CEOG Clinical and Experimental Obstetrics & Gynecology

Pregnancy-associated plasma protein a levels are decreased in obstetric cholestasis

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Summary

Objective: Obstetric cholestasis is a cholestatic disease usually commencing in the third trimester of pregnancy and characterized by pruritus, elevation of liver enzymes, and increase in bile acids. The objective of this study was to compare the first trimester serum indicators of obstetric cholestasis with normal pregnancies. *Materials and Methods:* Thirty-five patients diagnosed with obstetric cholestasis in a three-year period with first trimester biochemical assessment available were included in the study. Seventy patients with concordant pregnancy weeks, matched-age normal pregnancies were included as the control group. Pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (beta-hCG) levels were analyzed. *Results:* No difference was observed between the two groups in terms of age and week of pregnancy. While the mean PAPP-A level was 0.76 ± 0.31 multiples of the medians (MoM) in the obstetric cholestasis group, it was determined to be 1.5 ± 0.84 in the control group ($p = 0.0001$). Among the two groups, the hCG levels were found to be higher in the obstetric cholestasis group (1.2 ± 0.79 MoM *vs.* 0.98 ± 0.53, $p = 0.041$). *Conclusion:* In this study, the first trimester PAPP-A levels in the obstetric cholestasis cases were found to be significantly lower than the control group. Low PAPP-A levels should be a warning for obstetric cholestasis.

Key words: Obstetric cholestasis; Pregnancy-associated plasma protein A.

Introduction

Obstetric cholestasis is a cholestatic disease usually commencing in the third trimester of pregnancy and characterized by pruritus, elevation of liver enzymes, and increase in bile acids. Findings and symptoms disappear spontaneously in two to three weeks after delivery [1, 2]. The effect of obstetric cholestasis on the fetus is often fetal distress, preterm labor, and increased risk of sudden intrauterine infant mortality. Although the reason for obstetric cholestasis is not quite known, most recent studies emphasize genetic and hormonal factors. The incidence rate may differ regionally but is observed to be between 0.4% to 15% [3].

There are studies which indicate that the low levels of pregnancy-associated plasma protein A (PAPP-A) measured with the double screening test in the first trimester are associated with multiple pregnancy complications, particularly preeclampsia, intrauterine growth retardation (IUGR) or small for gestational age (SGA) and preterm labor.

The objective of this study was to compare the first trimester serum indicators of obstetric cholestasis with normal pregnancies.

Materials and Methods

Thirty-five patients diagnosed with obstetric cholestasis in a three-year period with first trimester biochemical assessment available were included in the study. The patients were included on the following criteria [4]: (a) generalized pruritis without skin changes in the second half of pregnancy, (b) increased liver function tests and/or serum bile acids, (c) exclusion of other conditions known to cause pruritis or increase liver function tests, and (d) postnatal resolution of clinic and laboratory abnormalities. All obstetrics cholestasis patients had elevated liver enzymes and serum bile acids. Seventy patients with concordant pregnancy weeks, matched-age normal pregnancies were included as the control group.

Age of the pregnant women, maternal weight, smoking habits, existence of diabetes mellitus, PAPP-A, and human chorionic gonadotropin (hCG) levels were recorded. Serum was obtained and analyzed from women who accepted a first trimester screening during the 11-14 weeks of pregnancy. PAPP-A and free beta-hCG levels were analyzed. Serum concentrations were converted to multiples of the medians (MoM). MoM values were adjusted according to maternal weight and smoking status. Biochemical parameters were compared.

The SPSS package was used to perform statistical analysis. Distribution of the groups was analyzed with one sample Kolmogorov–Smirnov test. All normally distributed data were compared using a students' two-tailed *t*-test. A p value < 0.05 was considered statistically significant.

Results

No difference was observed between the two groups in terms of age and week of pregnancy (Table 1). Bile acids in the obstetric cholestasis group ranged between 12.4 to 91.8 μmol/L (reference range was 0.00 - 10.00 μmol/L).

Revised manuscript accepted for publication April 17, 2014

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLII, n. 5, 2015
doi: 10.12891/ceog1917.2015

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Table 1. — *Demographic and laboratory characteristics of the two groups**.

Parameters	Obstetric cholestasis (n=35)	Control group (n=70)	*p*
Maternal age (years)	29.8 ± 4.5	27.8 ± 5.7	0.074
Maternal weight (kg)	68.2 ± 10.4	62.3 ± 10.3	0.081
PAPP-A (MoM)	0.76 ± 0.31	1.50 ± 0.84	0.0001
hCG (MoM)	1.2 ± 0.79	0.98 ± 0.53	0.041
NT (MoM)	0.94 ± 0.41	0.87 ± 0.27	0.32
CRL	60.4 ± 11.0	56.2 ± 11.0	0.074

Abbreviations: PAPP-A: pregnancy-associated plasma protein A; hCG: human chorionic gonadotropin; MoM: Multiples of the medians; NT: Nuchal translucency. CRL: Crown rump length. *: Values are mean ± SD.

While the average PAPP-A level was 0.76 ± 0.31 MoM in the obstetric cholestasis group, it was determined to be 1.50 ± 0.84 in the control group (p = 0.0001). Among the two groups, the hCG levels were found to be higher in the obstetric cholestasis group (1.2 ± 0.79 MoM *vs.* 0.98 ± 0.53, p = 0.041).

