Second-trimester levels of fetoplacental hormones among women with placenta accreta spectrum disorders

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Synopsis: Maternal serum human chorionic gonadotropin could be a useful biomarker in the prenatal diagnosis of placenta accreta spectrum disorders.

Human chorionic gonadotropin (hCG) and its free β-subunit (β-hCG) are exclusively synthesized by the villous trophoblast. α-Fetoprotein (AFP) is synthesized by the secondary yolk sac and fetal liver. Levels of both hormones differ between women with placenta accreta spectrum (PAS) disorders and those with non-accreta previa.[1,2] Second trimester MSAFP is increased[1] and first trimester MS β-hCG is decreased in women with PAS[2], compared with non-accreta placenta previa. An increased level of cell-free β-HCG mRNA has also been found in the maternal plasma of women with PAS.[3]The aim of the present study was to further assess the association between levels of serum markers measured as part of the triple test in the second trimester (β-hCG, AFP, and estriol) and the prenatal diagnosis of PAS disorders.

A retrospective study was conducted using data for 19 women with singleton pregnancies who had been diagnosed with a PAS disorder between January 1st, 2013 and December 30th, 2016 **[Author: Please provide exact dates.]** at Assaf Harofeh Medical Center, Zerifin, Israel. The diagnosis of PAS disorder was confirmed clinically in all cases at delivery. Detailed microscopy reports were obtained only for cases with partial myometrial resection or cesarean hysterectomy. Each case of PAS disorder was matched with three control cases (uncomplicated pregnancies) matched for maternal age and length of pregnancy at serum sampling. The study was approved by the institutional review board. Informed consent was deemed unnecessary because of the retrospective nature of anonymous data collection.

Assays for maternal serum levels of AFP, hCG, and estriol had been performed during pregnancy using Beckman Coulter Access reagents (Beckman Coulter, Brea, CA, USA). The measured marker levels are expressed as multiples of the median **[Author: This is the more widely used term.]** **ok** (MoM) for pregnancy length as determined by last menstrual period and confirmed by ultrasonography measurements of crown–rump length or biparietal diameter.

Statgraphics Plus version 3 (Manugistics, Rockville, MD, USA) was used for data analysis. The standard Kurtosis analysis indicated that some values were not normally distributed and therefore data are presented as median and interquartile range (IQR). The Mann-Whitney *U* test was used to compare the medians of the study and control groups. $P<0.05$ was considered significant.

Among the 19 cases, there were three women with placenta creta, seven with placenta increta, and nine with placenta percreta. The maternal serum concentration of hCG was significantly higher in the study group than in the control group ($P=0.0011$) (Table 1). No differences were recorded for estriol or AFP.

The present study's finding of increased hCG levels at 16–20 weeks among women with PAS disorders versus non-previa controls suggests that higher hCG levels are secondary to the abnormal vascularization observed in PAS disorders, in which the passage of hCG into the maternal circulation is modified.[4] The present data indicate that hCG could be a clinically useful biomarker in the prenatal diagnosis of PAS disorders. The main limitation of the present study was the fact that the surgical team

was not blinded to the ultrasound findings and the diagnosis of PAS during surgery was made by the surgeons in all cases in which hysterectomy was avoided.

[Author: Prof Jauniaux has requested that such terms be avoided in the themed issue. Please reword using terms used elsewhere in this paper.]

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Author contributions

All authors contributed to the study design. MP-Z and YM performed the data collection. EJ performed data analysis and together with other authors (MP-Z, YM and RM) drafted and revised the manuscript. All authors approved this final version for publication. **[Author: Please clarify what "critical discussion" means here. Individuals have to contribute to the write-up of the paper to meet the criteria for authorship, and only EJ and RM seem to have done so in this version of the contributions.]**

Conflicts of interest

The authors have no conflicts of interest.

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Table 1 Clinical characteristics and hormonal values.[a]

Variable	**Study group (n=19)**	**Control group (n=57)**	***P* value** [b]
Maternal age, y	35 (33–39)	35 (33–37)	0.499
Gravidity	4 (4–5)	3 (2–3)	0.017
Parity	2 (1–3)	2 (1–2)	0.682
hCG, MoM	2.27 (1.18–2.65)	1.10 (0.69–1.68)	0.0011
Estriol, MoM	0.95 (0.90–1.05)	0.99 (0.82–1.12)	0.627
α-Fetoprotein, MoM	1.20 (0.94–1.46)	1.07 (0.90–1.34)	0.267

Abbreviations: hCG, human chorionic gonadotropin; MoM, multiple of median.

[a] Values are given as median (interquartile range) unless indicated otherwise.

[b] Mann–Whitney *U* test.

[A: All values in the same row should be provided to the same number of decimal places. Please add second decimal place where indicated by the "x".]