Maternal serum Pregnancy Associated Plasma Protein-A (PAPP-A) as a potential marker of Intra Uterine Growth Restriction (IUGR)

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Naela El-Sayed Ismail

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AC	:	Abdominal circumference.
ADAM12	:	A disintegrin and metaloprotease 12.
AFI	:	Amniotic fluid index.
AFP	:	Alfa feto-protein.
BPD	:	Bipareital diameter.
BPP	:	Biophysical profile.
BMI	:	Basal metabolic index
cDNA	:	Complementary deoxyribonucleic acid.
CHL	:	Crown heel length.
CP	:	Cerebral palsy.
CRL	:	Crown rump length.
CS	:	Cesarean section.
E3	:	Oestriol.
ELISA	:	Enzyme Linked Immunosorbent Assay.
FGR	:	Fetal growth restriction.
FHM	:	Fundal height measurements.
FL	:	Femur length.
FPD	:	False positive prediction.
FSH	:	Follicular stimulating hormone.
GRIT	:	Growth restriction intervention trial.
Hb A1C	:	Heamoglobin A1C.
HC	:	Head circumference.
HMD	:	Hyaline membrane disease.
HPL	:	Human placental lactogen.

IGF	:	Insulin growth factor.
IGFBP	:	Insulin growth factor binding protein.
IgG	:	Imunoglobulin G.
IQ	:	Intelligence quotient.
IUGR	:	Intrauterine growth restriction.
LBW	:	Low birth weight.
LH	:	Luteinizing hormone.
LMP	:	Last menstrual period.
LNR	:	Lin notch repeats.
MMP	:	Matrix metalloproteinase.
MOM	:	Multiples of the median.
mRNA	:	Messenger ribonucleic acid.
NGC	:	National guideline clearinghouse.
NICU	:	Neonatal intensive care unit.
NPV	:	Negative predictive value.
NT	:	Nuchal translucency thickness.
PAPP-A	:	Pregnancy associated plasma protein-A.
PAPP-E	:	Pregnancy associated plasma protein-E.
PO2	:	Partial pressure of oxygen molecule.
PP13	:	Placental protein 13.
PPV	:	Positive predictive value.
proMBP	:	Proform of eosinophil major basic protein.
RI	:	Resistivity index.
ROC	:	Receiver operating curve.
SCR	:	Short consequence repeats.
SGA	:	Small for gestational age.
β-HCG	:	Beta human chorionic gonadotrophs.

INTRODUCTION

Intra uterine growth restriction (IUGR) remains a challenging problem for obstetricians and pediatrician and continues to be an important determinant of perinatal mortality and morbidity in modern obstetrics. ***(Kady and Gardosi , 2004).***

IUGR has a massive short term (increase fetal morbidity and mortality) and long term (increase incidence of cardiovascular disease in adulthood) health complications ***(Wareing et al., 2005).***

It is uncertain how many neonates who really are IUGR. ***Vandenbosche and Kirchner., (1998),*** suggest 4-7 % of neonates to be IUGR, whereas ***Brodsky and Cristou .,(2004),*** refer that the incidence of IUGR is 5-7% suggesting that up to 15% is identified when SGA and IUGR are defined as equivalent.

Before the development of ultrasonography, delayed fetal growth was indicated by low maternal weight gain, and fundal height measurement .IUGR is frequently detected in a pregnancy with a less than expected third-trimester weight gain (100 to 200 g [3.5 to 7 oz] per week) or as an incidental finding on ultrasound examination when fetal measurements are smaller than expected for gestational age ***(Calvet et al., 1982).***

Physical evidence of abnormal fetal growth becomes typically apparent in the second half of pregnancy ***(Gluckman and Liggins, 1992),*** although recent studies have suggested that indicators of aberrant fetal growth may be present as early as in the first trimester ***(Smith, 2004).***

In particular, two recent large prospective studies have shown that reduced pregnancy associated plasma protein-A (PAPP-A) levels are associated with an increased incidence of low birth weight (LBW) or delivery of small for gestational age (SGA) infants ***(Smith et al., 2002and Krantz et al., 2004).***

PAPP-A is a macromolecular glycoprotien produced in great amounts during pregnancy by the syncytiotrophoblast ***(Guibourdenche et al., 2003).***