Discussion

Some recently published studies indicate that low maternal serum PAPP-A levels could be effective in foreseeing different obstetric complications [5-8]. It has been suggested that PAPP-A levels below 0.04 MoM could be an indicator for disrupted placental functions [8].

Obstetric cholestasis is especially more frequent in the third trimester when the serum estrogen concentration has peaked and in multiple pregnancies where the hormone levels are higher [9]. The increased estrogen and progesterone, with addition of environmental factors, causes a cholestasis manifestation in pregnant women with convenient genetic background. In the present study, the first trimester PAPP-A levels in the obstetric cholestasis cases have been found to be significantly lower than the control group. There are numerous studies on first trimester low PAPP-A levels and associated developing pregnancy complications. A study by Carbone *et al.* in 2011 [10] demonstrated that low levels of PAPP-A in the screening test conducted during the first trimester have a relation with SGA at delivery. Kırkegaard *et al.* [11] have published a study in 2011, indicating that low PAPP-A levels are associated with SGA. Spencer *et al.* [12] conducted a study in 2010 on the association of low PAPP-A levels in the first trimester with future development of preeclampsia. Goetzinger *et al.* [13] published a study in 2010, significantly associating the increased preterm labour risk with low PAPP-A levels in the first trimester.

As far as the present authors are aware, there is only one study [14] determining PAPP-A levels in obstetric cholestasis. In contrast to the present results, they found increased serum levels of PAPP-A compared to controls but they had only 15 patients with obstetric cholestasis.

In the present study, PAPP-A levels were found to be significantly low in the obstetric cholestasis cases compared to the control group. Low PAPP-A levels should be a warning for obstetric cholestasis.

References

[1] Lammert F., Marschall H.U., Glantz A., Matern S.: "Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management". *J. Hepatol.*, 2000, *33*, 1012.

[2] Beuers U., Pusl T.: "Intrahepatic cholestasis of pregnancy—a heterogeneous group of pregnancy-related disorders?" *Hepatology*, 2006, *43*, 647.

[3] Kondrackiene J.. Kupcinskas L.: "Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems". *World J. Gastroenterol.*, 2008, *14*, 5781.

[4] Deveer R., Engin-Ustun Y., Celen S., Eryilmaz O.G., Tonguç E., Mollamahmutoğlu L., Oksuzoglu A., Danisman N.: "Two-year experience of obstetric cholestasis: outcome and management". *Clin. Exp. Obstet. Gynecol.*, 2011, *38*, 256.

[5] Westergaard J.G., Sinosich M.J., Bugge M., Madsen L.T., Teisner B., Gradzinskas J.G.: "Pregnancy-associated plasma protein A in the prediction of early pregnancy failure". *Am. J. Obstet. Gynecol.*, 1983, *145*, 67.

[6] Spencer K., Cowans N.J., Avgıdou K., Molina F., Nicolaides K.H.: "First trimester biochemical markers of aneuploidy and the prediction of small for gestational age fetuses". *Ultrasound Obstet. Gynecol.*, 2008, *31*, 15.

[7] Gagnon A., Wilson R.D., Audibert F., Allen V.M., Blight C., Brock J.A., *et al.*: "Obstetrical complications associated with abnormal maternal serum markers analytes". *J. Obstet. Gynaecol. Can.*, 2008, *30*, 918.

[8] Morris R.K., Cnossen J.S., Largejans M., Robson S.C., Kleijnen J.: "Serum screening with Down's syndrome markers to predict preeclampsia and small for gestational age: systematic review and meta-analysis". *BMC Pregnancy Childbirth*, 2008, *8*, 33. doi: 10.1186/1471-2393-8-33.

[9] Gonzalez M.C., Reyes H., Arrese M., Figueroa D., Lorca . Andresen M., *et al.*: "Intrahepatic cholestasis of pregnancy in twin pregnancies". *J. Hepatol.*, 1989, *9*, 84.

[10] Carbone J.F., Tuuli M.G., Bradshaw R., Liebsch J., Odibo A.O.: "Efficiency of first-trimester growth restriction and low pregnancy-associated plasma protein-A in predicting small for gestational age at delivery". *Prenat. Diagn.*, 2012, *32*, 724.

[11] Kirkegaard I., Henriksen T.B., Uldbjerg N.: "Early fetal growth, PAPP-A and free β-hCG in relation to risk of delivering a small-for-gestational age infant". *Ultrasound Obstet. Gynecol.*, 2011, *37*, 341.

[12] Spencer K., Cowans N.J., Nicolaides K.H.: "Low levels of maternal serum PAPP-A in the first trimester and the risk of preeclampsia". *Prenat. Diagn.*, 2008, *28*, 7.

[13] Goetzinger K.R., Cahill A.G., Macones G.A., Odibo A.O.: "Association of first-trimester low PAPP-A levels with preterm birth". *Prenat. Diagn.,* 2010, *30*, 309.

[14] Muravská A., Germanová A., Jáchymová M., Hájek Z., Svarcová J., Zima T., Kalousová M.: "Association of pregnancy-associated plasma protein A polymorphism with preeclampsia - a pilot study". *Clin. Biochem.*, 2011, *44*, 1380.

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