THE VALUE OF EARLY PREGNANCY SINGLE SERUM PROGESTERONE MEASUREMENT IN RELATION TO THE FIRST TRIMESTER VIABILITY

Assist Prof. Dr. Edwar Z. Khosho*, Dr. Mahasin M. Aiub**
Dr. Suror Adnan **

ABSTRACT

The diagnosis of pregnancy require a multi factorial approach using three main diagnostic test, these are: clinical , laboratory & ultrasound examination. There is no single test currently available which immediately differentiate continuing from non continuing intra uterine or tubal pregnancy[1].

Aim of the study

To assess the use of single serum progesterone measurement in early pregnancy and its relation to the 1st trimester fetal viability.

Patients and methods

A prospective study conducted in Basrah maternity and child hospital to assess and predict 1st trimester fetal viability using a single serum progesterone measurement for women who attend the hospital either as their 1st antenatal booking or hospitalization for vaginal bleeding or abdominal pain whom were followed for the end of 13th week of gestation and progesterone levels were compared to the fetal viability using ultrasound examination and results were analyzed statistically.

Result

The study group enrolled 78 pregnancies, 44 pregnancies had continue viable till 13th week of pregnancy and 34 ended with spontaneous abortion. Serum progesterone level was 5.7 ± 10.9 in continuing pregnancy and 6.7 ± 4.8 in spontaneous abortion.
The difference progesterone level was highly significant (p value<0.0001).

Conclusion

Serum progesterone measurement is a reliable biochemical test in establishing the diagnosis of early pregnancy failure and a predictive test for pregnancy continuation.

INTRODUCTION

The diagnosis of pregnancy requires a multifaceted approach using three main diagnostic. tools. These are history& physical examination, laboratory evaluation and ultrasonography .There is no single test currently available which immediately differentiates continuing from non continuing intrauterine or tubal pregnancy[1]. The most commonly assays are for the β subunit of hCG and other hormones that have been used include progesterone and early pregnancy factors. The value of serum progesterone estimation in early pregnancy has been

* F ICMS, DGO, University of Basrah medical college
** Obst /Gyncol, CABOG , DGO, Basra Maternity Hospital
** M.B.Ch. B, Basrah medical college

studied by many investigators and it was established that serum progesterone was of great help in differentiating between viable and non viable pregnancy [2, 3]. The main categories of early pregnancy disorders are spontaneous miscarriage, ectopic pregnancy and gestational trophoblastic disease [4]. The exact mechanisms responsible for miscarriage are not always apparent, but many conditions regarded as associated factors like :fetal abnormalities which is most common occur in about 40% and it include chromosomal, structural and genetic abnormalities, abnormal implantation, multiple pregnancy, intrauterine adhesions, uterine abnormalities, maternal diseases, infections, poisions, cervical incompetence, trauma, thrombophilia, immunological disease and endocrine abnormalities [5] of endocrine disorder is Insufficient progesterone secretion by the corpus luteum or placenta has been associated with an increased incidence of abortion. It has been suggested that abnormal levels of one or more hormones might help to forecast abortion. Unfortunately, reduced levels of these hormones are usually the consequence rather than the cause . There are well-documented cases of luteal phase defects, but they are uncommon[5]. Progesterone is produced in two ways by the ovarian cells : it is secreted in a tonic fashion by luteinized granulose cells and it is released in a pulsatile fashion by luteinized theca cells. Tonic released is independent of LH stimuli, and its purpose seems to involve sustaining appropriate endometrial maturation.Pulstile release is in indirect response to LH stimulation, and is responsible for responding to hCG in the event of conception to the assist the corpus luteum in supporting a successful pregnancy. Aging has been shown to effect pulsatile progesterone secretion[6].

Effects of Luteal Phase Defects

Main function of progesterone is to induce differentiation of the endometrium in preparation for implantation of the embryo , and to prepare the body for the demands of pregnancy. If the amount or timing of progesterone release or the response of the endometrium to its stimulation is inadequate, the embryo fail in its attempts to achieve successful implantation resulting in infertility or spontaneous abortion. Recent studies have revealed an additional effect of progesterone on the endometrium that enable implantation . K aul, et.al. investigated levels of endometrial Decay Accelerating Factor (DAF) , a complement regulatory protein in women diagnosed with leuteal phase defect .DFA is involved in protecting the semiallogenic (i.e partially antigenic, as it also consist of paternal genetic maternal) fetus from the maternal system by binding to activated C4b and C3b fragments and preventing the complement cascade mediated cytotoxic attack. Levels of this protein increase during the secretory phase in the human endometrium. The study found secretory phase DAF level in women with leuteal phase defect to be only 25% of the control population. It was discovered that DAF levels increased from a mean value of 12% to 88% in the leuteal phase defect group after progesterone therapy (vaginal progesterone suppositories 25 mg. b.i.d. for 14 days).Thus a progesterone effect on DAF expression in the secretory phase may be essential for successful implantation[7]. Other studies demonstrating the positive effect of progesterone on uterine blood

