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First and second trimester biochemical markers in familial mediterranean fever

F. TURKCAPAR, Y. ENGIN-ÜSTÜN, Ö.Y. SIMSEK, R. DEVEER, N. DANISMAN, U. DILMEN[1], L. MOLLAMAHMUTOGLU

Gynecology and Obstetrics Department, and [1]Neonatology Department, Zekai Tahir Burak Woman's Health Education and Research Hospital, Ankara, Turkey

Abstract. – OBJECTIVES: Our aim was to investigate whether the maternal serum concentrations of first and second trimester serum analytes are altered in familial Mediterranean fever (FMF) pregnancies.

MATERIALS AND METHODS: The screening tests were compared in a series of 16 serum samples from FMF pregnancies and in a cohort of 48 pregnant women with normal pregnancy. Serum samples were obtained between 11 and 13 weeks; 16 and 18 weeks gestation.

RESULTS: Serum pregnancy-associated plasma protein-A (PAPP-A) levels, expressed as multiples of the median (0.9 ± 0.45 MoM) in the control group, were significantly higher than FMF patients (0.6 ± 0.3 MoM) (p = 0.027). Analyses of alpha-fetoprotein, human chorionic gonadotropin and oestriol levels showed no significant differences between FMF and normal pregnancies.

CONCLUSIONS: Our study revealed that low levels of PAPP-A are associated with FMF.

Key Words:
Familial Mediterranean fever, Pregnancy-associated plasma protein A.

Introduction

The maternal triple-marker screen is a combined serum analyte measurement that is used routinely in standard clinical obstetric practice for the prenatal detection of Down syndrome and open neural-tube defects[1]. The screening test measures the levels of α-fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (E3). Estriol is an estrogen derived from the placental aromatization of fetal adrenal androgens. AFP is a glycoprotein that is normally produced in early pregnancy by the fetal yolk sac, liver, and gastrointestinal tract. Moreover, a considerable amount of AFP is synthesized by the choroid plexuses and is released into the cerebrospinal fluid. The first trimester combined screen measures maternal serum levels of free beta-hCG and pregnancy-associated plasma protein-A (PAPP-A) at 9-12 weeks gestation and measures nuchal translucency (NT) by ultrasound at 11-13 weeks gestation.

Recently, there is some evidence that low levels of maternal serum PAPP-A and free beta-hCG in the first trimester and elevated levels of AFP and hCG in the second trimester may be associated with an increased risk of various obstetrical complications, such as miscarriage, preterm delivery, pregnancy induced hypertension, fetal growth restriction[2-6].

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever and inflammation in the peritoneum, synovium, or pleura, accompanied by pain[7]. The disease is most prevalent among non-Ashkenazi Jews, Arabs, Turks and Armenians. Abdominal pain is the most common presenting feature of FMF, eventually occurring in 95% of patients[8].

Our aim was to investigate whether the maternal serum concentrations of first and second trimester serum analytes are altered in FMF pregnancies.

Materials and Methods

The screening tests were compared in a series of 16 serum samples from FMF pregnancies and in a cohort of 48 pregnant women with normal pregnancy outcome receiving routine antenatal care in our clinic between March 2009 and June 2010. A case-control study was conducted. The Institutional Ethics Committee approved the study protocol.

The study group comprised patients who met the clinical criteria of Livneh et al[9] for a diagnosis of FMF. The diagnosis of FMF was based on a typical clinical picture of recurrent attacks of fever

Corresponding Author: Figen Türkcapar, MD; e-mail: fcapar@yahoo.com

and pain affecting patients, and involving one or two of the following sites at a time: abdomen, chest, joints, muscles, scrotum, and skin. In addition, an increase in acute phase reactants during the attacks, a positive history among siblings or in the extended family, and a good response to colchicine helped to establish the diagnosis.

After each pregnancy with FMF, the following three normal pregnancies were selected as controls. Pregnancies were recruited consecutively. All pregnancies with FMF were matched one-to-one with those of age and parity matched controls who had conceived spontaneously. The controls were selected from the same database. Control pregnancies were selected for the same age and parity as the index pregnancies and from women who delivered in the same calendar month.

Self-reported last menstrual period and an early ultrasound (scheduled between gestational weeks 6-7 and no later than 14 weeks), both obtained during the first trimester, were combined with infant date of birth to estimate gestational age at birth. We recorded demographic information (maternal age, reproductive history, gestational age, presence of regular antenatal follow-up), preterm delivery, hypertension, diabetes mellitus rates, and number of hospitalizations during pregnancy, birth weight, Apgar scores, and neonatal intensive care unit admission rates. All the patients recorded that they used colchicine throughout in pregnancy.

Serum samples were obtained between 11 and 13 weeks; 16 and 18 weeks gestation. First-trimester screening was performed after informed consent at 11-13^{6} weeks of pregnancy with a crown-rump length (CRL) of 45-80 mm. The Down's syndrome screening programme in our laboratory includes free beta- hCG and PAPP-A; AFP, HCG and free oestriol as biochemical markers. Levels of PAPP-A, free beta-hCG, AFP, total hCG and unconjugated E3 were measured with the Immulite 2000 Analyzer (EURO/DPC Ltd, Llanberis, UK). Screening for Down's syndrome is performed once a week (~80 samples each run). Correction was performed for weight and smoking. In cases of multiple pregnancies (twins), we used the correction factors published by Wald (10). Concentrations of the serum markers were expressed in multiples of the medians (MOM) for pregnancies of the same gestational age. All markers were expressed as multiples of the normal median for women with unaffected pregnancies at a given gestational age. Fetal NT was measured by transabdominal ultrasound examination as the maximum vertical distance between the skin and subcutaneous tissues at the back of the neck in a sagittal section of the fetus lying in the neutral position, by sonographers who received Certificate of Competence in first-trimester scanning.

