Research Paper

Volume : 2 | Issue : 3 | Mar 2013 • ISSN No 2277 - 8179

Study of Pregnancy Associated Polypeptide-A & B – Human Chorionic Gonadotropin in Relation to The Adverse Pregnancy Outcome & Fetal Chromosomal Anomalies

Medical Science

KEYWORDS:

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ABSTRACT

Study of Pregnancy Associated Polypeptide-A & B – Human Chorionic Gonadotropin in relation to the adverse pregnancy outcome & fetal chromosomal anomalies .Introduction : In our prospective study , we have screened 200 pregnant women in the first trimester of pregnancy by doing B-hcg & Papp-A levels. We tried to find out what is the average serological levels of B-hcg & Papp-A in Indian Pregnant mothers in first trimester of pregnancy. We have studied the clinical outcome of pregnancy in patients having serological levels of B-Hcg & Papp-A far away from the median.Aims & Objectives :To study the variation of b-hcg & Papp-A levels in the first trimester of pregnancy & its correlation to the pregnancy outcome .To study the incidence of fetal anomalies (chromosomal) in view of abnormal serological levels of B-hcg & Papp-A.Material & Methods : Prospective trial has conducted at Bharati Hospital & Research Centre, Pune where 200 pregnant patients are included into the trial. Every patients included into the trial are counseled & consented to the serological evaluation in the first trimester of pregnancy. During the 11-13 weeks of pregnancy blood is collected in a vacutainer & sent for analysis at PerkinElmer Lab Chennai. Reports are generated in Multiple Of Median & their values are studied. For analysis at the PerkinElmer lab , Delfia express technology is used which assures to be a correct level.Observations : Average B-Hcg level found in the study is 1.2 MOM in 200 patients . In 2 patients B-Hcg level is found to be more than 5 MOM while in 14 patients level of B-hcg was less than 0.5 MOM.In Patients having b-hcg levels more than 5 MOM were found to have Papp-A level less than 0.5 MOM , which on further screening found to have Downs Fetus. Average Papp-A level found in the study 1.1 MOM in 200 patients we have screened. 17 patients in our study group were having Papp-A levels less than 0.5 MOM. In these patients 2 patients were having B-Hcg levels more than 5MOMs were found to have Downs Fetus on further screening , while rest of the patients have normal B-hcg levelsConclusion :B-hcg as a sole determinant of pregnancy outcome cannot be effective because variation in B-Hcg levels away from the average MOM values has not been found with significant adverse pregnancy outcome. Papp-A level , if low ie. less than 0.5 MOM has been associated with Preterm labour & increased incidence of fetal growth restrictions (associated with pre-eclampsia).

Introduction :

Maternal levels of pregnancy-associated plasma protein-A (PAPP-A) and free β human chorionic gonadotropin (β hCG) has been shown to be effective in first trimester screening for chromosomal abnormalities, primarily trisomy 21, 13 and 18(1-4). In combination with nuchal translucency measured by ultrasound the risk for trisomi 13, 18 and 21 can be calculated. The sensitivity of this screening test is estimated as high as 90% for detecting trisomy 21, with a false positive rate of only 5%(5). The screening test , called First Trimester Screening now offered to all pregnant women; the maternal serum levels of PAPP-A and free B- hcg are measured through a blood sample obtained between gestational week 8+0 and 13+6 and the ultrasound is performed in gestational age 11+3 - 13+6. Previous studies suggest that there might be an adjunct value to the screening, because maternal levels of PAPP-A and free β hCG measured in first trimester in addition to screening for chromosomal abnormalities, may provide a potential screening tool to identify women at increased risk of subsequent adverse outcome of pregnancy.

In our prospective study , we have screened 200 pregnant women in the first trimester of pregnancy by doing B-hcg & Papp-A levels. We tried to find out what is the average serological levels of B-hcg & Papp-A in Indian Pregnant mothers in first trimester of pregnancy. We have studied the clinical outcome of pregnancy in patients having serological levels of B-Hcg & Papp-A far away from the median.