flow suggest that progesterone supplementation decrease blood flow impedance and uterine artery pulsatility index in women with leuteal phase defect treated with ovulation inducing agents. This was hypothesized to improve pregnancy rates secondary to improved uterine perfusion, but whether similar results would be obtained with women not on those specific drugs or spontaneous cycles was not studied[8]. In pregnancy progesterone is initially produced by the corpus luteum which is the main source of this hormone until about the tenth week of pregnancy. The syncytiotrophoblast of the placenta produce significant amount from about the sixth or seventh week onwards, and after a transitional period , is responsible for all the production of progesterone from the 14th week onwards.90% of progesterone produced in the placenta enters the maternal blood stream and only 10% enters the fetus[9]. There is progressive increase in maternal plasma progesterone levels from about 40ng/ml in the first trimester to 160ng/ml at term. The plasma levels of 17 α-hydroxyprogesterone, which is mainly derived from the ovary, rapidly increase up to about the eighth week, after which it remains relatively constant until the 32nd week when there is a further increase due to the production of increasing amounts of 17 α -hydroxyprogesterone by the fetal adrenal. Progesterone has been regarded as the main pregnancy hormone balancing and inhibiting the stimulatory effect of estrogen until the last few weeks of pregnancy[9]. The first demonstration of an intrauterine pregnancy by means of transvaginal ultrasound was reported in 1967 [5]. As ultrasound findings are not diagnostic in a significant number of women with early pregnancy failure, many units now measure various biochemical

parameters to predict pregnancy outcome as well as in predicting the success of expectant management of failing pregnancies both intrauterine and ectopic. To use this approach effectively one requires access to the results of biochemical parameters within 24–48 hr. This is feasible for HCG and in some cases progesterone, but not at present for inhibin A and insulin growth factor binding protein1, which at present can only be recommended within a research setting [10]. Measuring serum progesterone may be a useful adjunct for evaluating abnormal early pregnancy. Serum progesterone is a reflection of progesterone production by the corpus luteum, which is stimulated by a viable pregnancy. Measurement of serum progesterone is inexpensive and can reliably predict pregnancy prognosis [11]. Currently, radioimmunoassay and fluoroimmunoassays are available that can be completed in 3-4 hours . ELISA can determine a serum progesterone level of less than 15 ng/ml which is helpful as a screening tool for at risk patients because progesterone levels of greater than 15 ng/ml make ectopic pregnancy unlikely[11]. Viable intrauterine pregnancy can be diagnosed with 97.5% sensitivity if the serum progesterone levels are greater than 25 ng/ml (>79.5 nmol/L). Conversely, finding serum progesterone levels of less than 5ng/ml (<15.9 nmol/L) can aid in the diagnosis of a nonviable pregnancy with 100% sensitivity. Finding serum progesterone level of less than 5 ng /mL allow diagnostic evaluation of the uterus in a stable patients , further testing using ultrasound, additional hormonal assays, or serial examinations is warranted to establish viability of pregnancy[12,13].

AIM OF THE STUDY

To assess the use of single serum progesterone measurement in early pregnancy and its relation to the 1st trimester fetal viability.

PATIENTS & METHODS

A prospective study carried out in Basrah maternity hospital from January 2010 to August 2010.The study involved those pregnant women in their first trimester(lower than 13weeks of gestation) who attended the hospital either as their first antenatal booking or hospitalized for vaginal bleeding or abdominal pain.

