Relation between single serum progesterone assay and viability of the first trimester pregnancy

Tek serum progesteron tayini ile ilk trimesterde gebeliğin canlılığı arasındaki ilişki

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Abstract

Objective: This study was designed to detect the relation between serum progesterone and viability of pregnancy during the first trimester.

Material and Methods: Two hundred and sixty women during the first trimester of their pregnancies were hospitalised due to vaginal bleeding and/or abdominal pain and were included in this study. Criteria for inclusion in this study were: certain dates, foetus conceived spontaneously with no history of infertility and a positive serum pregnancy test. Blood samples were taken from women included in this study for serum progesterone assay; the patients were followed by ultrasound until the end of the first trimester for the viability of the pregnancy and the outcome of their pregnancy was recorded.

Results: By the end of the first trimester, women included in this study were classified into: viable pregnancy group (n=178; 68.5%) and non-viable pregnancy group (ended by miscarriage) (n=82; 31.5%). The mean serum progesterone of the studied population was significantly higher in the viable pregnancy group (46.5±7.4 ng/mL) compared to non-viable pregnancy group (9.9±4.8 ng/mL; $p<0.05$). The serum progesterone cut-off level of 10 ng/mL was 79.3% sensitive for diagnosing non-viable pregnancy and 93.3% specific for the diagnosis of viable pregnancy, while a cut-off level of 20 ng/mL was 95.1% sensitive for the diagnosis of non-viable pregnancy and 98.9% specific for diagnosing viable pregnancy.

Conclusion: Serum progesterone is a reliable marker for early pregnancy failure and a single assay of its serum level can differentiate between viable and non-viable pregnancies.

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Key words: First trimester, pregnancy, serum progesterone, single, viability.

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Özet

Amaç: Bu çalışma serum progesteron ile ilk trimesterde gebeliğin canlılığı arasındaki ilişkiyi saptamak için tasarlandı.

Gereç ve Yöntemler: İki yüz altmış kadın gebeliklerinin ilk trimesterinde vajinal kanama ve/veya abdominal ağrı nedeniyle hastaneye yatırıldı ve bu çalışmaya dahil edildi. Bu çalışma için dahil etme kriterleri şunlardı: kesin tarihler, infertilite öyküsü olmaksızın spontan oluşmuş fetüs ve pozitif serum gebelik testi. Bu çalışmaya dahil edilen kadınlardan serum progesteron tayini için kan örnekleri alındı; gebeliğin canlılığı açısından ilk trimesterin sonuna kadar hastalar ultrason ile takip edildi ve gebeliğin akibeti kaydedildi.

Bulgular: İlk trimesterin sonunda çalışmaya dahil edilen kadınlar şu şekilde sınıflandırıldı: canlı gebelik grubu (n=178; %68.5) ve canlı olmayan gebelik grubu (düşük ile sonlanan) (n=82; %31.5). Çalışılan popülasyonda ortalama serum progesteronu canlı olmayan gebelik grubuna kıyasla (9.9±4.8 ng/mL) canlı gebelik grubunda anlamlı şekilde daha yüksekti (46.5±7.4 ng/mL; $p<0.05$). Serum progesteron için 10 ng/mL'lik kesim (cut off) değeri canlı olmayan gebeliği teşhis etmede %79.3 sensitif ve canlı gebeliği teşhis etmede %93.3 spesifik iken 20 ng/mL'lik bir kesim değeri canlı olmayan gebeliği teşhis etmede %95.1 sensitif ve canlı gebeliği teşhis etmede %98.9 spesifikti.

Sonuç: Serum progesteronu erken gebelik kaybı açısından güvenilir bir belirteçtir ve serum seviyesinin tek bir analizi canlı ve canlı olmayan gebelikleri ayırt edebilir.

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Anahtar kelimeler: İlk trimester, gebelik, serum progesteron, tek, canlılık.

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Introduction

Ultrasound scanning is probably the best single diagnostic and prognostic test available for diagnosing early pregnancy failure. However, there were certain conditions where both sonographic and clinical findings were indeterminate or inconclusive (1).

Progesterone is a C-21 steroid hormone secreted by granulosa cells of the ovary. This hormone is important for promoting endometrial decidualisation to prepare the uterus for implantation of the blastocyst and to maintain the pregnancy (2). The physiological functions of progesterone include inhibition of smooth muscle contractility and inhibition of immune responses, like those involved in graft rejection (2).