Aims & Objectives ;

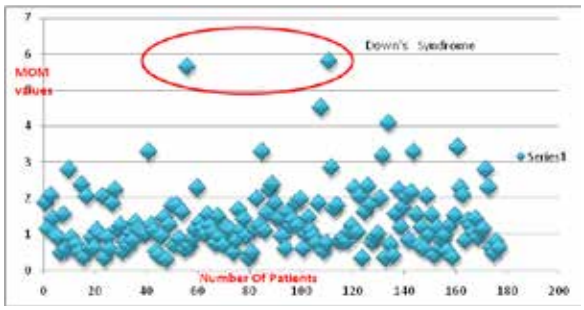
To study the variation of b-hcg & Papp-A levels in the first trimester of pregnancy & its correlation to the pregnancy outcome To study the incidence of fetal anomalies (chromosomal) in view of abnormal serological levels of B-hcg & Papp-A.

Material & Methods

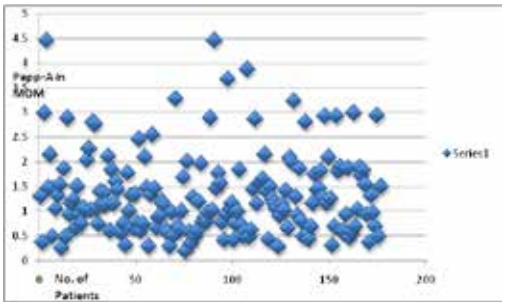
Prospective trial has conducted at Bharati Hospital & Research Centre, Pune where 200 pregnant patients are included into the trial. Every patients included into the trial are counseled & consented to the serological evaluation in the first trimester of pregnancy. During the 11-13 weeks of pregnancy blood is collected in a vacutainer & sent for analysis at PerkinElmer Lab Chennai. Reports are generated in Multiple Of Median & their values are studied. For analysis at the PerkinElmer lab , Delfia express technology is used which assures to be a correct level.

Observations ;

Average B-Hcg level found in the study is 1.2 MOM in 200 patients . In 2 patients B-Hcg level is found to be more than 5 MOM while in 14 patients level of B-hcg was less than 0.5 MOM.In Patients having b-hcg levels more than 5 MOM were found to have Papp-A level less than 0.5 MOM , which on further screening found to have Downs Fetus.

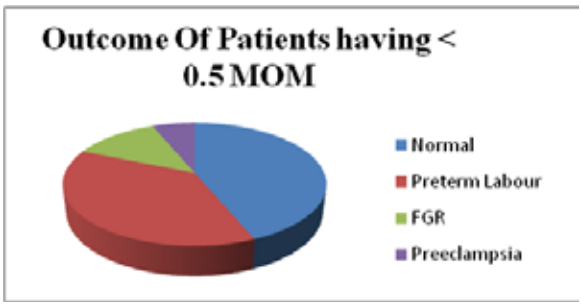


Average Papp-A level found in the study 1.1 MOM in 200 patients we have screened. 17 patients in our study group were having Papp-A levels less than 0.5 MOM. In these patients 2 patients were having B-Hcg levels more than 5MOMs were found to have Downs Fetus on further screening , while rest of the patients have normal B-hcg levels.



These patients we have further observed & were found to have

increased incidence of Preterm deliveries .Six patients were developed preterm deliveries on their consecutive follow up. Two patients had Fetal growth restriction associated with preeclampsia out of which one patient required termination of pregnancy because of uncontrolled hypertension.



Low B-hcg in the first trimester of pregnancy has not been found to be associated with any significant pregnancy outcome or any fetal anomalies. Combined assessment of B-hcg , Papp-A & their variations from the average MOM values are associated with certain chromosomal anomalies in the fetus. Higher MOM of B-Hcg & low level of Papp-A less than 0.5 MOM is associated with chromosomal anomalies in the Fetus.

