Cross-sectional study of serum parathyroid hormone level in high-risk pregnancies as compared to nonpregnant control

J. B. Sharma, Subhadra Sharma¹, B. R. Usha, Manisha Yadav, Sunesh Kumar, A. K. Mukhopadhyay¹
Departments of Obstetrics and Gynaecology and ¹Lab Medicine, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Objectives: To note the value of serum parathyroid hormone (PTH) levels in normal and high-risk pregnancies (HRP) in patients attending antenatal visits at All India Institute of Medical Sciences (AIIMS). Materials and Methods: This is a cross-sectional study where a total of 282 patients attending Gynecology Outpatient Department at AIIMS, New Delhi were recruited. Among the 282 subjects, 251 were pregnant, and 31 were controls. The serum was tested for serum PTH levels using Beckman coulter access 2 immunoassay. Results: The median value of PTH level in pregnant women was 31.6 pg/ml with range being 0.8–505.5 pg/ml in contrast to 45.9 pg/ml with range being 19–102.7 pg/ml in nonpregnant female. This difference was statistically significant (P = 0.0012). There was no significant difference in median level of PTH in different age group. Although the median PTH levels were lower in second trimester (25.25 pg/ml) than in first trimester (35.5 pg/ml) and in third trimester (32.4 pg/ml), the difference was not statistically significant. There was no significant difference in PTH level in HRP (median value – 31.6 pg/ml) as compared to low-risk pregnancies (31.5 pg/ml). Conclusion: Serum PTH levels are significantly lower during pregnancy as compared to nonpregnant state. However, age, parity, and HRP did not alter PTH level during pregnancy.

Key words: High-risk pregnancy, parathyroid hormone, parity

INTRODUCTION

Parathyroid hormone (PTH) is a very essential hormone in calcium homeostasis. It has a very short half-life of 5 min and is influenced by subtle changes in serum calcium levels. Calcium requirement increases during pregnancy. Maternal PTH levels are positively associated with birth weight, fetal upper arm, and calf circumferences.[1] Parathyroid hormone regulates feto-placental mineral homeostasis and skeletal development and stimulates placental calcium transfer.[2]

Pregnancy and perinatal period are hallmarked by alterations in calcium homeostasis. The regulation of calcium homeostasis involves PTH, 1,25-dihydroxyvitamin D (1,25(OH)²D) and calcitonin (CT) but the exact role of each in pregnancy and in the 1st day of life is not well understood. Some authors found high amino-terminal PTH levels and increased biological activity of PTH in the third trimester of pregnancy[3-7] whereas others showed normal values of the carboxyl-terminal,[8] amino-terminal,[9] and intact[10,11] hormone.

Corresponding Author: Dr. J. B. Sharma, Department of Obstetrics and Gynaecology, Room No. 3056, 3rd Floor, Teaching Block, All India Institute of Medical Sciences, New Delhi -110 029, India. E-mail: jbsharma2000@gmail.com

Access this article online

Quick Response Code: 
Website: www.ijem.in
DOI: 10.4103/2230-8210.172288

Cite this article as: Sharma JB, Sharma S, Usha BR, Yadav M, Kumar S, Mukhopadhyay AK. Cross-sectional study of serum parathyroid hormone level in high-risk pregnancies as compared to nonpregnant control. Indian J Endocr Metab 2016;20:92-6.
During pregnancy, the requirement of the growing fetus for calcium generally results in profound changes in maternal calcium homeostasis to allow for the active transport of calcium across the placenta.\(^1\) Similarly, lactation requires the active transport of large quantities of calcium for the production of milk.\(^6\)

**Materials and Methods**

This cross-sectional study was done during November 2012 and March 2013. Ethical clearance was obtained from our institutional ethics committee. A total of 282 patients were included in the study after taking informed consent. These were either pregnant ladies attending the antenatal clinic at All India Institute of Medical Sciences or healthy nonpregnant ladies presenting with simple gynecological complaints excluding malignancies or other major morbidities. We obtained blood samples from 251 pregnant ladies, and other 31 non pregnant women were included as controls. We drew 2 ml of venous blood in a plain vial, and the serum was assayed for PTH level by double sandwich assay.