Recent studies have suggested that serum progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome in natural conceptions (1). Few

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studies have attempted to use serum progesterone assays to predict the outcome of pregnancy in *in-vitro* fertilisation (IVF)/ intra-cytoplasmic injection (ICSI) or in natural pregnancies, but none have produced convincing conclusions (3). It is essential to study women after natural conception without exogenous progesterone support, when the relation between serum progesterone and viability of the first trimester pregnancy was evaluated (4, 5). Therefore, this prospective study was designed to detect the relation between serum progesterone and viability of the pregnancy during the first trimester.

Material and Methods

This study was carried out over 3 years from February 2009 to February 2012. Two hundred and sixty (260) women were hospitalised due to vaginal bleeding and/or abdominal pain during the first trimester of their pregnancy and were included in this prospective study after providing informed consent, following approval of the study protocol by institute ethical committee of both hospitals (Ahmadi and Al-Rashid Hospitals).

Data were collected from women included in this study by direct questionnaire to identify age, parity, gestational age (calculated from the 1st day of last menstrual period (LMP)) and past history of early pregnancy miscarriages. Women included in the study were certain of dates, had conceived spontaneously with no history of infertility and had a positive serum pregnancy test.

Two mL blood samples were taken from women included in this study for serum progesterone assay; the samples were collected without anticoagulant in dry tubes. Serum was separated by centrifugation and stored at 2-8°C until hormonal assay was performed. The assay principle combines an enzyme immunoassay competition method with final fluorescent detection. Women included in the study were examined by ultrasound for viability of the pregnancy and accordingly the results were classified into viable and non-viable pregnancies. Those with inconclusive sonographic findings were re-examined by ultrasound after two weeks and were reclassified into viable and non-viable pregnancies according to the findings (anembryonic or missed miscarriage). Women included in this study were followed by ultrasound for the viability of the pregnancy until the end of first trimester and the outcome of their pregnancy was recorded, while women with exogenous progesterone support or multiple pregnancies or suspected ectopic pregnancy or hydatidiform mole were excluded from this study.

The ultrasound was done by an expert sonographer, who was blinded to the patients' data, using Philips HD9 (Philips HealthCare International, Amsterdam, Netherlands) with a 2D convex probe (4-9 MHz). Data were collected and statistically analysed to detect the relationship between serum progesterone level and viability of the pregnancy during first trimester.

Using data of previous studies (6, 7), setting the type-1 error (α) at 0.05, the power (1-β) at 0.8 and assuming a 5% dropout rate, the number of participants needed to produce a statistically acceptable figure was more than two hundred women. Data were collected, tabulated then statistically analysed using the Statistical Package for Social Sciences (SPSS) computer software version 15. Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number and percentage. Chi-square test (X^2) was used for comparison between groups as regard qualitative variables. A difference with a p value <0.05 was considered statistically significant. Sensitivity is the proportional detection of individuals with the disease of interest in the population; specificity is the proportional detection of individuals without the disease of interest in the population.

Results

Two hundred and sixty women were hospitalised due to vaginal bleeding and/or abdominal pain during first trimester of their pregnancy and were included in this study. The mean age of the studied population was 32.7±5.1 years (ranged from 18-38 years), their mean parity was 4.2±5.7 (ranged from 0-9) and the mean gestational age at progesterone assay was 9.7±0.5 weeks (ranged from 7-11 weeks) (Table 1).

By the end of the first trimester, women included in this study were classified according to the viability of their pregnancies into the viable pregnancy group (n=178; 68.5%) and the non-viable pregnancy group (ended by miscarriages) (n=82; 31.5%); data are shown in Table 2.

The mean serum progesterone was significantly higher in viable pregnancy group (46.5±7.4 ng/mL; range 18.7-86.3 ng/mL), compared with non-viable pregnancy group (9.9±4.8 ng/mL; range 1.67-26.2 ng/mL) (Chi-square test, $p<0.05$); results are shown in Table 3.

The relations between serum progesterone and maternal age or gestational age of the studied populations were statistically insignificant; also, the relation between serum progesterone and past history of early miscarriage was statistically insignificant (Chi-square test; $p>0.05$); see Table 4.