Information were collected by direct questioner to the patients including: woman age, parity, gestational age which determined by last menstrual period and any previous early pregnancy miscarriage were recorded . All women included in the study were conceived spontaneously with no history of infertility and all thy had a positive urinary or serum pregnancy test. After taking informed consent from the patients ,2ml of peripheral blood sample were taken for serum progesterone measurement the sample were obtained without anticoagulant collected in dry tube .In the lab. ,serum was separated by centrifugation and stored at $2\text{-}8^{\circ}C$ until hormonal level measurement. The assay principle combines an enzyme immunoassay competition method with final fluorescent detection. At the end of the assay, result were analyzed using ng/mL unit . All patients included in the study were examined by ultrasound for confirmation of pregnancy and for fetal viability and accordingly results were classified into:

- Viable pregnancy with visible fetal heart

- Anembryonic pregnancy(blighted ovum)
- Missed abortion
- Suspicion of ectopic pregnancy
- Inconclusive ultra sound
- Hydatidiform mole
- Multiple pregnancy

Those with inconclusive ultra sound re-examined by further ultra sound after two weeks and again the result were reclassified into viable, anembryonic, missed or ectopic pregnancy. Cases with normal pregnancy and those with threatened abortion, were followed by the ultrasound for the end of first trimester and the outcome of their pregnancy were recorded, while cases of multiple pregnancy, suspected ectopic pregnancy & Hydatiform mole were excluded from our study. The relationship between serum progesterone level and first trimester pregnancy outcome was analyzed using the SPSS program ,the mean, range & the standard deviation were calculated. P value less than (0.05)was considered as statistically significant.

RESULT

Our study enrolled 78 women in Basrah maternity hospital between January 2010 & August 2010.Majority of them attended the hospital as antenatal visit for check up & the others were already admitted to the hospital either with vaginal bleeding or abdominal pain. All women had serum progesterone measurement in early pregnancy.

TABLE I show data of women included in the study :the mean age of the women was 27.2 year with range of (16-41) and their parity ranged from (0-9) .The gestational age at the time of progesterone assay ranged from 7-11 wks (mean= 8.2 , SD= 0.8).

Table II Show the result of u/s examination in 78 women included in the study .As shown from the table that 41 case (52 .6%) ,the u/s revealed a viable fetus ,while unembryonic or missed abortion was diagnosed by u/s in 34 case (43.6%) and the u/s examination was in conclusive in 3 cases (3.8%). Patients were followed for the end of 1st trimester (13 wks) and we found that 44 (56.4%) had continues viable pregnancy and 34 case (43.6%) women had miscarriage .

Table III show 1st trimester pregnancy outcome and progesterone level. As shown is the table the pregnancies which continued had a serum progesterone level varying between 8.7 – 41.3 ng/mL.(mean +SD=25.7+10.9) and 95%CI (confidence interval)was 21.3 - 28.1 ,while the rang of serum progesterone in pregnancies which ended with miscarriage was varying between 0.81 - 20.1 ng/mL (mean +SD=6.7+4.8) and 95% CI was 4.8-8.7.When the pregnancy out com was compared using T-test the difference of serum pregnancy level was highly significant (p.value <0.0001).

In the 44 women with viable fetus only (4.5%)had a value below (10.)ng/mL,While 20.6% of spontaneous miscarriage had a value of >10ng/mL .

Multivariate analysis showed that age &previous pregnancy loss did not affect the outcome, there was no correlation between gestational age and progesterone level (p 0.36) and correlation (0.104).

As shown in table IV there was no correlation between gestational age and serum progesterone level (P =0.36&correlation coefficient=0.104)

DISCUSSION

The measurement of serum progesterone is a valuable test in the diagnosis of early pregnancy failure. We have studied 78 woman in their first trimester who attended Basrah maternity hospital. Those women were tested using a single serum progesterone measurement for assessment and prediction of first trimester fetal viability. Follow up was limited to the end of first trimester because of the short period of study, and we used measurement of serum progesterone level as a predictor of fetal viability because the assaying is in expensive and the level change little during pregnancy [14]. In our study, we found that there was no correlation between gestational age and progesterone level(correlation coefficient =0.104,value 0.36) and this is agree with Hahlin et al study which reported that the discriminatory efficacy of a single progesterone determination was not increased by serial estimation of progesterone level [15]. We found that of 78 women included in our study 44(56.4%)had viable pregnancy by u/s examination ,34(43.6%)had a missed abortion .After comparison between the two groups we found that the difference of serum progesterone level between viable and missed was statically highly significant (P value <0.0001). The cut off level of serum progesterone value which can differentiated between viable and missed pregnancies has varied between 10 – 20 ng/mL according to different studies [1,16,17]. In our study 4.5% of viable pregnancies had serum progesterone level less than 10 ng/ ml While 20.6% of spontaneous miscarriage had a value of more than 10 ng/ml. Sensitivity 79.4%for failed pregnancy and specificity 95.5% for the value less than 10 ng/ml. However no viable pregnancy was present with progesterone level of less the 8.7 ng/mL and this agree with result of stoval *et al* [18]. Other studies showed that serum progesterone level of ≥25ng\ml can

exclude ectopic pregnancy with 97.5% sensitivity and a value of ≤5ng\ml is 100% sensitive for diagnosis of missed abortion. In pregnancies with progesterone value above 5ng or below 20ng\ml. viability must be established by sonographic examination (12)