All pregnant women irrespective of their age, gestational age, and high-risk status were recruited. High-risk pregnancies (HRP) included gestation related high-risk factor (e.g., preeclampsia) or preexisting medical disease (e.g., cardiac disease). Pregnancies with intrauterine death, miscarriage, or sepsis were excluded.

The blood sample was centrifuged, and the serum stored at \(-20^\circ\text{C}\). PTH assay was done on Access 2 Immunoassay System, Beckman Coulter, USA. The access intact PTH (iPTH) assay is a two-site immunoenzymatic (“sandwich”) assay. The Beckman coulter access 2 analyzer is a random access immunoassay instrument. The test was performed using dioxetane-based chemiluminescent (LumiPhos) and a chemiluminescent detector. Unfortunately, due to financial constraints, we could not perform Vitamin D levels in our study.

**Statistics**

For variables with normal distribution curve, mean ± standard deviation is used; \(P\) value is calculated by Students \(t\)-test and ANOVA (for multiple variables). For variables with nonnormal distribution curve, median with minimum and maximum values is used. The test of significance used initially is Kruskall–Wallis test to note \(P\) value.

If the \(P < 0.05\) and if multiple variables are found, then Ranksum (Mann–Whitney) test is applied for post-hoc analysis to further note the significance. The software used for the analysis is SPSS version 19.0 (IBM, Armonk, NY, USA).

**Results**

A total of 282 women were recruited, among whom 251 were pregnant, and another 31 were nonpregnant. The characteristics of women are given in Table 1. There were 88 (35.1%) primigravidae and 163 (64.9%) multigravidae in the study. There were 71 (28.3%), 76 (30.3%), and 104 (41.4%) women in first, second, and third trimester, respectively in the study.

Correlation of serum PTH level with age is shown in Table 2. Although the median PTH levels were lowest (28.1 pg/ml) in 30–34 year age group as compared to 20–24 years (34 pg/ml), 25–29 years (34.9 pg/ml), and above 35 years (34.5 pg/ml), the difference is not statistically significant. Correlation of serum PTH level with parity and gestation is shown in Table 3.

The median PTH level were similar in primigravidae (30 pg/ml) and multigravidae (31.6 pg/ml), and the difference is not statistically different \((P = 0.15)\). Although
the median level of PTH were lower (25.5 pg/ml) in second trimester as compared to first trimester (35.5 pg/ml) and third trimester (32.4 pg/ml), the difference was not statistically significant (P = 0.10).

Correlation of serum PTH level in pregnant and nonpregnant female is shown in Table 4. The serum PTH levels are lower in pregnant women compared to pregnant women and difference is statistically significant (P = 0.0012).

Correlation of serum PTH level in high-risk and low-risk pregnancies is shown in Table 5. There were 77 pregnancies with at least one high-risk factor in them. These are labeled as HRP. Among the 77 HRP, 20 had gestational diabetes, 16 had heart disease, 13 had intrahepatic cholestasis of pregnancy, 11 had thyroid disorders (9 had hypothyroidism and 2 hyperthyroidism), 11 had anemia, 9 had coagulation disorders, 9 had hypertensive disorders of pregnancy, and another 3 had epilepsy. Of the 77 HRP with at least one high-risk factor, 13 had multiple high-risk factors. The comparison was made with PTH levels in high-risk pregnancy (31.6 pg/ml) and nonhigh risk pregnancy (31.5 pg/ml), and the difference was not statistically significant (P = 0.24).