Discussions

PAPP-A is a glycoprotein, that is derived from the syncytiotrophoblast and is present in the maternal circulation soon after implantation and increases in concentrations throughout pregnancy(6). It has been identified as a protease specific for insulin-like growth factor-binding protein-4 (IGFBP-4)(7). IGFBP-4 binds IGF-1 and IGF-2 inhibiting their interactions with cell surface receptors and therefore play a key role in regulating IGF activity. Because PAPP-A cleaves IGFBP-4, low levels of PAPP-A, are associated with higher levels of IGFBP-4 and consequently with lower levels of free IGFs. The IGFs play a role in the regulation of fetal growth by controlling uptake of glucose and amino acids in cultured trophoblast and are thought to have an important role in the autocrine and paracrine control of trophoblast invasion of the decidua(8-10). Low levels of IGFs are thus expected to result in impaired placental formation and implantation in early pregnancy leading to abnormal placenta function in the rest of the pregnancy, which again might lead to development of pregnancy complications that can be attributed to impaired placental function. In summary low levels of PAPP-A resulting in low levels of IGF might lead to abnormal development of the placenta in early pregnancy, which hypothetically might cause reduced fetal growth and adverse pregnancy and perinatal outcome.

β hCG is a part of the glycoproteine hCG produced by the syncytiotrophoblast(11). It is also present in the maternal circulation immediately after implantation and throughout the pregnancy, but with increasing levels until 10 weeks of gestation and then declines to a constant level from 20 weeks of gestation(12). Because β hCG is produced by the placental tissue, the maternal serum level of β hCG is thought to correlate with the amount of placental tissue and the placental function, and thus might be correlated with impaired fetal growth and adverse pregnancy and perinatal outcome.

Human chorionic gonadotropin interacts with the LHCG receptor and promotes the maintenance of the corpus luteum during the beginning of pregnancy, causing it to secrete the hormone progesterone. Progesterone enriches the uterus with a thick lining of blood vessels and capillaries so that it can sustain the growing fetus. Due to its highly negative charge, hCG may repel the immune cells of the mother, protecting the fetus during the first trimester. It has also been hypothesized that hCG may be a placental link for the development of local maternal immunotolerance. For example, hCG-treated endometrial cells induce an increase in T cell apoptosis (dissolution of T cells). These results suggest that hCG may be a link in the development of peritrophoblastic immune tolerance, and may facilitate the trophoblast invasion, which is known to expedite fetal development in the endometrium. It has also been suggested that hCG levels are linked to the severity of morning sickness in pregnant women.

Previous studies evaluating PAPP-A and free β hCG measured in first trimester in relation to adverse pregnancy outcome have provided conflicting results. PAPP-A is the most thoroughly investigated of the two markers and in relation to preterm delivery, the results are conflicting

(12-23), but the largest three of the studies have provided a significant association(15;16;18). Low levels of PAPP-A have more constantly been reported to be associated with intrauterine growth retardation(15-18;20;21;23;24) and miscarriage/intrauterine stillbirth(13;17;18;20;25-27), with only a few studies failing to confirm this(14;19;21). Only one study evaluated PAPP-A levels in relations to the causes of intrauterine stillbirth, and it showed that women with low PAPP-A had a 40 times increased risk of experiencing intrauterine stillbirth because of impaired placenta function(26).

Furthermore an association between low levels of PAPP-A and pregnancy-induced hypertension and pre-eclampsia has been suggested(13;15;18;20;21;28). Free β hCG measured in first trimester has only to a certain extent been evaluated in relation to pregnancy outcome, and the results show a great deal of controversy(13;15;16;18-20;22;25-27;28). Thus, the largest study evaluating free β hCG in relation to pregnancy outcome, only showed an association to miscarriage, whereas there was no relation to intrauterine growth retardation, preterm delivery or pre-eclampsia(18). However, other studies found low levels of free β hCG related to these outcomes but with less significance than PAPP-A(16;20;25).

Furthermore there is some evidence that elevated levels of free β hCG measured in second trimester are associated to pregnancy complications(30-31).No previous studies have evaluated PAPP-A and /or free β hCG in relation to neonatal complications, such as admission to the neonatal care unit, treatment for neonatal sepsis or need for assistent ventilation.

