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The association between pentraxin 3 in maternal circulation and pathological intrauterine fetal growth restriction

Moustafa I. Ibrahim [a], Essam M. Ammar [a], Ahmed Ramy [a], Mohamed I. Ellaithy [a,*], Rehab M. Abdelrahman [a], Rania Elkabarity [b]

[a] Obstetrics and Gynecology Department, Ain-Shams Faculty of Medicine, Cairo, Egypt
[b] Clinical Pathology Department, Ain-Shams Faculty of Medicine, Cairo, Egypt

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ABSTRACT

Objective: To assess the diagnostic accuracy of maternal serum pentraxin 3 (PTX3) in identifying pathological intrauterine fetal growth restriction (IUFGR) among women presented in the third trimester of pregnancy with a small for gestational age (SGA) fetus.
Study design: This case control study was conducted in Ain-Shams University Maternity Hospital, Abbasiya Square, Cairo, Egypt and included women diagnosed at the third trimester of pregnancy as having a SGA fetus. Cases included pregnant women with pathological IUFGR, while women with physiologically SGA fetus were included in the control group. Diagnosis of antenatal SGA fetus was based on the presence of abdominal circumference <10th percentile. Pathological IUFGR was provisionally diagnosed antenatally by the presence of falling percentiles on serial ultrasound scans and then the definitive diagnosis was established postnatally after comprehensive neonatal evaluation. Maternal venous blood samples were collected from the eligible participants, once at the time of enrollment, to assess serum PTX3 levels using enzyme-linked immunosorbent assay (ELISA). Both groups were then followed up till delivery to confirm the diagnosis.
Results: Among the 68 pregnant included in the study, PTX3 was found to be significantly elevated in women with SGA fetus due to pathological IUFGR ($n = 34$) than those with physiologically SGA fetus ($n = 34$) [6.5 ng/ml (2.5–11.0) versus 1.2 ng/ml (0.8–2.5) respectively], with a best cutoff value of ≥1.3 ng/ml [sensitivity of 85.3% (95% confidence interval (CI), 68.9–95.0) and a specificity of 73.5% (95% CI, 55.6–87.1)]. Using multivariable binary logistic regression model, amniotic fluid index (AFI) ($P = 0.010$), estimated fetal weight (EFW) ($P = 0.016$), PTX3 level ($P = 0.041$), and umbilical artery pulsatility index (UA-PI) ($P = 0.027$) were all found to be independent diagnostic markers for pathological IUFGR.
Conclusion: PTX3 is a promising marker that deserves further evaluation as it may differentiate normal and abnormal fetal growth among women presenting at third trimester of pregnancy with a SGA fetus.

Introduction

The term, small for gestational age (SGA) fetus, describes that fetus with growth parameters below the 10th percentile. This term cannot differentiate between physiological and pathological smallness, distinction necessitates the assessment of the fetal growth potential. Intrauterine fetal growth restriction (IUGFR) describes the fetus that failed to reach its growth potential because of intrinsic (genetic) and/or extrinsic (placental) causes. This term is not designated to describe a constitutionally small, but otherwise healthy fetus [1]. It is essential to differentiate between physiological (constitutional) smallness and a fetus with pathological IUFGR, as the latter is at more risk for serious short and long term consequences while the earlier is not at high risk of perinatal mortality or morbidity if it is simply small because of constitutional elements [2].

Pentraxin 3 (PTX3) is a well-known long pentraxin [3] produced by many cells (epithelial cells, endothelial cells, fibroblasts, monocytes, polymorphonucelar leucocytes, macrophages, and dendritic cells) [4]; it plays an essential role in female fertility, innate immunity, and inflammation [5]. Recently, the role of PTX3 has been investigated in normal pregnancy [6,7], preeclampsia [7–13], intrauterine fetal growth restriction [8,11,12], preterm

* Corresponding author at: Building 14, Block 14, Alwaha District, Nasr City, Cairo, Egypt. Tel.: +201006873417.
E-mail address: drmellisy@hotmail.com (M.I. Ellaithy).

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labor [14,15], premature rupture of fetal membranes [15–17]; intraamniotic inflammation [15,16,18], recurrent miscarriage [19] and implantation disorders [20,21].

Antenatal diagnose of pathological IUFGR secondary to extrinsic (placental) factors is sometimes challenging especially in late onset disease, the presence of an easily accessible marker in the maternal circulation, would help to classify SGA fetuses into high and low risk groups [22]. Women with pathological IUFGR secondary to altered placentation have increased PTX3 levels [8,11]; however, this finding warrants further investigation [8]. The current study tested the diagnostic accuracy of PTX3 in identifying pathological IUFGR secondary to extrinsic (placental) factors among women presented in the third trimester of pregnancy with a SGA fetus.

Materials and methods

This case–control study was conducted at Ain-Shams University Maternity Hospital, after being approved by the local institutional ethics and research committee, the study purpose and procedures was fully explained to all enrolled women and a written informed consent was obtained from each participant.

The study consecutively enrolled women at 28–40 weeks of gestation with SGA fetus and a provisional diagnosis of either pathological IUFGR or physiologically SGA fetus [based on the prior serial U/S scans (Fig. 1)]. The calculation of gestational age (GA) was based on the date last menstruation and was confirmed by the results of the first trimester ultrasound (U/S) scanning; the antenatal diagnosis of SGA fetus was based on the presence of abdominal circumference (AC) <10th percentile [23].