CONCLUSION

In summary, though the number of cases were small, a significant difference of serum progesterone level was shown between viable and non viable pregnancy. This study has demonstrated that serum progesterone measurement is a reliable biochemical test in establishing the diagnosis of early pregnancy failure.

TABLES

TABLE I : DATA OF (78) WOMEN IN THE STUDY

	MEAN	SD	RANGE
AGE (year)	27.2	6.2	16 - 41
Parity	2.1	1.8	0 - 9
Gestational AGE (week) at progesterone assay	8.2	0.8	7 - 11

TABLE II : RESULT OF U/S EXAMINATION

U/S RESULT	NO.	PERCENTAGE
Viable pregnancy	41	52.6
Missed abortion	34	43.6
Inconclusive	3	3.8
Total	78	100

TABLE III : PREGNANCY OUTCOME AND PROGESTERONE LEVEL IN 78 PREGNANCIES

OUTCOME	NO.	PROG. RANGE (ng/mL)	MEAN (SD)	95% CI
Pregnancy continue to 13 weeks	44	8.7 – 41.3	25.7 (10.9)	21.3 - 28
Miscarriage (BLIGHTED)	34	0.8 – 20.13	6.7 (4.8)	4.8 – 8.7

Table IV Correlation between gestational age & serum progesterone level

	GESTATIONAL AGE	S.PROGESTERONE
- Gestational age pearson correlation -Sig.(2-tailed) -No.	1 78	0.104 0.36 78
-S.Progesterone Pearson correlation -Sig.(2-tailed) -No.	0.104 0.366 78	1 78

Table v. Cut off level of serum progesterone value between viable and non viable pregnancies.

STUDY	CUT OFF LEVEL ng/ml	SENSITIVITY %	SPECIFICITY %
Al Sebai et al	14.1	87.6	87.5
Hubinont et al	15	64.7	88.9
Saver et al	20	98	100
Yeko et al	15	97	100

Buck et al	20	92	89
Hahlin et al	9.4	86	100
Hahlin et al	9.4	87.6	87.5
Zanab	10	69.2	95..2
Present study	10.1	79.4%	95.5%

REFERENCES

1.Al sebai MAH,Kingsland CR , Diver M.et al.The rule of a single progesterone measurement in the diagnosis of early pregnancy failure in the progress of fetal viability.Br J obstetrics & gynecology 1995;102:364_69.

2.Nyberg DA ,Mack,Jeffrey,et al.Endovaginal sonographic evaluation of ectopic pregnancy :A prospective study.AJR 1987;149:1181_6.

3. al sebai MAH,Diver M,Hipkinl.the rule of a single progesterone measurement in the diagnosis of early pregnancy failure& the prognosis of fetal viability.[correspondence],Br J. obstetrics & gynecology 1996;103:391.

4. Joanne Topping and Roy G. Farquarson (spontaneous miscarriage), Role of u\s , and u\s feature in early pregnancy loss classification , diagnosis of miscarriage ,Dewhursts text book of obstet. And Gynaec. Seventh edition . 2007 . ch . 12. P. 94- 98.

٥-F. Gary Cunningham, Kenneth et al, spontaneous abortion. William, obstetric 2nd edition p 232, 2005.

6.Ellison,"progesterone",saliva as diagnostic fluid.ANAS 1993;694.p 165_173.

7.Kaull A,Negamani M,Nowicki B.Decreased expression of endometrial decay factor (DAF),a complement regulatory protein in patient with luteal phase defect. A JRI 1995;34.p236_240.

8.Strignini FAL، et al، modifications in uterine and intraovarian artery impedance in cycle of treatment with exogenous gonadotrophin effect of luteal phase support .Fort-Sterol .1995,64.p76-80.

9. . D.K . EDMONDS : intersexuality , Dewhurst,s Text book of obstet. and Gynaeco 5th edition . 1995 , p.14 .

