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Gestational Diabetes and Other Endocrine Disorders in Pregnancy

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OBJECTIVE - To review the authors' experience of 20 endocrine disorders during pregnancy. **METHOD** - Our database of over 30,000 cases since 1975 is analysed and relevant literature, refered to. **RESULTS** - 80.3% of gestational diabetics had history of diabetes in first degree relatives. In Chennai, diabetes mellitus was seen in 1.19% and gestational diabetes in 0.56%. We had 23 cases of thyroid problems and four cases of adrenal neoplasm during pregnancy. **CONCLUSION** - Endocrine diseases other than gestational diabetes mellitus are rare in pregnancy. With clinical evaluation careful interpretation of laboratory investigations, most can be managed with good fetal and maternal outcome.

Key words : gestational diabetes, endocrine disorders

Except gestational diabetes mellitus, which by definition occurs only in pregnancy, other endocrine diseases may occur in the non-pregnant as well as the pregnant state. This presentation is an overview of gestational diabetes, and other endocrine diseases of pregnancy. The main focus is on features peculiar to pregnancy, in terms of clinical findings, investigations and management.

Gestational diabetes mellitus

Definition : Gestational diabetes mellitus is defined as'... glucose intolerance with onset or first recognition during pregnancy . It is possible that unrecognized glucose intolerance might have begun earlier or during pregnancy.

Prevalence : Prevalence of GDM varies from 1 to 14% of all pregnancies according to US figures. At our centre, among 13,408 consecutive persons with diabetes, 99 had a diagnosis of gestational diabetes[1]. In addition 18 women had diabetes mellitus who had later become pregnant, and did not meet the criterion of gestational diabetes mellitus.

Among 66 consecutive women with gestational diabetes (age range 19-44 years), the weight ranged from 47.1 to 91.0 kg (n: 63) and body mass index from 19.11 to 36.45 (n:29). The fasting blood glucose ranged between 58mg/dl and 287 mg/dl (n:46). A majority of them had a family history of diabetes mellitus in first degree relatives (53/66; 80.3%).

It is evident that gestational diabetes can present at a wide range of age, weight, body mass index and blood sugar, but with an underlying theme of strong family history of diabetes. In Chennai, diabetes mellitus was seen in 1.19% and gestational diabetes mellitus in 0.56%[2].

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Detection : The American Diabetes Association Clinical Practice Recommendations of 1998 advise that screening be performed in pregnant women between 24th and 28th week of gestation. According to their criteria, ethnic group of Asian (implies all Indians) should be screened. The other inclusion criteria are :

- Age 25 years or more
- Age less than 25 years, if obese (BMI equal to or more than 27 kg/m^2)
- Family history of diabetes in first-degree relatives

The screening test is a 50 gm oral glucose, followed by a plasma glucose determination one hour later.

The woman need not be fasting. A value equal to or more than 140 mg%/dl must be followed up by a full diagnostic 100 gm 3-hour oral glucose tolerance test done when fasting.

Diagnosis of gestational diabetes : According to Carpenter and Coustans modification of O'Sullivan and Mahan's criteria, GDM is diagnosed if following a 100gm oral glucose load two or more venous plasma glucose concentrations are met or exceed -

*	Fasting	:	105 mg%/dl
*	1 hour	:	190 mg% / dl
*	2 hour	:	165mg% / dl
*	3 hour	:	145 mg% / dl

Principles of management : The aim is to achieve euglycemia by diet and if necessary pharmacotherapy which is insulin in gestational diabetes. Both the fetus and the mother must be closely monitored. Maternal urinary glucose testing is not useful.

Diet : Diet must provide adequate calories and nutrients for pregnancy and at the same time maintain maternal euglycemia. Use of sucrose is avoided

Energy in the first half of pregnancy : 30 kcal x standard body weight before pregnancy + 150 kcal additional energy

Energy in the second half of pregnancy : 30 kcal x standard body weight before pregnancy + 350 kcal additional energy

Obese pregnant women should receive a restricted calorie diet. The goal of treatment is to normalize blood glucose and to limit body weight gain during pregnancy to 6-8 kg.

If fasting plasma glucose of 105 mg /dl or less and /or a two hour postprandial level of 120 mg /dl or less is not maintained twice or more often at 1-2 week intervals, insulin must be used. The purest form of insulin that can be afforded (best is human insulin) is preferred. Self monitoring of blood glucose is ideally employed to prevent both hypo- and hyperglycemia. Oral hypoglycemic agents are not recommended during pregnancy. Active lifestyle should be encouraged. Non-caloric sweeteners may be used in moderation. Breast feeding is also encouraged postpartum.

Prognosis after delivery : Women with gestational diabetes mellitus are at risk for developing diabetes later on. Oral glucose tolerance test must be done at least six weeks postpartum and the woman classified. If the result is normal, testing may be done every three years, but the frequency depends on clinical condition. They are educated on lifestyle modifications to lessen the risk of insulin resistance. For contraception low dose estrogens may be safely used in women with previous gestational diabetes.