Women with an evidence of pathological IUFGR were included in the cases group. The antenatal diagnosis of pathological IUFGR was based on the presence of fetal abdominal circumference <10th percentile [23] and the presence of falling percentiles on prior serial U/S measurements (i.e. >40 percentiles decrease from its expected growth curve) [24]. Participants with comparable maternal and gestational ages who had been diagnosed provisionally as having physiologically SGA fetuses were included in the control group. The provisional diagnosis of physiologically SGA fetus was based on the presence of AC <10th percentile without any evidence of pathological IUFGR [i.e. absence of falling percentiles by serial U/S measurements. At least three prior serial measurements showing non-declining percentiles were required to allocate the participants in the physiologically SGA fetuses group].

Every effort was performed to exclude women with pathological IUFGR secondary to intrinsic (genetic) factors, so women with multifetal gestation, congenital fetal anomalies, evidence of fetal chromosomal aberrations, antenatal infections, symmetrical type of IUFGR, especially the severe cases [i.e. symmetric growth restriction implies a fetus whose entire body is proportionally small with normal head circumference (HC): AC ratio], and/or previous or current maternal diseases were excluded from the study. Also women with systemic lupus erythematous, preeclampsia, antiphospholipid antibody syndrome, vascular disease, and/or taking acetylsalicylic acid or enoxaparin treatment were excluded from the study, as these factors are likely to affect PTX3 levels and fetal growth.

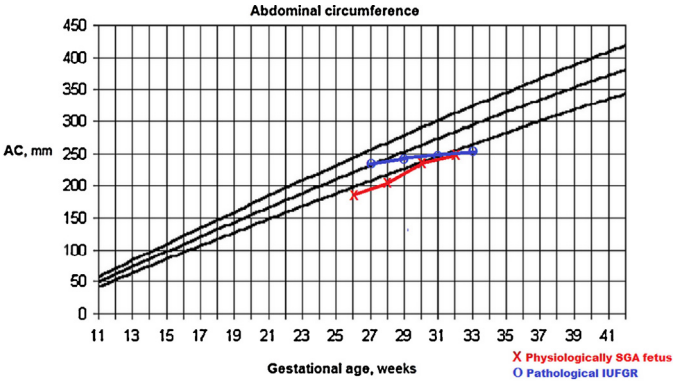

Fig. 1. Example of fetal growth pattern in the two study groups.

At the time of enrollment [i.e. time of provisional diagnosis], all participants were thoroughly evaluated via history taking, physical examination, and U/S scanning and venous blood samples were withdrawn for PTX3 assay.

For assessment of serum PTX3 level, maternal venous blood samples (5 ml) were collected from the eligible participants under complete aseptic precautions, once at the time of enrollment, put in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 1500 × *g* for 15 min. The separated plasma was then transferred into aliquots and stored at −20 °C for subsequent analysis using enzyme-linked immunosorbent assay (ELISA) via reagents provided by Quantikine R&D International, Inc. [R&D International, Inc., 614 McKinly Place N.E., Minnespolis, MN55413 USA]; the intra-assay and inter-assay coefficients of variation for PTX3 were 5.1% and 3.9% respectively and the sensitivity was 0.025 ng/ml. This laboratory work up was conducted under direct supervision of the same experienced author (R.E.) who was blinded to the study outcomes.

U/S scanning [Voluson 730 PRO© 2004, General Electric Healthcare Company, U.S.A.] was performed for assessment of fetal biometry, fetal weight (EFW), amniotic fluid index (AFI), and umbilical artery (UA) Doppler indices. Fetal biometry included biparietal diameter (BPD), abdominal circumference (AC) and femur length (FL), the observed biometry were expressed as absolute measurement in millimeter, centile, delta value % [i.e. the percentage difference from the corresponding expected mean] and *Z* score [i.e. the difference between the observed and expected mean biometric measures in standard deviations (SD)]. After fetal biometry was completed and while fetal movements were absent and maternal breathing was withhold; UA Doppler recording was done in the plane of a free-floating cord loop. The systolic to diastolic (S/D) ratio, resistance index (RI) and pulsatility index (PI) were calculated automatically from ≥3 consecutive uniform waveforms [S/D = systolic velocity/diastolic velocity, PI = (peak systolic velocity − end diastolic velocity)/time averaged velocity, RI = (peak systolic velocity − end diastolic velocity)/peak systolic velocity]

At the time of delivery [i.e. time of definitive diagnosis], all neonates were thoroughly evaluated for GA, birth weight, APGAR scoring, cord PH, congenital malformations and karyotyping (if indicated). Postnatal confirmation of SGA newborn was based on the presence of neonatal weight <10th percentile according to the national standards adjusted for birth weight and gestational age. All included women had neonates free from any major congenital malformations with normal karyotype that was done in cases of early onset or severe IUFGR (<3rd percentile) or when an anomaly was suspected.

Sample size was calculated using EpiInfo® version 6.0, setting the type-1 error (α) at 0.05 and the power ($1 - \beta$) at 0.8. Data from a previous study [11] showed that the median (interquartile range) of plasma PTX3 was 3.9 ng/ml (2.2–8.2 ng/ml) in women who had IUFGR. Calculation according to these values produced a minimal sample size of 34 women in each group.

Statistical analysis was done on a personal computer using IBM© SPSS© Statistics version 21 [IBM© Corp., Armonk, NY] and MedCalc© version 11.4 [MedCalc© Software, Ostend, Belgium]. Normality of numerical data distribution was tested using the