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Unilaterally Increased Uterine Artery Pulsatility and Urinary Hyperglycosylated HCG Predicts Miscarriage in Threatened Abortion

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Abstract

Objective: to study the role of uterine artery Dopper and urinary hyperglycosylated hCG (hCG-H) in predicting threatened abortion outcome.

Methods: A prospective observational study was conducted on 93 cases with threatened abortion (study group) and 50 cases with normal pregnancy (control group) at 6-12 weeks gestation. Uterine artery Doppler examination was performed and urinary hCG-H was measured in all cases. Cases were followed up till delivery and number of aborted cases was recorded.

Results: Urinary hCG-H concentration was significantly higher in control group and cases who continued than in cases who miscarried 5.3 ± 3.9 vs. 2.1 ± 3.0 mIU/ml equivalents (p=0.002) for the first and 5.1 ± 4.5 vs. 2.1 ± 3.0 mIU/mlEq (p=0.003) for the second respectively. The ratio of hyperglycosylated hCG to total hCG was >51% in the 116 term outcome cases while it was below 49% in the 29 cases who miscarried. Unilaterally increased uterine artery pulsatility index and Δ uterine artery pulsatility index value were significantly higher in women who miscarried than in those with continuing pregnancies or the control groups (P < .0001).

Conclusion: Unilaterally increased uterine arteries pulsatility index and decreased urinary hCG-H production in first trimester could predict miscarriage in threatened abortion.

Keywords: Threatend abortion; Uterine artery doppler; Hyperglycoslated HCG; Pregnancy outcome

Introduction

Threatened abortion was defined as a history of vaginal bleeding in an ongoing pregnancy of less than 20 weeks of gestation [1]. It is considered the most common complication of early pregnancy and occurs with an incidence of 15-20% of ongoing pregnancies [2].

Ultrasound scanning is probably the best single diagnostic and prognostic test in managing cases of threatened abortions. However, at least one repeated scan is usually necessary [3]. Several ultrasound findings that increase the likelihood of an early pregnancy failure have been identified, these include; an intrauterine blood collection, a slow fetal heart rate, a small or irregular gestational sac, abnormal echogenicity of the placenta, a smaller than expected embryo, an abnormal appearance of the yolk sac, or a duplicated yolk sac [4,5]. Nevertheless, a high number of apparently normal first-trimester pregnancies still end in miscarriage

Studies evaluating Doppler changes in patients with threatened abortion are conflicting, with some showed that the use of transvaginal color Doppler ultrasound is not useful for predicting the outcome [6-8], while others showed that an abnormally high plasticity index value in one uterine artery is associated with miscarriage in a significant number of early viable pregnancies [9].

Fertility specialists have devised numerous test protocols in order to predict pregnancy failures. Most specialists now measure the hCG doubling rate over a 2-day period as the best indicator [10]. However, hCG doubling test only detects 28% of miscarriages with a 36% false positive rate. This test only has a 25% predictive value [11,12].

Hyperglycosylated hCG (hCG- H) is an hCG molecule with additional sugar residues on its oligosaccharide side chains [13,14]. hCG-H has been shown to be the predominant form of hCG present in serum and urine samples in early pregnancy, during the time when implantation is occurring and the month that follows [15,16] .

It has been previously shown that significantly lower proportions of hCG-H (vs. hCG) are found in spontaneously aborting pregnancies [15,16]. Another study found that on the day of pregnancy implantation, it is hCG-H that can make an absolute differentiation between pregnancies that will go to term and pregnancies that will fail [17]. Considering the lower concentrations of hCG in failing pregnancies [18-20] and the lower proportions of hCG-H [14,15], we suppose that measurement of hCG-H concentrations com may provide an amplified means of detecting failing pregnancies with improved prediction of pregnancy outcome.

The aim of this work was to study the role of both uterine artery Dopper waveform analysis and urinary hCG-H in predicting the outcome of threatened abortion.

