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## Review article on endocrine diseases during pregnancy

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### Abstract

Pregnancy is the period where a woman undergoes several physical and hormonal changes in accordance to the growth of the fetus. Wide alteration in the levels of hormones from the normal values affect the state of gestation and the growth of the baby. Especially the most commonly encountered disorders like pregnancy induced thyroid disorder effects the neuro development of the baby whereas gestational diabetes makes mode of delivery complex. Hormonal imbalance can be investigated by haematological findings like thyroid stimulating hormone (TSH), T3 and T4 tests to identify thyroid disorders whereas HbA1C, Random blood sugar (RBS), fasting random blood sugar (FRBS), post prandial blood sugar (PPBS) and oral glucose tolerance test (OGTT) to screen gestational diabetes. Apart from these there are some uncommon hormonal pregnancy disorders like cushing syndrome, conns syndrome, congenital adrenal hyperplasia, adrenal insufficiency. These complexes can be rectified up to certain extent by diagnosing them before hand thereby implementing life style changes, dietary changes and taking medications. Therefore, prior screening of the diseases is important in suppress further complications in pregnancy and to have healthy progeny.



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## Introduction

Pregnancy is defined as the period during which a fetus develops inside a woman's womb which usually lasts about 40 weeks or just over 9 months, as measured from last menstrual period to delivery.

Pregnancy is correlated with diverse variations of normal physiological processes and many disorders anticipate the pregnancy, whereas others are afflicted by the pregnancy. Parturition is cleft into three trimesters [1].

### 1. First trimester

The 1<sup>st</sup> trimester lasts from the last menstrual period throughout week 12. Important events that occur are:

- At days 8–10, a positive pregnancy test will be obtained by HCG assay.
- At week 12, the uterine fundus is detectable at the pubic symphysis; Doppler fetal heart rate is first audible.

### 2. Second trimester

The second trimester continues from the end of the first trimester till week 27. Major events that occur are:

- At weeks 14–18, amniocentesis is enforced when dubiety of fetal chromosomal abnormalities exists.
- At week 16, the uterine fundus is palpable midway mid the pubic symphysis and the umbilicus.

- At weeks 16–18, first fetal movements occur in a woman's second or higher pregnancy.
- At weeks 17–20, the fetal heart rate is distinct with fetoscope.
- At week 18, female and male external genitalia can be remarked by ultrasound (i.e., sex determination).
- At weeks 18–20, first fetal movements occur in a woman's first pregnancy.
- At week 20, the uterine fundus is prominent at the umbilicus.
- At weeks 25–27, lungs become adept of respiration; surfactant is bred by type II pneumocytes. There is a 70%–80% liability of survival in infants born at the end of the second trimester. If death occurs, it is roughly as a consequence of lung immaturity and resulting respiratory distress syndrome (hyaline membrane disease).
- At week 27, the fetus weighs about 1000 grams.

### 3. Third trimester

The third trimester extends from the end of the second trimester until term or week 40. Important events that occur are:

- Pupillary light reflex is prevailing.

- b. Inclination of the fetal head to the pelvic inlet (called **lightening**) occurs.
- c. Herniation of the amnio chorionic membrane occurs, with labour usually beginning about 24 hours later.
- d. The fetus weighs about 3300 grams (about 7-7.5 pounds). [2]

## Symptoms

### Trimester 1 (week 1 to week 12)

- Extreme tiredness
- Tender, swollen breasts.
- morning sickness
- Cravings or distaste for certain foods
- Mood swings
- Constipation
- Need to pass urine more often
- Headache
- Heartburn
- Weight gain or loss [15]

### Trimester 2 (week 13 to week 28)

- Body aches, such as back, abdomen, groin, or thigh pain
- Stretch marks on the abdomen, breasts, thighs, or buttocks
- Darkening of the skin around the nipples
- Patches of darker skin, usually over the cheeks, forehead, nose, or upper lip. Patches often match on both sides of the face. This is sometimes called the mask of pregnancy.
- Numb or tingling hands, called carpal tunnel syndrome
- Itching on the abdomen, palms, and soles of the feet.
- Swelling of the ankles, fingers, and face [2].