To our knowledge only three previous studies have evaluated PAPP-A and/or free β hCG in relation to fetal growth in first trimester; one study found low PAPP-A levels associated with the length of fetal bones such as humerus, femur and tibia in 10-14 weeks of gestation(32). Another study evaluated both PAPP-A and free β hCG as independent predictors of biparietal diameter (BPD), abdominal circumference (AC) and femur length (FL), and found both PAPP-A and free β hCG correlated with AC and FL but not with BPD in the second trimester(33) and yet another study found low PAPP-A levels correlated with fetal maxillary bone length(34). Thus, all these three studies suggests that PAPP-A and free β hCG are of importance regarding fetal growth. Furthermore, previous studies showed a correlation between CRL measured in first trimester and birth weight(35-36).

Intrauterine growth retardation, preterm delivery and pre-eclampsia are major determinants of perinatal mortality and morbidity. Much of the routine antenatal care involves detecting women at increased risk of these adverse events and targeting intensive monitoring and interventions against them, but oftenly they are detected at a time, where it is too late to provide the optimal intervention or they are not detected at all. It would be quite advantageous to identify women at increased risk in the first trimester or second trimester, because it then might be possible to offer treatment interventions, or at least, to institute increased surveillance for high risk pregnancies.

The previous studies that found an association between low PAPP-A and free β hCG levels in early pregnancy and adverse pregnancy and perinatal outcome, unfortunately found a relatively low sensitivity and positive predictive value. Thus, low PAPP-A or free β hCG levels alone seems to be a poor predictor of these outcomes, but maybe in combination with ultrasound the prediction value might be improved.

In summary previous studies suggests an association between low first trimester levels of PAPP-A and free β hCG and adverse pregnancy and perinatal outcome, even though the results still

Volume : 2 | Issue : 3 | Mar 2013 • ISSN No 2277 - 8179

show some controversy. To our knowledge no previous studies investigated a possible assoociation between low first trimester levels of PAPP-A and free β hCG and neonatal outcome beyond what is suspected from the perinatal outcome (e.g. preterm delivery and IUGR) and low first trimester levels of PAPP-A and free β hCG in relation to early fetal growth has only been studied to a limited extent. Since PAPP-A and free β hCG is measured in all pregnant women accepting the first trimester screening test, it would be advantageous if these measures, perhaps in combination with impaired fetal growth measured by ultrasound, could help identifying pregnant women at risk of subsequent adverse pregnancy and perinatal/neonatal outcome

Perspectives

With the present project we wish to achieve more information about the possible adjunct values of the two biomarkers PAPP-A and free β hCG, that is now primarily used in the first trimester screening for chromosomal abnormalities. We would like to know whether they, alone or in combination with ultrasound measures of fetal growth, can help identifying women at risk of adverse pregnancy or perinatal/neonatal outcome. If the results show an association with a high predictability it would be reasonable to consider the possibility of instituting increased surveillance for these high risk pregnancies, or maybe offer treatment interventions early in pregnancy, which in the long term might reduce perinatal mortality and morbidity due to these adverse outcomes.

Furthermore we hope that this project will bring increased knowledge about the mechanisms of pregnancy complications, such as preterm delivery, IUGR, intrauterin stillbirth, pregnancy-induced hypertension and pre-eclampsia.

Conclusion :

B-hcg as a sole determinant of pregnancy outcome cannot be effective because variation in B-Hcg levels away from the average MOM values has not been found with significant adverse pregnancy outcome. Papp-A level , if low ie. less than 0.5 MOM has been associated with Preterm labour & increased incidence of fetal growth restrictions (associated with pre-eclampsia). In patients having higher B-hcg levels & low Papp-A levels are at risk of having chromosomal anomalies ies. Downs Syndrome. Though deviation from normal MOM values of these serological values may suggest us increased incidence of adverse outcome but has got very less sensitivity & specificity . Combination of Ultrsound markers of fetal chromosomal anomalies ie. Nuchal translucency , nasal bone , Ductus venosus flow & Fronto maxillary facial angle along with serological markers may increase the probability of detection of chromosomal anomalies. Low Papp-A level is significantly associated with increased incidence preterm deliveries but more studies associated with larger study group is recquired to ascertain its predictive value.

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