Patients and Methods

This prospective observational study was conducted in the antenatal care clinic and feto-maternal unit in Zagazig University hospitals between April 2010 and September 2011. Approval by the local ethical committee and informed written consent from all participants were obtained.

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One hundred forty three consecutive women with first-trimester pregnancy were included in this study and classified into; a study group included 93 cases with singleton living intrauterine pregnancy at 6-12 weeks gestation calculated according to the date of reliable last menstrual period and confirmed by ultrasound examination with clinical diagnosis of threatened abortion, and another 50 cases with no threatened abortion with the same criteria before were settled as control group. Exclusion criteria: included multiple pregnancy, ectopic pregnancy, missed abortion, and pregnancy before 6 weeks' gestation with no detectable cardiac activity. For the purposes of this study only the first scan that showed detectable fetal cardiac activity was considered for risk analysis.

All cases were subjected to the following: Full history taking, routine general and obstetric examinations and routine antenatal care investigations. Obstetric ultrasound examination was done by transvaginal ultrasound (TVS). The machine used were medical system (GE healthcare, Voluson 730 pro V, Austria) equipped with a multi frequency 5-7.5-MHz abdominal and TVS probes. Abnormal ultrasonographic findings were : intrauterine hematoma, a slow fetal heart rate less than 100 beats/min., a small or irregular gestational sac, abnormal echogencity of the placenta, a smaller than expected embryo, an abnormal appearance of the yolk sac, such as an irregular shape, calcifications, increased echogenicity, or a duplicated yolk sac, and abnormal amnion and amniotic cavity [3].

Transvaginal Color Doppler blood flow velocity examination of the uterine artery was done after visualization of both uterine arteries at the level of the corporocervical junction [7], measurements of both the right and left uterine artery indices were taken and the mean was considered. Doppler measurements were taken across three to six cardiac cycles with calculation of systolic/diastolic ratio (S/D), Resistance index (RI) and Pulsatility index (PI).

Once an enrolled patient had a positive pregnancy test, a tube of urine was collected at the clinic, whenever possible, from the 6th to the 12h weeks of pregnancy (6weeks 0 days to 11weeks ± 6 days since the start of their last menstrual period). Pregnancy was confirmed in all cases using serum hCG point-of-care tests. Patients with favorable outcomes are those reaching term deliveries. Cases that had spontaneous abortion before 20 weeks are those with unfavorable outcome.

Urine samples were frozen at − 80°C following collection. Samples are then thawed and assayed for total hCG and hCG-H. Total hCG was measured using the Siemens Immulite 1000automated test. This test has been calibrated for urine application as described previously [21]. Hyperglycosylated hCG was determined using the specific microtiter plate assay with antibody B152 as the capture and antibody 5008 with peroxidase label as the tracer, as described previously [22]. Calculation of percentage hyperglycosylated hCG normalizes values for urine concentration as much as both hyperglycosylated hCG and total hCG are subject to urine dilution. Thus, the percentage of hyperglycosylated HCG was calculated as: hyperglycosylated hCG/total Hcg.

Statistical analysis

Data were collected and analyzed statistically, the following tests were done: mean, SD, chi-square test, paired t test, anova test, validity tests [sensitivity, specificity, positive predictive value(PPV), negative predictive value(NPV)], The cut-off values were determined by calculating the sensitivities and positive predictive values at different hormonal levels according to the mean ± 2 SD of reference population, two-tailed value of $P < 0.05$ was considered statistically significant and $P > 0.005$ was considered highly significant; The SPSS Version 13.0 (SPSS Inc., Chicago, IL, USA) statistical package was used to analyze data.

Results

One hundred fifty four cases initially were recruited for the study but 11 cases were excluded [5] cases missed follow up, congenital fetal malformation was detected in one case, induced abortion was done for 2 cases, and twin pregnancy was confirmed in 3cases] thus 143 cases represented the final study population.