Statistical Analysis

All data sets were subjected to normality testing using the Kolmogorov–Smirnov method. The data were reported as mean ± standard deviation (for normally distributed data) or as median and range (for non-normally distributed data). Comparisons between two groups were performed using Student's *t*-tests or Mann–Whitney rank sum tests. All analyses were performed using the SPSS statistics package (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was considered to indicate a statistically significant difference.

Results

In the unit 26329 deliveries occurred during the study period representing prevalence of (16/26329) 0.06% of FMF in pregnancy. The principal demographic characteristics of the two groups are shown in Table I. The mean ages (± standard deviation) of the FMF and control groups were 28.1 ± 5.1 and 27.5 ± 5.2, respectively. There was no statistically significant difference for the age of individuals in the two groups ($p > 0.05$). In addition, no statistically significant differences were noted between the groups regarding the gestational age, body mass index and gravidity.

Serum first and second trimester serum analytes were determined in a case-control study of 16 cases of FMF and 48 unaffected controls. Serum PAPP-A levels, expressed as multiples of the median (0.9 ± 0.45 MoM) in the control group, were significantly higher than FMF patients (0.6 ± 0.3 MoM) ($p = 0.027$). Serum fβ-hCG, expressed as multiples of the median (MoM) of the FMF group, was not significantly different in control group pregnancies ($p = 0.115$). Analyses of AFP, hCG and oestriol levels showed no significant differences between FMF and normal pregnancies (Table I).

Adverse pregnancy complications, comprising pregnancies with adverse perinatal outcomes (prematurity) and/or obstetric complications (pregnancy-induced hypertension, gestational diabetes, intrauterine growth retardation) were sim-

Table I. Demographic, laboratory and clinical characteristics in two groups.

	Control (n = 48)	FMF (n = 16)	p
Maternal age (years)*	27.5 ± 5.2	28.1 ± 5,1	0.682
Gestational age (days)**	274 (226-289)	274 (223-287)	0.593
Gravida**	2 (1-6)	2 (1-4)	0.922
Parity**	1 (0-3)	1 (0-2)	0.482
Body mass index (kg/m^2)*	28.4 ± 4,0	32.4 ± 5.1	0.071
PAPP-A* (MoM)	0.9 ± 0.45	0.6 ± 0.3	0.027
HCG* (MoM)	1.0 ± 0.5	1.4 ± 1.1	0.115
Free oestriol* (MoM)	1.6 ± 0.7	1.3 ± 0.5	0.134
AFP* (MoM)	1.1 ± 0.5	0.9 ± 0.4	0.491
HCG* (MoM)	1.0 ± 0.6	1.2 ± 0.8	0.373
Primary section rate	7 (14.6)	6 (37.5)	< 0.05
Antenatal complications (n, %)	6 (12.5)	7 (40)	0.052
Birth weight (g)	3238 ± 502	2856 ± 716	0.024
Female fetus (n, %)	24 (50)	10 (66.7)	0.375
NICU admission (n, %)	3 (6.5)	4 (25)	0.055
Maternal hospitalization (n, %)	12 (25)	9 (56.2)	0.027

Abbreviations: FMF: Familial Mediterranean fever; PAPP-A: Pregnancy-associated plasma protein-A; AFP: α-fetoprotein, hCG: human chorionic gonadotropin; NICU: Neonatal intensive care unit. *Values are mean ± SD; **Values are median (minimum-maximum).

ilar in both groups ($p = 0.052$). Preterm delivery rate was 13.3% in FMF group and 0% in control group. Birth weight, primary cesarean section and maternal hospitalization rates showed statistically significant differences (Table I).

Discussion

FMF is the prototypic recessively inherited autoinflammatory disease. The etiopathophysiology of FMF is not fully understood. The underlying clinical and pathological picture seems as acute peritonitis. Few studies evaluated pregnancy in FMF patients[11-14]. Iltemir et al[15] discussed diagnostic difficulty of FMF during pregnancy.

Measurement of maternal serum analytes is a well established screening test for Down syndrome (trisomy 21). In literature, maternal low levels of PAPP-A have been shown to be associated with adverse outcome including, hypertensive disorders of pregnancy, fetal growth disorders, preterm delivery, and miscarriage[2-6,16]. This is the first study, to our knowledge, to evaluate PAPP-A, fβ-hCG, AFP, hCG and oestriol levels in FMF patients. Our study revealed that low levels of PAPP-A are associated with FMF. Analyses of AFP, hCG and oestriol levels showed no significant differences between FMF and normal pregnancies.

The exact mechanism responsible for altered levels of PAPP-A in FMF pregnancies remain unclear. PAPP-A produced by the trophoblast reflects placental function. The association between abnormal PAPP-A and FMF may be related to impaired first trimester placentation[17].

Despite this is the first data set regarding maternal serum analytes and FMF, our study includes a relatively small sample size. Larger studies are needed to better understand the findings of this study.

Conclusions

In pregnancies with reduction in PAPP-A levels, after the exclusion of common etiologies such as fetal growth disorders, it is essential that FMF be considered as a causative etiology.

Conflict of Interest

None declared.

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