In this study, 6.7% of viable pregnancies had a serum progesterone level <10 ng/mL, while 20.7% of the non-viable pregnancies had a serum progesterone level >10 ng/mL; the serum progesterone at a cut-off level of 10 ng/mL was 79.3% sensitive for the diagnosis of non-viable pregnancy and was 93.3% specific for diagnosing viable pregnancy. Also, in this study, 1.1% of viable pregnancies had a serum progesterone level <20 ng/mL, while

Table 1. The characteristics of the studied population

Variables	Mean±SD	Range
Age (Year)	32.7±5.1	18-38
Parity	4.2±5.7	0-9
Gestational age at progesterone assay (Weeks)	9.7±0.5	7-11

Table 2. Classification of the studied population according to the viability of the pregnancy

Ultrasound Findings	Number	Percentage
Viable pregnancy group	178	68.5%
Non-viable pregnancy group	82	31.5%
Missed abortion	53	20.4%
Anembryonic (blighted ovum)	29	11.1%
Total number of cases	260	100%

4.8% of non-viable pregnancies had a serum progesterone level >20 ng/mL; the serum progesterone at a cut-off level of 20 ng/mL was 95.1% sensitive for diagnosing non-viable pregnancy and 98.9% specific for the diagnosis of viable pregnancy (see Table 5).

Discussion

Recent studies suggest that serum progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome in natural conceptions (1, 5, 6). Therefore, this prospective study was designed to detect the relation between serum progesterone and viability of the pregnancy during the first trimester.

Progesterone level and daily change in human chorionic gonadotropin (β-hCG) were determined in the serum of 307 patients with suspected ectopic pregnancy by Hahlin et al. (7), who found that 99% of the viable intrauterine pregnancies had serum progesterone more than 30 nmol/L (9.42 ng/mL; 1 nmol/1 = 0.314 ng/mL), whereas 75% of the ectopic pregnancies and 81% of the spontaneous abortions had serum progesterone less than 30 nmol/L (9.42 ng/mL). Also, serum samples were taken to assess progesterone, inhibin A, hCG, and urine β-core hCG from 220 women who presented in the first trimester of pregnancy with complaints of pain, cramping, bleeding or spotting by Phipps and colleagues, in order to evaluate whether those biomarkers could predict viable and non-viable outcomes in pregnancy; they concluded that serum progesterone was the most specific single biomarker for distinguishing viable from non-viable pregnancies (6).

However, Lijun et al. (8) concluded that serum progesterone combined with β-hCG measurements, with a diagnostic accuracy of 85.7%, had the best prognostic reliability for predicting the outcome of threatened miscarriage compared to serum progesterone alone or β-hCG alone. Daily et al. (9) found that the mean serum progesterone was significantly higher for viable pregnancies (22.1 ng/mL) compared to non-viable pregnancies (10.1 ng/mL) and they concluded that a serum progesterone assay alone is predictive of pregnancy outcome, especially during the first 8 weeks of gestation. Also, Al Jufairi (5) found that serum progesterone level was significantly higher in patients with viable pregnancies (20.48±6.066 ng/mL) compared with patients with non-viable pregnancies ended by spontaneous abortion (7.78±2.06 ng/mL); this author concluded that serum progesterone alone is a reliable marker for the prediction of early pregnancy failure.

The relations between serum progesterone and maternal age or gestational age of the studied population were statistically insignificant; also the relation between serum progesterone and past history of early miscarriage was statistically insignificant.

In this study, 6.7% of viable pregnancies had serum progesterone level <10 ng/mL, while 20.7% of non-viable pregnancies had serum progesterone level >10 ng/mL; the serum progesterone at a cut-off level of 10 ng/mL was 79.3% sensitive for the diagnosis of non-viable pregnancy and was 93.3% specific for diagnosing viable pregnancy. Also in this study, 1.1% of viable pregnancies had a serum progesterone level <20 ng/mL, while 4.8% of non-viable pregnancies had a serum progesterone level >20 ng/mL; serum progesterone at a cut-off level of 20 ng/mL was 95.1% sensitive for diagnosing non-viable pregnancies and was 98.9% specific for the diagnosis of viable pregnancy.