**DISCUSSION**

During pregnancy, a remarkable series of physiologic adaptations aimed at preserving maternal calcium homeostasis and at providing the requirements for growth and skeletal mineralization of the fetus occur. The increase in serum 1,25(OH)2D levels during pregnancy may be the primary factor responsible for the maintenance of maternal calcium homeostasis.[9,13,14] The stimulus for enhanced renal and/or placental 1-alpha-hydroxylase activity is unclear. Some investigators have found a rise in PTH levels during pregnancy and suggested that PTH increase could stimulate 1,25(OH)2D synthesis.[3,15,16]

Maladkar et al. in their study on Vitamin D deficiency in Indian scenario found that insufficient outdoor activity, dark skin color, and poor dietary calcium account for Vitamin D deficiency in the country. And this deficiency is linked with preeclampsia, gestational diabetes mellitus, preterm labor, and increased chances of cesarean delivery. Marwah et al. studied 541 pregnant women and found a significant negative correlation between serum Vitamin D and iPTH.[14] In our study, we did not find an increase of serum PTH level in pregnant women, suggesting that 1,25(OH)2D increase is not caused by augmented PTH secretion. These data do not confirm the “physiologic” hyperparathyroidism of pregnancy previously reported.[3,15,16]

Gillette et al. have found that nephrogenous c-AMP and tubular reabsorption of phosphate did not change during pregnancy.[17] Thus, the biological actions of PTH are not enhanced; therefore other mechanisms could be responsible for the increased 1,25(OH)2D levels found during pregnancy.

Adverse pregnancy outcome such as preeclampsia and preterm labor are associated with calcium deficiency and, therefore, physiologic hyperparathyroidism is reported to be associated. As we are supplementing all pregnant females with calcium and Vitamin D, no raised serum PTH level were found in high-risk pregnant females.

Conflicting information regarding PTH concentrations in pregnancy[18-20] may reflect the use of antibodies with different specificities to PTH and the heterogeneity of inactive fragments of the hormone that result from peripheral metabolism and from increased glomerular filtration that occur in pregnancy.

Naylor et al. reported a longitudinal study with 16 subjects. PTH levels were found to decrease by 47% during the first trimester of pregnancy and subsequently increased but remained below baseline.[8,9,21]

A study by Ardawiet et al. found that intact-PTH concentrations increased from 1.31 pmol/l in the first trimester to 2.26 pmol/l in the second trimester, but then declined to values of the first trimester and increased significantly postpartum. While pregnancy induced, increase in calcitriol concentration was postulated to be the primary mediator of changes in maternal calcium metabolism.[22] Similarly, Rasmussen et al. in their study on 20 apparently healthy pregnant women concluded that

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**Table 4: Correlation of serum PTH level in pregnant and nonpregnant female**

| Characteristics          | Number of women | Range of PTH level (in pg/ml) | Median PTH level (in pg/ml) | P       | Significance |
|--------------------------|-----------------|------------------------------|----------------------------|---------|--------------|
| Nonpregnant women        | 31              | 19-102.7                     | 45.9                       | 0.0012  | Significant  |
| Pregnant women           | 251             | 0.8-505.5                    | 31.6                       |         |              |

PTH: Parathyroid hormone
pregnancy is not associated with a state of physiological hyperparathyroidism.\textsuperscript{23}

Another longitudinal study also reported PTH to decrease during pregnancy in comparison to their prepregnant levels ($P < 0.01$).\textsuperscript{24} Davis \textit{et al.} studied serum iPTH in pregnant women by immuno-radiometric assay and found a decline during pregnancy and attributed the concept of physiological hyperparathyroidism of pregnancy to traditional RIA methods which detect the inactive PTH fragments and thus high value of PTH.\textsuperscript{23} In our study, we found PTH levels to be reduced during pregnancy in comparison to nonpregnant controls.

**CONCLUSION**

No support for the concept of “physiological hyperparathyroidism” of pregnancy could be demonstrated in the present work. More studies with larger sample size will be required to formulate a nomogram of PTH during pregnancy.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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