Distribution of cases with threatened abortion and control group according to GA was shown in Table 1.

the demographic characteristic between the studied population, , abnormal ultrasound findings were detected in 19 cases (20.4%) with threatened abortion compared to 2 cases (4%) in the control group and this was statistically significant, also, cases with threatened abortion whose pregnancy ended in abortion had a significantly higher abnormal ultrasound findings than those whose pregnancy continued (55.2% versus 4.7% respectively), As regard pregnancy outcome, spontaneous abortion had occurred in 29 cases (31.18%) with threatened abortion compared to 4% in control group (Table 2).

The mean ± standard deviation total hCG concentration(hCG + hyperglycosylated hCG) in the control group was 5.1 ± 4.6 mIU/ml and 4.9 ± 5.2 mIU/ml in threatened abortion cases who continued to term. In threatened abortion cases which terminate in miscarriage total hCG concentration was 4.6 ± 4.9 mIU/ml with insignificant difference between the three groups (Table 3).

Urinary hyperglycosylated hCG mean concentration was significantly higher in control group and cases who continued than in cases who miscarried 5.3 ± 3.9 vs. 2.1 ± 3.0 mIU/ml equivalents ($p=0.002$) for the first and 5.1 ± 4.5 vs. 2.1 ± 3.0 mIU/ml equivalents ($p=0.003$) for the second respectively.

After normalizing individual hyperglycosylated hCG concentration to individual total hCG concentrations(hyperglycosylated hCG ÷ total hCG), the 116 term pregnancies produced 91 ± 34% for control and 89 ± 21% for cases who continued respectively. Thus the ratio of hyperglycosylated hCG to total hCG was >51% in each of the 116 term outcome cases. In the 29 cases who miscarried this ratio was below 49% as they produced 46 ± 24% ($p=0.003$).

In all pregnancies ending in miscarriage the scan was performed be-tween 6 and 8 weeks' gestation. Among Doppler velocimetric parameters studied only the highest uterine artery pulsatility index

Gestational weeks	Threatened abortion N=93	Control N=50
6 weeks	11 (11.8%)	5 (10%)
7 weeks	15 (16.1%)	8 (16%)
8 weeks	17 (17.2%)	11(22%)
9 weeks	19 (20.4%)	8 (16%)
10 weeks	13 (13.9%)	5 (10%)
11 weeks	10 (10.7%)	6 (12%)
12 weeks	8 (8.6%)	7 (14%)

Table 1: Distribution of cases according to GA.

	Threatened abortion			Control N=50
	Total N=93	Aborted N=29	Continued N=64	
Age (X± SD)	29.3 ± 4.1	29.6 ± 4.6	29.1 ± 3.8	28.7 ± 5.4
Parity : parous Nulliparous	41 (44.09%) 52 (55.91%)	11 (37.9%) 18 (62.1%)	30 (46.9%) 34 (53.1%)	31 (60%) 19 (40%)
BMI	25.07 ± 3.6	25.3 ± 3.2	24.9 ± 3.9	24.6 ± 3.8
Gestational age	9.1 ± 1.68	8.95 ± 1.71	9.2 ± 1.63	9.08 ± 1.58
US findings: normal abnormal	74 (79.6%) 19 (20.4%) ** a	13 (44.8%) 16(55.2%)**b	61 (95.3%) 3 (4.7%)	48 (96%) 2 (4%)
Spontaneous abortion	29 (31.18%)** a	----------	----------	2 (4%)

BMI = body mass index, **=highly significant p> 0.005, a = total versus control, b = aborted versus continued.

Table 2: Comparison of demographic characteristic and pregnancy outcome between the studied groups.

Variable	Aborted N=29	Continued N=64	Control N=50	P Value
Total hCG (hCG + hCG –H) mIU/ml	4.6 ± 4.9	4.9 ± 5.2	5.1 ± 4.6	0.23
Urinary HCG-H mIU/ml equivalents	2.1 ± 3.0 **b	5.1 ± 4.5	5.3 ± 3.9	0.002**
(hCG -H ÷ total HCG)	46 ± 24%	89 ± 21%	91 ± 34%	0.003**
Uterine A. RI	0.82 ± 0.18	0.79 ± 0.1	0.78 ± 0.11	0.17
Highest uterine artery PI (mean ± SD) Lowest uterine artery PI (mean ± SD) Δ Uterine artery PI (mean ± SD)	3.9 ± 1.0 2.8 ± 1.0 1.2 ± 0.5	3.1 ± 0.8 2.5 ± 0.7 0.7 ± 0.6	2.85 ± 0.14 2.6 ± 0.4 0.8 ± 0.4	P < .0001 P = NS P < .0001

*= significant p> 0.05, **=highly significant p> 0.005 b = aborted versus continued.

