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Determination of Reference Interval of Oestrogen during Each Trimester of Pregnancy

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ABSTRACT

Background: Hormonal milieu of pregnancy may be an important determinant of subsequent cancer and other chronic diseases both in the mother and the offspring. Depending on the outcome of interest, hormone concentrations measured at different periods during pregnancy may be of relevance. A reference range of these hormones is needed to understand any deviation in pathological condition.

Aims and Objective: Among several important hormones, oestrogen is selected and this study is aimed to establish trimester specific and assay-specific reference interval of oestrogen .

Materials and Methods: In this study, a total of 276 pregnant ladies were included as study subjects with a distribution of 81, 111, and 84 in 1st, 2nd & 3rd trimester respectively. Selection of subjects was done using pre-defined inclusion and exclusion criteria. Serum of first trimester, second trimester and third trimester of pregnant women, was analysed for estradiol by Enzyme linked immune sorbent assay .

Result: After the end of our study that serum estradiol level was found to be increased gradually throughout pregnancy and their reference range was established in our laboratory.

Conclusion: Trimester specific reference interval of estradiol was measured by ELISA and estradiol level increased gradually throughout pregnancy.

Keywords: estradiol, reference interval, trimester.

INTRODUCTION

Normal reproductive endocrine function involves a wide variety of hormones controlled by a number of intricate feedback mechanism. This is particularly true during the menstrual cycle, in which serum levels of luteinizing hormone (LH), follicle-stimulating hormone(FSH), estradiol, and progesterone follow a cyclical pattern closely coordinated by hypothalmic-pituitary-gonadal axis (1,2). Accurate establishment of the pregnancy duration is essential for optimum pregnancy care. It is used to assess pregnancy normality and mother/fetus well-being, and to potentially guide delivery timing.

The hormonal milieu of pregnancy may be an important determinant of subsequent cancer and other chronic diseases both in the mother and the offspring (3, 4). Depending on the outcome of interest, hormone concentrations measured at different periods during pregnancy may be of relevance.

For instance, hormones measured in early pregnancy, during which fetal organogenesis takes place, may be important when neurodevelopmental conditions in the offspring are of interest, whereas hormone concentrations during late pregnancy may be relevant in relation to maternal risk of breast and ovarian cancers, given evidence that complete pregnancies are associated with these malignancies (5, 6).

Estradiol (E2) and progesterone (P) produced by the corpus luteum regulate initial stage of pregnancy and sustain pregnancy until the luteal–placental shift. Therefore, hormone levels in early luteal phase may be useful in predicting the likelihood of conception as well as pregnancy outcome.

The fetal adrenal provides DHEAS as precursor for placental production of estrone and estradiol. The maternal contribution of DHEAS to total estrogen synthesis must be negligible because, in the absence of normal fetal adrenal glands. The fetal adrenals secrete more than 200 mg of DHEAS daily, about 10 times more than the mother. Estriol is the estrogen produced in greatest quantity during pregnancy; estrone and estradiol are derived equally from fetal and maternal precursors. A rise in estrone begins at 6–10 weeks, and individual values range from 2 to30 ng/mL at term (7, 8).

If reference range of this hormone is available, then only it can be understood whether any deviation had occurred or not which can be a result of some underlying pathological condition. Most of the data regarding this is obtained from foreign literature, where the age group of pregnancy varies a lot with respect to that of Indian population. Thus it seems to be necessary to establish reference range of these hormones by a systematic manner.

Materials and Methods

This study was undertaken in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, NRS Medical College and Hospital, Kolkata, West Bengal. The approval of the study was taken from the Institutional Ethics Committee of NRS Medical College & Hospital. A written informed consent was taken from every patient participating in this study.

All healthy pregnant females having no history of pre existing disease or any complication were included in this study. Those who had treatment for infertility, or found to have impairment in concentration of blood haemoglobin, fasting glucose, serum urea, creatinine, liver function and lipid profile, were excluded in this study.

The cases were selected from the pregnant females attending Antenatal clinics in the Department of Obstetrics and Gynaecology of N.R.S. Medical College & Hospital, Kolkata, according to inclusion and exclusion criteria.

Proper history was taken regarding age, parity, detail history of previous pregnancy, history of hypertension, family history, history of taking any medicine, and history of whether suffering from any other medical disorders.

An amount of 5 ml blood was collected from each patient aseptically by disposable syringe and was allowed to clot. The clotted blood sample was centrifuged at 2500 rpm for 5 minutes. The serum was separated, analysed and was kept in aliquots and stored in minus forty degree Centigrade (-40°C) in deep freezer. On the day of analysis, they were thawed and analysed for estradiol by Enzyme linked Immunosorbant assay.

Results

In this study, a total of 276 pregnant ladies were included as study subjects. The trimester wise distribution of study population is given in Table 1, which is 81, 111, and 84 in 1st, 2nd & 3rd trimester respectively. Table 2 shows trimester specific reference interval of estradiol. Selection of subjects was done using pre-defined inclusion and exclusion criteria, following a routine clinical and investigational procedure. The values of the hormones were extrapolated in Microsoft excel sheet and calculation was done using MedCalc software (version 18.9).