Further evidence of the relationship of PAPP-A to fetal growth comes from work of ***Leung et al., (2006),*** who showed that levels of PAPP-A were positively correlated with certain ultrasound parameters of fetal growth such as femur length**.** PAPP-A action in bone arises from studies on characterization of PAPP-A knockout mice ***(Bale and Conover, 2005)***, functional disruption of the PAPP-A gene in mice resulted in proportional dwarfism and a delay in embryonic skeletal ossification ***(DeChiara et al., 1990***)**.**

PAPP-A has been identified as a protease for insulin–like growth factor binding proteins (IGFBP) especially IGFBP-4 ***(Laursen et al., 2001 and Monget et al., 2003).***

These IGFBPs are able to bind insulin like growth factors (IGF-I and IGF-II), and hence inhibit their action in growth promotion ***(Clemmons, 1998).***

Therefore, a higher level of PAPP-A would be expected to be associated with an increase in IGF activity. In vitro experiments have shown that PAPP-A can promote bone growth by inhibiting IGFBP-4 since IGFBP-4 is found abundantly in fibroblast and osteoblasts ***(Bunn et al ., 2004; Prefumo et al., 2004and Leung et al., 2006).***

Several previous studies have looked at the value of PAPP-A in the first trimester on predicting adverse outcomes later on in pregnancy. Many studies support the view that IUGR and decreased PAPP-A are associated ***(Krantz et al., 2004).***

AIM OF THE WORK

The aim of this work is to assess that maternal serum first trimester pregnancy associated plasma protein-A (PAPP-A), as a potential biomarker to detect Intra Uterine Growth Restriction (IUGR) through estimating both fetal bone length and birth weight.

- ***DEFENITION:***

Intrauterine growth restriction (IUGR) is failure of the fetus to achieve his or her intrinsic growth potential, due to anatomical/functional diseases or disorders in the feto-placental-maternal unit ***(Malamitisi et al., 2006).***

Intrauterine growth restriction (IUGR) is a condition whose name and definition have changed but consistently has contributed significantly to prenatal morbidity and mortality. The term Intrauterine growth restriction has evolved from being expanded as intrauterine growth retardation to current term, Intrauterine growth restriction this change probably better reflects the pathophysiology of this disorder and avoids the emotionally change and frequently misunderstood term retardation ***(Scott, 2002, and Baschat, 2004).***

The common definition of IUGR is a birth weight less than the 10^{th} percentile for gestational age ***(Resnik, 2002).***

- ***EPIDEMIOLOGY:***

Regardless the definition of IUGR, the problem is widespread among developed as well as underdeveloped countries

and population. Risk factors for IUGR include small maternal size(height and pregnancy weight) and low maternal weight gain, but more importantly, this characteristics interacts and other risk factors to impact on fetal growth, especially in thin women ***(William et al.,1997).***

The epidemiology of fetal growth restriction varies internationally. In developed countries, the most frequently identified cause of growth restriction is smoking, while in developing countries, maternal nutritional factors (pregnancy weight, maternal height) and infections (malaria) are the leading identified causes ***(Kramer et al., 2000).***

Additionally, in developing countries, there is a direct correlation between the incidence of low birth weight (less than 2500 grams) and IUGR, the high incidence of low-birth-weight (LBW) infants is almost exclusively due to the incidence of IUGR. Data from developed countries show the opposite, rates of low birth weight being explained almost exclusively by prematurity rates ***(Martinez and Simmons, 2005).***

Outcome studies of the effect of IUGR have been confounded by heterogeneity of population studies. This includes various causes and definitions of intra uterine growth failure, the effects of the associated perinatal and neonatal complications on

outcomes, the age of the children are studied, and postnatal influences on the children, especially those related to sociodemographic factors ***(William et al., 1997 and Menendez et al., 2000).***

- ***INCIDENCE of IUGR:***

Intrauterine growth restriction (IUGR) is considered a severe complication of pregnancy ***(Kiely et al., 2005)***. IUGR is associated with short and long term negative outcome in fetuses, infants and children. It may be associated with development of disease in adult life. IUGR also has adverse consequences for future generations. It forms part of an intergenerational vicious cycle of deprivation ***(Steketee, 2003).***

Intrauterine growth restriction (IUGR) is of public health importance as it is prevalent in developing countries. The highest rates are in South Asia and parts of sub-Saharan Africa affecting about 40% as compared to less than 10% in most developed countries ***(Bernstein and Gabbe, 1996).***

In accurately dated pregnancies, approximately 80-85% of fetuses identified as being small for gestational age (SGA) are constitutionally small but healthy, 10-15% is true IUGR cases, and the remaining 5-10% of fetuses is affected by