Principles of testing for endocrine disorders

The endocrine system is characterized by checks and balances. Diagnosis is made of the two arms: one from hypothalamus - pituitary and second from the resultant hormone secretion from the target organ.

When hyperfunction is suspected, a suppression test is done: more of the hormone secreted from the suspected target organ is given and the response is seen for normal suppression. In hypersecreting states this normal suppression does not occur [4].

Similarly in suspected hypofunctioning states, stimulating tests are done: by giving a stimulating hormone, it is seen whether the target gland can respond with secretion of hormone. If the gland is dysfunctional a normal secretory response is not seen.

Other endocrine disorders

Thyroid dysfunction is the next common endocrine disorder in pregnancy. In our database of 20,513 patients, 23 had a diagnosis of both pregnancy and thyroid condition.

The commonest was hypothyroidism (on treatment n=11), closely followed by thyrotoxicosis (untreated n=4, on treatment n= 2, off treatment n=1) and others such as autoimmune thyroid disorder (n=1), goiter (n=2) and thyroid nodule (n=2).

Besides there was one pregnant woman with hypoadrenocortisolism and one with diabetes insipidus.

Thyroid disorders in pregnancy

Assessment of thyroid function during pregnancy is difficult because of overlapping clinical signs (tachycardia, tremor, small goitre) and elevated level of total T4. It therefore needs a careful evaluation of both symptoms, as well as measurement of TSH and free T3 and free T4 hormone levels. Detection of thyroid autoantibodies may help in diagnosing autoimmunity [5].

Pregnancy is associated with alterations in thyroid function, such as increased production of autoantibodies, increased glomerular filtration of iodine, especially in iodine deficient regions, and possible stimulating effect of chorionic gonadotropin on the TSH receptor [6].

Hypothyroidism : Untreated hypothyroidism impairs fertility. Currently due to earlier and effective treatment untreated hypothyroidism in pregnancy is uncommon. Diagnosis and treatment : Elevated serum TSH level together with low total or free T4 levels is diagnostic of primary hypothyroidism.

Women who have clinical features of hypothyroidism, goitre or history of thyroid disease should be screened by TSH level in the first visit. Newly diagnosed hypothyroid women with pregnancy should be treated with thyroxine in dose close to anticipated requirement (0.14-0.15 mg a day). When possible serum TSH may be measured four to six weeks after starting replacement and T4 dose adjusted to normalise TSH levels.

In a report of 26 pregnancies complicated by hypothyroidism from AIIMS, New Delhi, two women were diagnosed to be hypothyroid during pregnancy. Maternal complications were anemia, pregnancy induced hypertension, postpartum hemorrhage, intrauterine growth retardation and deficient lactation. Perinatal mortality was 3.9% [7].

The dose of thyroxine may need to be upwardly revised during pregnancy.

Neonatal screening for hypothyroidism : Neonatal hypothyroidism occurs once in about 3,500 births and neonatal screening for hypothyroidism is standard practice in developed countries. Ideally both serum T4 and TSH are measured. T4 is low and TSH is elevated in primary hypothyroidism. If hypothyroidism is uncorrected within the first four weeks of birth, mental impairment in the child is permanent.

Thyrotoxicosis - Two main forms of hyperthyroidism are described in pregnancy.

Graves' disease may have onset before or during pregnancy. Hyperthyroid women on treatment should ideally not conceive while toxic. It is difficult to identify thyrotoxicosis during pregnancy because both have similar features such as tachycardia, heat intolerance, perspiration, emotional lability and palpitation.

Features suggesting thyrotoxicosis are lid lag, proximal muscle weakness and goitre. Biochemically, serum free T4 levels are high, and serum TSH low. Radionucleide scans should not be done during pregnancy. When antedating pregnancy, thyroid-stimulating immunoglobulins may be high enough to induce fetal hyperthyroidism. The goal of antithyroid treatment in pregnancy is to use antithyroid drugs, avoiding overdose, which could result in goitre and / or fetal hypothyroidism.

Gestational transient thyrotoxicosis is associated with direct stimulation of maternal thyroid by human chorionic gonadotrophin. It is usually transient, seen at the end of the first trimester, and frequently associated with hypermesis.

Neonatal thyrotoxicosis is a related condition that occurs about once in 70 cases of thyrotoxic pregnancy. It is mostly due to transplacental passage of thyroid stimulating antibodies from the mother. It is manifested by irritability, tachycardia, hypertension, poor weight gain, thyroid enlargement and exophthalmos. Treatment consists of sedatives and digitalization as necessary, iodine and antithyroid drugs (methimazole and carbimazole 5-10 mg / kg / d, in eight hour intervals).

