinoma reduces the risk of significant tumor enlargement during pregnancy [22]. However, surgery during first or second trimester is associated with an increased risk of fetal loss. Nonetheless, surgery or delivery (in advanced pregnancy) should be attempted if there is lack of response to dopamine agonist or progression of visual deficits.

Sheehan's syndrome

During pregnancy, the normal pituitary gland enlarges by about one-third, primarily from an increase in lactotroph size, and number in response to the elevated plasma estrogens. The pituitary gland enjoys an abundant blood supply, thus any interruption of blood flow to the anterior pituitary lobe will result in infarction of the gland [28]. Hypotension from severe hemorrhage at peri- or postpartum period is the major causal factor [29,30]. Pituitary edema from the cellular damage, and local vasospasm from shock will further compromise the blood flow. The degree of subsequent pituitary deficiency is related to the quantity of pituitary tissue damage [28]. This is variable and may need reassessment.

The acute phase is associated with 90% infarction of the pituitary gland, and is potentially lethal if not recognized and treated immediately with glucocorticoid replacement [5]. The clinical presentation is similar to pituitary apoplexy. A high index of suspicion is the key to early diagnosis. In the setting of an obstetric haemorrhage (which is extremely rare with current good obstetric practice), patients may complain of sudden-onset headache, nausea, vomiting, and vision impairment associated with an

increase in the intracranial blood pressure. Hemodynamic instability with persistent hypotension and tachycardia that is especially nonresponsive to volume challenge may be present [22]. Magnetic resonance imaging of the pituitary gland is the investigation of choice, and usually reveals an enlarged, low-density sellar mass, often with rim enhancement following contrast administration. The minimal blood tests performed should include a full blood count, urea and electrolytes, coagulation profiles, and a hormonal profile. Hypoglycaemia and severe hyponatremia may occur. Visual field assessment should be performed as it may help to decide on surgical treatment. It must be reinforced that treatment with stress doses of glucocorticoids should be instituted as soon as the clinical diagnosis is made, and should not await the result of diagnostic testing [22]. Aggressive fluid resuscitation and blood product replacement may minimize the extent of pituitary necrosis and improve long-term clinical outcomes.

Late and delayed Sheehan's syndrome (less tissue damage) usually exhibits variable hyposecretion of anterior pituitary hormone, and may occur months or years after the partum event [31]. Diagnosis may be delayed for years [32]. Failure of lactation (due to lack of prolactin) and secondary amenorrhea (due to loss of gonadotrophins) are the most common features [33]. Secondary hypothyroidism and hypoadrenalism may present with subclinical symptoms and signs (e.g. fatigue, loss of energy, loss of axillary and pubic hair, anorexia, loss of weight, orthostatic giddiness etc). An MRI of the pituitary gland usually reveals a partially or completely empty sella [34]. The diagnosis is made by demonstrating low basal anterior pituitary (TSH, GH, LH, FSH, Prolactin, ACTH) and target organ (IGF-1, free thyroxine, cortisol, estrogen) hormones. Deficiencies in multiple hormones may occur, although some patients have isolated ACTH or TSH deficiency. Stimulation tests (insulin tolerance test, TRH and GnRH stimulation test) may be needed to assess the degree of hormonal deficiencies [33].

Long-term treatment of Sheehan's syndrome includes lifelong end-organ replacement hormone therapy with levothyroxine and glucocorticoid [33]. Estrogen may be given to reduce the risk of osteoporosis and to improve the woman's sense of well-being. Growth hormone and vasopressin may be replaced as needed.

Pituitary apoplexy

Pituitary apoplexy (acute bleeding into the pituitary gland) during pregnancy is very rare. Several cases of pituitary apoplexy occurring during pregnancy have been reported in the literature [35]. Pituitary apoplexy is an endocrine emergency with significant morbidity and mortality. Pituitary apoplexy occurs most commonly in patients with pituitary adenomas, often a macroprolactinoma when the tumor undergoes infarction due to haemorrhage, ischemia or both. Predisposing factors include radiation therapy, hypertension, diabetes mellitus, anticoagulant therapy, use of bromocriptine and disseminated intravascular coagulopathy [35].

Sudden onset of severe headache and vomiting are the usual presenting complaints, and indicate increased intracranial pressure [36]. Meningism and altered mental status are fairly frequent. Ophthalmoplegia and cranial nerve palsy may occur when the enlarged pituitary gland extends laterally into the cavernous sinus or compresses on the optic chiasm. Pituitary apoplexy is a clinical diagnosis and a high index of suspicion is critical to ensure timely intervention. Urgent blood for anterior pituitary hormones, full blood count, coagulation profiles and renal panel should be taken at diagnosis. Hypotension, refractory to volume expansion, and hypoglycaemia indicates acute ACTH deficiency. Treatment should be instituted immediately before imaging is undertaken, aiming at measures to maintain hemodynamic stability. Intravenous hydrocortisone 100 mg should be administered without delay and continue every 6 hours. Hydrocortisone can also be given intramuscularly or by infusion pump, e.g. 5–10 mg/hr once the vital signs (i.e. blood pressure) stabilize. MRI with dynamic contrast of the pituitary shows high signal on T1 and T2-weighted images and helps to elucidate the extent of tumor enlargement. Expectant medical management may be adequate in cases with minimal visual impairment and rapid clinical improvement. Patients should be observed closely in the intensive care unit for deterioration in neurological symptoms or signs. Transphenoidal decompression surgery is advocated early if there is deterioration in conscious level or in visual deficits.

All patients with pituitary apoplexy should have an endocrinological evaluation for pituitary function at four to eight weeks following the event. They should have full biochemical assessment of

pituitary function to dictate next hormonal treatment, and formal ophthalmic assessment and visual fields perimetry study. Long-term management aims to monitor for tumor regrowth, replace the missing hormones and restore endocrine homoeostasis.

Conflict of interest

Nil.

Practice points

- Good control of hyperthyroidism should be undertaken before attempting pregnancy.
- Thyroid storm should be suspected in patients with unexplained fever, tachycardia and altered mental status, especially in women with pre-existing hyperthyroidism.
- Diabetes ketoacidosis may be precipitated by pregnancy, even in women with optimal glycaemic control prior to pregnancy.
- Diabetes ketoacidosis in pregnancy may present at glucose levels that are normally considered as less dangerous (in non-pregnant diabetics) due to enhanced ketogenesis and lower buffer capacity for acidosis during pregnancy.
- In oriental women, acute fulminant diabetes may occur de novo.
- Macroprolactinoma carries a high risk of tumor enlargement during pregnancy, indicated by visual disturbance and symptoms of increased intracranial pressure.
- Bromocriptine is safe and should be restarted if prolactinoma enlargement occurs during Pregnancy.
- Pituitary apoplexy is a clinical diagnosis and should be suspected in patients with sudden onset of headache, meningism and altered mental status.

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