Ninety-five pregnant women of 13 weeks gestation or less were recruited as a study group and fourteen normal pregnant women were recruited as controls, to determine the role of serum progesterone as a marker of early pregnancy failure after single assay by Hanita et al. (2). They found that the serum progesterone levels were significantly lower in women with non-viable pregnancies compared with women with viable pregnancies (10.7 ng/mL vs. 45.9 ng/mL, respectively). Hanita et al. (2) concluded that serum progesterone can be used as a marker for early pregnancy failure

Table 3. The relation between serum progesterone and viability of the pregnancy

Pregnancy outcome	Number (%)	Serum Progesterone (ng/mL)	Test used p value (significance)
Viable Pregnancy group	178 (68.5%)	46.5±7.4 (18.7-86.3)	Chi-square (X^2) p<0.05 = 0.036 (significant)
Non-viable Pregnancy group	82 (31.5%)	9.9±4.8 (1.67-26.2)	

Table 4. The relation between serum progesterone and maternal age, gestational age or past history of early miscarriage

Variables	Number (%)	Serum Progesterone (ng/mL) Mean±SD	Test used p value (Significance)
Maternal age			Chi-square (X^2)
> 35 years old	142	24.62±8.2	p>0.05 = 0.76
< 35 years old	118	18.52±6.8	(Non-significant)
Past history of early miscarriage			Chi-square (X^2)
Positive	48	12.26±2.3	p>0.05=0.07
Negative	212	27.81±5.7	(Non-significant)
Gestational age			Chi-square (X^2)
> 10 weeks gestation	77	16.27±4.7	p>0.05 = 0.27
< 10 weeks gestation	183	26.45±3.9	(Non-significant)

Table 5. Relations between serum progesterone cut off levels and viability of the pregnancy

Variables	Viable Pregnancy group (Total number=178)	Non-viable Pregnancy group (Total number=82)
Serum Progesterone at cut off level 10 ng/mL		
Number of cases with serum progesterone <10 ng/mL (%)	12 (6.7%)	65 (79.3%=Sensitivity)
Number of cases with serum progesterone >10 ng/mL (%)	166 (93.3%=Specificity)	17 (20.7%)
Serum Progesterone at cut off level 20 ng/mL		
Number of cases with serum progesterone <20 ng/mL (%)	2 (1.1 %)	78 (95.1%=Sensitivity)
Number of cases with serum progesterone >20 ng/mL (%)	176 (98.9%=Specificity)	4 (4.8%)

and at a cut-off value of 32.7ng/mL serum progesterone had 90% sensitivity with 75% negative predictive value (NPV) and 92% specificity with 97% positive predictive value (PPV) to diagnose early pregnancy failure.

Four hundred and eighty-nine women presenting with singleton pregnancy, vaginal bleeding and/or abdominal pain in the first 18 weeks of pregnancy were included in a prospective comparative study by Al-Sebai et al. (10), to assess the role of a single maternal serum progesterone measurement in the immediate diagnosis of early pregnancy failure and in the long-term prognosis of foetal viability. They found that serum progesterone levels were significantly lower in the non-continuing and tubal pregnancy groups compared to threatened-continuing groups and a cut-off level of 45 nmol/L (14.13 ng/mL) was found to differentiate between the viable pregnancies and the abnormal (non-continuing) pregnancies with 87.6% sensitivity and 87.5% specificity. Al-Sebai et al. (10) concluded that a single serum progesterone measurement taken in early pregnancy is valuable in the immediate diagnosis of early pregnancy failure and the long-term prognosis of viability.

Also, a prospective study was conducted by Ioannidis and colleagues to investigate the relation between early (14 days after oocyte recovery) serum progesterone assay and pregnancy outcome in women undergoing in-vitro fertilization (IVF)/intracytoplasmic injection (ICSI) and receiving rectal progesterone supplements. They found that the single progesterone assay on day 14 post-oocyte retrieval was significantly higher in women with on-going pregnancies compared to women with an abnormal pregnancy. Ioannidis et al. (11) concluded that a single serum progesterone measurement could be a useful indicator of pregnancy outcome in women undergoing IVF/ICSI treatment. Also, the result of this study suggests that serum progesterone is a reliable marker for early pregnancy failure and that a single assay of its serum level can differentiate between viable and non-viable pregnancies. Future trials and large population studies are needed to support our findings and to establish the cut-off values of serum progesterone to differentiate between viable and non-viable pregnancies.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committees of both Ahmadi Hospital (Kuwait Oil Company) and Al-Rashid Hospital.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

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