Treatment of toxicosis in pregnancy - The treatment is difficult. Medical therapy is the method of choice. Both carbimazole and propylthiouracil cross the placenta, but propylthiouracil is traditionally the preferred agent if available. Fetal heart rate should be monitored and the dose of antithyroid adjusted if fetal tachycardia occurs. The level of free T4 in the mother is best maintained at the upper limit of normal. Lactation is also best avoided in women taking antithyroid drugs[3].

In a study reported from India 13 women (16 pregnancies) required antithyroid drug therapy during pregnancy. The drug dosage remained the same during pregnancy in eight women; it was increased in five and reduced in three. Drug therapy was therefore reported to control thyrotoxicosis during pregnancy with improved maternal and fetal outcomes.

Diabetes insipidus

Diabetes insipidus is a rare complication of pregnancy[11]. Usually polyuria begins in the third trimester and resolves postpartum. Women with pre-existing diabetes insipidus are treated with desmopressin, without any change in dose. There is no evidence of fetal morbidity or mortality associated with this drug. Diabetes insipidus is a rare cause of oligohydramnios during pregnancy and is identified by 24 hour urine volume and serum electrolytes.

Pituitary diseases and tumours

Pituitary adenomas are the most common pituitary disorder in pregnancy[14]. Prolactinomas are the most common of the hormone-secreting pituitary adenomas. If the tumour is a microadenoma the risk of enlargement during pregnancy is less than 2% in contrast to 15% risk with macroadenomas. Treatment options in macroadenomas include stopping bromocriptine when pregnancy is diagnosed and reinstituting it with tumour enlargement, continuous bromocriptine throughout pregnancy and prepregnancy surgical debulking of the tumour.

The risk of developing visual loss is generally less in microadenomas, in contrast to macroadenomas (where the size of the pituitary tumour is > 1 cm)[14].

Treatment for pituitary tumours is generally deferred until after delivery.

Parathyroid disorders

Parathyroid disorders are uncommon in women of childbearing age. Total serum calcium is lower in normal pregnancy but ionized serum calcium is normal[15].

Primary hyperparathyroidism : Primary hyperparathyroidism is commonly caused by a single parathyroid adenoma. The mother may develop acute pancreatitis, hypercalcemia and toxemia. When maternal hypercalcemia is significant prematurity and neonatal hypocalcemia may develop.

Hypoparathyroidism : Hypoparathyroidism, though rare in pregnancy may develop after surgical thyroidectomy. The dose of vitamin D and calcium do not change during pregnancy. Serum calcium should be regularly monitored.

Where available, monitoring of serum 1,25 (OH) 2 D3 should be done and serum calcium levels kept in the lower normal range.

The evaluation of late-onset neonatal hypocalcemia should consider maternal hyperparathyroidism as a cause[14].

Adrenal disorders

Adrenal insufficiency : Women with adrenal insufficiency who are on adequate replacement with glucocorticoid and mineralocorticoid go through pregnancy, labour and delivery uneventfully[15].

During labour, saline hydration and 25 mg of intravenous hydrocortisone should be given every six hours. At the end of delivery or if labour is prolonged, parenteral hydrocortisone is given, 100 mg six hourly.

Adrenal tumours : Adrenal tumours are rarely first diagnosed during pregnancy. From a computer-based registry of pregnant women from 1975 through 1996 (n:30,246), four cases of adrenal neoplasms associated with pregnancy were identified (0.13%) [16].

Cushings syndrome : Untreated Cushings syndrome in pregnancy is associated with abortion, premature delivery and rarely neonatal adrenal insufficiency. Maternal complications are hypertension, gestational diabetes mellitus and congestive heart failure, with a mortality rate of about 4%.

Pheochromocytoma : Pheochromocytoma in pregnancy is difficult to manage. Unprepared spontaneous labour with vaginal delivery is disastrous to both mother and fetus[17]. MRI is the diagnostic method of choice for localization. The tumour is removed with adequate adrenergic blockade.

Adrenal tumours are rare in pregnancy, but diagnosis should be considered in the presence of hypertension, headaches and other manifestations. Identified adrenal lesions are surgically removed.

Congenital adrenal hyperplasia : Women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency have lower fertility. Pregnancy outcomes in such women treated with glucocorticoids resulted in four healthy female newborns with normal female external genitalia. Despite high maternal levels of androgens, placental aromatase prevented masculinization of the external genitalia of the female fetus. Placental aromatization of androgens to estrogens is the principal way the female fetus is protected from masculinizing effects of maternal hyperandrogenis.

Prenatal treatment of fetus by giving dexamethasone to the mother can prevent genital ambiguity in females at birth[18].

Virilising tumours : Rare virilizing tumours in pregnant women such as sclerosing stromal cell tumour result in nonvirilized female infants at birth[19,20].

Insulinoma

Insulinoma is rare, and even more so in pregnancy. In rare reports despite maternal hypoglycemia fetal malformations were not seen[21]. The tumour may be removed after delivery, while maintaining plasma glucose by parenteral glucose infusion.

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