### Trimester 3 (week 29 to week 40)

- Shortness of breath
- Heartburn
- Swelling of the ankles, fingers, and face.
- Haemorrhoids
- Tender breasts, which may leak a watery pre-milk called colostrum
- Trouble sleeping
- The baby "dropping", or moving lower in abdomen
- Contractions [1,2].

During pregnancy many physiological adaptations are takes place which may result in serious adjustments in endocrine system such as serum and urine electrolytes, secretion of endocrine hormones and also structural changes of endocrine glands. The Endocrine tests during pregnancy have need of proper awareness of the changes of endocrine system [3].

### Types of Pregnancy induced Endocrine Disorders:

- Pituitary disorders
  - Adrenal disorders
  - Thyroid disorders [4].
1. **Pregnancy induced pituitary disorders:**
    - i. Prolactinoma
    - ii. Acromegaly

- iii. Craniopharyngioma
- iv. Diabetes [5].

### 2. Pregnancy induced Adrenal Disorders:

- i. Cushing's Syndrome
- ii. Primary hyperaldosteronism
- iii. Pheochromocytoma [6].

### 3. Pregnancy induced thyroid disorders

- i. Hypothyroidism
- ii. Hyperthyroidism [7].

The most prevalent endocrine disorders observed are thyroid disorders and diabetes.

### Gestational Diabetes Mellitus

GDM is one of the most prevailing medical intricacies of pregnancy, and its skimpy treatment can lead to sternt adverse health effects for the procreator and juvenile [8]. The raise in the extent of GDM also leads to a substantialpecuniary burden and deserves greater attention and awareness [9]. Mothers with GDM are at risk of cultivating gestational hypertension, pre-eclampsia and termination of pregnancy via Caesarean section. Mostly GDM symptoms are not observable. [10].

### Risk factors

- Age
- Obesity
- Multiple pregnancies
- Family history
- Changes in dietary

### Pathophysiology

Pregnancy is a plight constituted by heightened insulin resistance that begins during amid of gravidity. In the dilatory phase of pregnancy, insulin sensitivity descends by half. The main reinforceof insulin resistanceis:

1. Increased maternal adiposity
2. Insulin desensitizing effects produced by the placenta [11].

Placenta propagateshuman chorionic somatomammotropin (HCS) bound and free cortisol, estrogen and progesterone. HCS arouse pancreatic secretion of insulin in the fetus and hinderperipheral uptake of glucose in the source. [12]As the pregnancy continues the proportionof the placenta also expands accordingly leading to more insulin – resistant state. In non- diabetic pregnant women, the 1<sup>st</sup> and 2<sup>nd</sup> phase insulin responses countervail for the shrinkage in insulin sensitivity and is corelated with  $\beta$ -cell hypertrophy and hyperplasia. Women who have a scantiness in this appended insulin secretory capacity foster GDM [13].

### Diagnosis

Sno.	LAB TESTS	NORMAL VALUE
1.	HbA1C	4.5-5.7%
2.	Fasting blood sugar	70-100 mg/dl
3.	Post blood sugar	70-110 mg/dl
4.	GCT	100-150 mg/dl

### Treatment

Monitoring glucose levels at the dormitory and intervening the diet and exercise plan accordingly is the modest way to control GDM rather than using medication. Controlled sugar and carbohydrate intake and minimal exercises every day is the prominent way to keep control of blood glycaemic levels. At the severe times when the blood sugar levels are out of the control

pharmacological therapy is initiated depending on the patient's condition. [16]

#### Pharmacological therapy:

- INSULIN: if the threshold of the fasting glucose level is greater than 95 mg/dl and post fasting levels greater than 120 mg/dl than insulin therapy is recommended. It is the one of the effective gold standard therapies with minimal side effects declared by WHO.
- METFORMIN: it is an oral hypoglycaemic agent which improves insulin tolerance and sensitivity during pregnancy [17].