Discussion

Hormones play an important part in defining the optimal conditions for human life to start. Up until now, there is a struggle to reliably measure and reproduce hormonal concentration during gestation. During the first 9 weeks of pregnancy the corpus luteum and, to a lesser extent, the maternal ovary and the adrenal cortex, contribute to circulating concentrations of maternal estradiol, estrone, and progesterone. After this period, the placenta becomes the predominant source of maternal steroids. Gradually, for estrogens and progesterone, the major site of synthesis shifts to the placental trophoblast (9,10,11) and their concentrations continue to increase Reference value is calculated based on mean, median and the subset of reference individuals. The reference values can be further partitioned according to age and parity. In this study, the age distribution of study population is between 17 to 36years. Among them, 51 were primi gravida women and 225 were multigravida. Reference interval is the interval between and including two reference limits, between maximum and minimum values. It is designed as the central interval of values bounded by the lower reference limit and the upper reference limit at certain designated percentiles.

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According to table 2 the reference interval of serum estradiol for first trimester based on robust method was 19.41-3494.44 pg/ml, for second trimester was 97.46-9910.39pg/ml, for third trimester was 1840.97-47527.78pg/ml. This provides here a useful image of the reference interval and distribution.

The study of Melnick AP et al. represented decreased odds of live birth in patients with E2 levels of ≤50 pg/mL and in patients with levels of 51–100 pg/mL compared with patients with levels >100 pg/mL. They found that lower E2 levels are associated with significantly increased odds of biochemical and ectopic pregnancies and significantly decreased odds of a live birth.

Estradiol concentrations in maternal serum rise steadily from the first trimester until term and decline rapidly in the post-partum period, as in the studies of Nelson et al., 2010; Smith et al., 2009; and our finding is similar with these studies.

Third trimester maternal estriol is elevated in high birth weight pregnancies in the study of Nagata et al, 2006,

There are few previous data characterising hormone variations in the first trimester. Our results for first compared with subsequent full-term pregnancies confirm previous findings of higher oestradiol (Bernstein et al, 1986).

Conclusion

This study was undertaken with the aim to establish trimester specific and assay-specific reference interval of estrogen in healthy pregnant female in a tertiary care hospital of Kolkata. No such study is so far available from Kolkata or North East region of India. Most of the data regarding this is obtained from foreign literature, where the age group of pregnancy varies a lot with respect to that of Indian population. Reference interval of estradiol is found to be19.41pg/ml to 3494.44pg/ml in first trimester, 97.46pg/ml to 9910.39pg/ml in second trimester and 1840.97pg/ml to 47527.78pg/ml in third trimester. The study needs further validation.

Table 1: Showing number of pregnant ladies in each trimester

Sl.no	Trimester	Number of study subjects
1	First	81
2	Second	111
3	Third	84

Table 2: Reference Interval of Estradiol (pg/ml)

Trimester	Lower limit	Confidence interval (90%)	Upper limit	Confidence interval (90%)
First (n=81)	19.41	11.72-33.29	3494.44	2516.48-5242.24
Second (n=111)	97.46	64.36-159.67	9910.39	6293.18-15557.36
Third (n=84)	1840.97	1364.14-2669.24	47527.78	34463.77-66453.08

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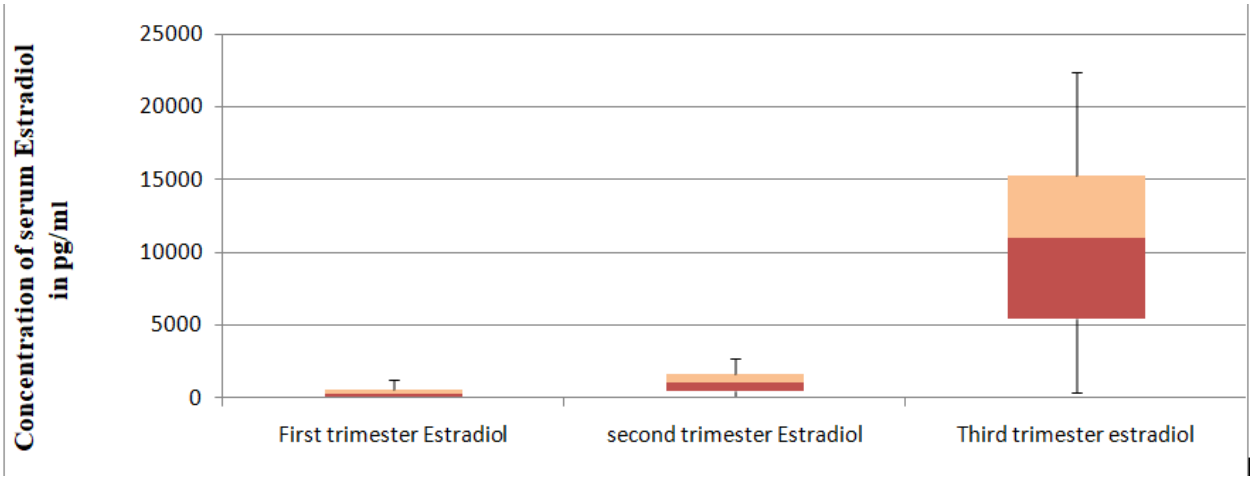

Figure 1: Reference values of estradiol of pregnant subjects in each trimester

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