Table 3: Comparison of urinary HCG-H and uterine artery Doppler RI and PI between the study population.

value and Δ uterine artery pulsatility index value were significantly different between women who miscarried and those with continuing pregnancies or the control groups (P < .0001). Unilaterally increased uterine artery pulsatility index and Δ uterine artery pulsatility index value were significantly higher in women who miscarried than in those with continuing pregnancies or the control groups.

Discussion

The ultimate cause of threatened abortion cannot be determined in most cases. When bleeding occurs, it could be speculated that a vascular injury might be the primary or secondary cause. Indeed, histologic studies have shown that insufficient trophoblastic invasion of the spiral arteries results in the spontaneous abortion of live fetuses [22]. Therefore, an assessment of early placentation could be useful for predicting pregnancy outcome in cases of threatened abortion with a living embryo.

Three studies performed to predict risk of miscarriage in threatened abortion cases were unable to detect any significant difference in uterine arteries Doppler indices obtained at the time of the vaginal bleeding when compared with matching normal pregnancies, and concluded that Doppler findings were not useful predictors of the pregnancy outcome [6-8]. On the other hand, another study concluded that a discordant PI values of the two uterine early as early as 6 weeks gestation can be a predictor of subsequent miscarriage. In their study including 318 pregnancies, 24 ended in spontaneous abortion in the first trimester and the event of a miscarriage was significantly associated with a history of previous miscarriage and the magnitude of the difference in PI values between both uterine arteries [9].

In this study we observed an association between unilaterally increased uterine arteries pulsatility index in the first trimester and the risk of subsequent miscarriage as previously reported [9]. The difference in the uterine arteries impedance indices could be caused by the location of the trophoblastic reaction for which one artery develops the physiologic changes before the contralateral artery, and we would suggest that a vasoconstrictive effect triggered by pregnancy may impair blood flow supply to the uterus and eventually cause early pregnancy loss.

As discussed previously, hCG-H may have a role in promoting the invasive process in implantation of pregnancies. It is speculated that low hCG-H production, or trophoblast differentiation of the hatched blastocyst at the time of implantation, may lead to inappropriate implantation and spontaneous abortion of pregnancy [21,22].

In pregnancies that spontaneously abort in the first trimester an unusually low proportions of hCG-H was detected. These low proportions started when hCG was first detected and continue until the time of spontaneous abortion [15].

Another study showed that at a cut-off 13 ng/mL, hCG-H in serum could be used to detect 73% of early pregnancy failure between 4 and 7 weeks with 5% error rate compared to 42% detection rate at a comparable cut-off for hCG. The use of this cut-off for detecting pregnancy failures was also demonstrated in urine samples, and the authors showed that an hCG-H single test or multi-point doubling time test was superior to an hCG single point or doubling time test in detecting failing pregnancies [24].

In this study the ratio of hyperglycosylated hCG to total hCG was >51% in the 116 term pregnancies, while in the 29 cases who miscarried this ratio was below 46%. Our results runs in agreement with one recent study which showed that diminished hCG-H production by a blastocyst at the time of implantation is a predictor of pregnancy failure and in some circumstances, plays a primary role in pregnancy failure.

Because hCG-H is an important signal for cytotrophoblast cells to become invasive for proper implantation, failure to produce an appropriate amount or proportion of hCG-H could well lead to suboptimal or wholly inadequate implantation.

We conclude that unilaterally increased uterine arteries pulsatility index in the first trimester and decreased urinary hCG-H production could predict miscarriage in threatened abortion.

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