#### Thyroid Disorder

Thyroid hormones modulates metabolism and it instigates the way the body utilizes energy and impinge nearly every organ in the body. Elevated levels thyroid hormone is called hyperthyroidism and depreciated levels of thyroid hormone is called hypothyroidism. Thyroid hormone plays a captious role amid pregnancy both in the eventuation of the sound baby and mothers health. Women with thyroid complication can have a robust pregnancy and Armor their foetus by acknowledging the pregnancy effect on thyroid function by prospecting patients' thyroid function and making interventions accordingly [21].

#### pathophysiology

Pregnancy allied hormones human chorionic gonadotropin (HCG) and estrogen can surge thyroid levels in the blood. HCG tepidly innervate the thyroid to produce more thyroid hormone. Increased estrogen prevails higher levels of thyroid-binding globulin, also known as thyroxine-binding globulin, a protein that transit thyroid hormone in the blood [21]. These hormonal changes can at times make thyroid function difficult during pregnancy to interpret. Thyroid hormone is pivotal for the amassment of the baby's brain and nervous system. In the course of first trimester, the fetus depends on the mother's cache of thyroid hormone, which comes through the placenta. At about 12<sup>th</sup> week, the blastula's thyroid impels to function by itself [22].

#### Risk factors

- Age
- Weight
- Family history
- Multiple pregnancies
- preeclampsia
- miscarriage
- premature birth
- low birth weight [21].

#### Diagnosis

- Thyroid stimulating hormone [18].

Sno.	Trimester	Values
1.	First	0 – 2.5 mIU/L
2.	Second	0.2 -3.0 mIU/L
3.	Third	0.3 – 3.5 mIU/L

- T3 [19]

Sno.	Trimester	Values
1.	First	1.21 – 1.32 ng/ml
2.	Second	1.13 – 1.64 ng/ml
3.	Third	1.16 – 1.51 ng/ml

- T4 [20]

Sno.	Trimester	Values
1.	First	0.95 – 1.53 ng/dl
2.	Second	0.87 – 1.45 ng/dl
3.	Third	0.87 – 1.54 ng/dl

#### Treatment

Thyroid level fluctuation is the most common endocrinal change in the women from the age puberty. Alteration during pregnancy might have effect on the fetus as well therefore, care must be taken and appropriate medication and life style modifications must be done like, controlled iodine intake, mild exercises, avoidance of sea food etc.. depending upon the patient's condition and her hormone levels thyroid supplements are prescribed with appropriate dose.

Thyroxine supplements increase basal metabolic rate and uprise the utilization and mobilization of glycogen stores which in turn promotes gluconeogenesis thereby involves growth development and stimulates protein synthesis [23].

#### CUSHING'S SYNDROME:

Cushing's Syndrome is an adrenal disorder results when the adrenal gland produces large amounts of a hormone named Cortisol [24].

#### Symptoms include:

- Hirsutism
- Gaining weight
- Pinkish stretch marks on the body
- Buffalo hump
- Fatigue
- Muscle weakness
- High blood pressure
- Pigmentation
- Bone loss
- Retards growth in children.
- Irregular periods in women.
- In males it results in infertility and decreased sexual activity [25].

#### Pathophysiology:

Hypothalamus produces corticotropin releasing hormone (CRH) which stimulates the pituitary gland to release ACTH. The ACTH thus produced is released into petrosal venous sinuses and stimulates the adrenal gland, which produces Cortisol and other steroidal hormones [26].

#### Treatment:

The first line therapy includes the surgery with or without any radiation therapy. The second line treatment includes the administration of glucocorticoid antagonist to the patients who are diabetic. ketoconazole, metyrapone, and etomidate are used to inhibit the steroid synthesis. cyproheptadine, Valproic acid and octreotide are used to modulate the release of pituitary ACTH [27].

#### CONN'S Syndrome

It is the rarest disorder caused when the aldosterone hormone is excessively released by the adrenal gland [28].

#### Symptoms

- High blood pressure
- Hypokalaemia
- Thirstiness
- Fatigue

- Weakness
- Muscle cramps
- Urine urgency
- Visual disturbances [29].