10.Elson J &Jurkovic D(2004) biochemistry in diagnosis & management of abnormal early pregnancy.Cur.opin obstet. Gyaencol. 16,339_44.

11.Davies S, Byrn F, Cole LA.Human chorionic gonadotropin testing for early pregnancy viability & complications.Lab mel. Jun 2003(2):257_64. Vil[medline].

12.Stovall TG,Ling FW, Coop BJ, et al , preventing rupture ectopic pregnancy with a single serum progesterone , Am J obstet. Gyaencol. 1989;160:1425-31.

13.Gelder MS, Bats LR, Young JB.use of single random serum progesterone levels in normal & abnormal early human pregnancy.Fertil. Steril 1990;54:537_8.

14-Carcor SA, Bustr J.Current concept: ectopic pregnancy. The new England J.med.1993;329:1174-8.

15-Hahlin M, wallin A, Sjoblom p, et al. single progesterone assay for early recognition of abnormal pregnancy . Hum Reprod 1990;5:622-6.

16- Saver MV , Sinosich MJ , Yeko TR, et al. predictive value of a single serum pregnancy associated plasma protein A or progesterone in the diagnosis of abnormal pregnancy .Hum Reprod 1989;4:331-4.

17- Hahlin M, Sjoplom p,Lindblom P. Combined use of progesterone and human chorionic gonadotrophin determination for differential diagnosis of very early pregnancy.Fertil Steril 1991;55:492-6.

18-Stovall TG,Ling FW, Carson SA, et al . Serum progesterone and uterine curettage in differential diagnosis of ectopic pregnancy .Fertil Steril 1992;57:456-8.

استخدام قياس قيمة هرمون البروجستيرون في دم الامهات الحوامل في بداية الحمل كمؤشر لحيوية الحمل

الاستاذ المساعد الدكتور ادور زيا خوشو*، الدكتورة محاسن محمد ايوب **
الدكتورة سرور عدنان عبد النبي

الخلاصة

ان تشخيص الحمل يتطلب عوامل متعددة وباستخدام ثلاث طرق تشخيصية هي: التشخيص السريري ، التشخيص المختبري ،والتشخيص بالامواج الفوق صوتية .لكن يوجد في الوقت الراهن اي تحليل عن طريقة نستطيع ان نفرق بين الحمل الذي سيستمر من الحمل الذي لا يستمر او عن طريقه نفرقه عن الحمل عندما يكون خارج الرحم.

الهدف من الدراسة

لاختبار قياس قراءة واحدة لهرمون البروجستيرون في دم الام الحامل في بداية الحمل وعلاقته بحياه الجنين في الاشهر الثلاثة الاولى من الحمل .

طرق الدراسة

اخذنا عينة من المريضات الحوامل اللواتي راجعن مستشفى البصرة للنسائية والاطفال في بداية الحمل وكانت مراجعتهن لغرض المتابعة الشهرية او ادخلن المستشفى بسبب حصول نزف مهبلي او بسبب الام البطن ثم تابعنا المريضات في نهاية الاسبوع ١٣ للحمل وقارنا قراءة قياس هرمون البروجستيرون في دم الام الحامل مع متابعتهن بفحص الامواج الفوق الصوتية لبيان وضع الاجنة ثم تم تحليل كل نتائج الدراسة لطرق الاحصاء الحياتي .

النتائج

عدد النساء الحوامل في عينة الدراسة هو ٧٨ حامل منهن ٤٤ حامل استمر الحمل والجنين حي لغاية ١٣ اسبوع ،٣٤حامل انتهى الحمل باسقاط . وتبين ان قيمة البرويتيجيرون في دم الام الحامل في الحوامل الذي استمرمنه الجنين هو ١٠،٩ ±٥،٧ وقيمة البروجستيرون في دم الام الحامل للنساء الحوامل الذي انتهى فيه الحمل باسقاط كان ٦،٧±٤،٨ وهذة النتائج لها قيمة احصائية جيدة.

الاستناجات

من هذة الدراسة نستنتج ان قياس قيمة هرمون البروجستيرون في دم الام الحامل له اهمية في تحديد او تشخيص فشل الحمل في الاشهر الثلاثة الاولى وكذلك له القدرة على توقع استمرارية الحمل من دونه .

----

* اختصاص نسائية وتوليد ، شهادة البورد العربي

** اختصاص نسائية وتوليد، شهادة البورد العراقي