#### Pathophysiology

The Underlying issues like idiopathic bilateral adrenal hyperplasia results in the secretion of excessive aldosterone. The aldosterone shows its action on epithelial sodium channels of collecting duct results in the sodium reabsorption. Excessive aldosterone leads to excessive sodium reabsorption and results in hypokalaemia and also metabolic alkalosis [30].

#### Congenital Adrenal Hyperplasia

It is a group of recessive autosomal disorders affecting the biosynthesis of cortisol [31].

#### Symptoms

- Growth alterations
- Early puberty
- Irregular periods
- Deepening voice
- facial hair in females
- Enlarged Clitoris
- Alterations in blood pressure, blood sugar levels [32].

#### Pathophysiology

CAH is developed by the mutation of the genes of the enzymes that acts on cholesterol in the biochemical steps to yield mineralocorticoids, glucocorticoids and other steroidal hormones by the adrenal gland [33].

#### Treatment:

The combination treatment of Mineralocorticoids, glucocorticoid, Flutamide and Aromatase inhibitor. GnRH antagonists are used to suppress the early puberty [34].

#### Adrenal Insufficiency

Adrenal insufficiency is a clinical presentation of the shortfall of the glucocorticoids with or without the deficiency of Mineralocorticoids [35].

#### Symptoms

- Diarrhea
- Nausea
- Vomiting's
- Hypoglycaemia
- Muscle weakness
- Fatigue
- Weight loss
- Loss of appetite
- Abdominal pain [36].

#### Pathophysiology

Adrenal insufficiency is majorly due to the occurrence of damage to the adrenal gland. The autoimmune antibodies causes damage to the enzymes of the cortex of the adrenal gland. Several genetic factors are also responsible for adrenal insufficiency [37].

#### Treatment

Corticosteroids such as hydrocortisone and dexamethasone and Fludrocortisone are used in the replacement of hormones cortisol and aldosterone [38].

#### Hyper Para Thyroidism

This condition arises when the parathyroid gland secretes high amounts of parathormone [39].

#### Symptoms

- Depression
- Abdominal pain
- Weakness
- Fatigue
- Thirsty
- Constipation
- Loss of appetite [40]

#### Pathophysiology

The parathyroid hormone shows its action by binding to cell surface G protein coupled receptors. cAMP is the secondary messenger of Parathormone. PTH also synthesizes the other secondary messengers like inositol triphosphate and diacyl glycerol to mobilize intracellular calcium. The PTH shows its direct action on bones and various other non-targeting organs and indirect action on homeostasis of the minerals finally leads to the calcium insufficiency and demineralisation of bones [41].

#### Treatment

Calcimimetics which mimics the circulating calcium in the blood Cinacalcet or the combination of cinacalcet and vitamin D analogues, bisphosphates are used in the Treatment Hormone replacement therapy can be chosen in the female of menopause with osteoporosis [41].

#### Diabetes Insipidus

Diabetes insipidus is an uncommon and treatable condition which produces unsatiable thirst and large volumes of colourless and odourless urine [42, 43].

#### Symptoms

- Peeing more than 3lit in a day
- Bed wetting
- Severe thirst
- Pale and colourless urine
- Dehydration
- Muscle pains
- Weakness
- Fatigue
- Loss of conscious
- Nausea and vomiting [44].

#### Pathophysiology

Diabetes insipidus is directly relates to the amount of ADH released and also the sensitiveness of the terminal distal convoluted tubule and collecting tubule to the ADH. A wide range of changes will be takes place in the body when the mechanism of ADH is disrupted. Such as water loss, electrolyte imbalance, changes in osmolality of serum and urine [45].

#### Treatment

Synthetic hormone Desmopressin and chlorpropamide are generally used to treat diabetes insipidus. In some patients with nephrogenic diabetes insipidus, a diuretic called hydrochlorothiazide will be effective [46].

#### Conclusion

Endocrinal changes during pregnancy are common. To have normal and healthy pregnancy and baby its suggested to undergo prior screening of the hormonal functions and

perform interventions and therapy accordingly to surpass complications.

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