

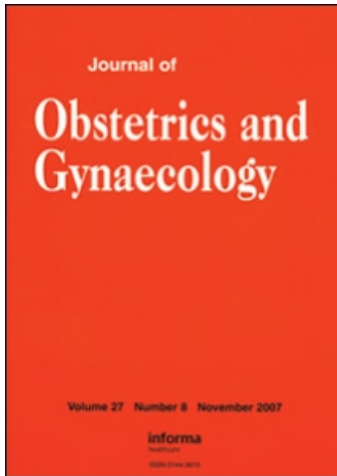
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The role of single serum progesterone measurement in conjunction with β hCG in the management of suspected ectopic pregnancy

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Summary

Our aim was to test the use of single serum progesterone measurement together with β hCG in the management of women with pregnancy of unknown location. This was a retrospective study of 126 patients presenting with a clinical picture suggestive of ectopic pregnancy, when ultrasound examination was inconclusive. All the patients had serum progesterone level measured by radioimmunoassay in conjunction with β hCG. The study showed that a protocol combining single serum progesterone measurement and β hCG is helpful in managing women with suspected ectopic pregnancies, when the ultrasound examination is inconclusive. High levels of progesterone are reassuring as regards ongoing viable pregnancies and low levels allow a definitive differentiation between viable and non-viable pregnancies. However, low progesterone could not efficiently differentiate between miscarriage and ectopic pregnancy. The use of β hCG levels in conjunction with serum progesterone is helpful, particularly with serum progesterone levels between 16–80 nmol/l.

Keywords

Progesterone, ectopic, β hCG, miscarriage, viable

Introduction

In the UK, there are around 11,000 cases of ectopic pregnancy per year (incidence 11.5 per 1,000 pregnancies), with four deaths (a rate of 0.4 per 1,000 ectopic pregnancies) (Tay et al. 2000). The most common location of an ectopic pregnancy is in the fallopian tube, rarely ectopics occur in the ovary, cervix and the abdomen (Bakken and Skjeldestad 2003). The incidence has gradually increased over the years, with advancing maternal age, tubal surgery, pelvic inflammatory disease and assisted reproductive techniques all contributing to the increasing trend (Bouyer et al. 2002).

Ectopic pregnancy is potentially life-threatening and remains the leading cause of maternal death. The recent three confidential enquires have shown, disappointingly, that deaths from ectopic pregnancies have not fallen. The main reason for this has been non-diagnosis (Lewis and Drife 2004).

The role of β hCG has been accepted universally but that of serum progesterone is still controversial. Following implantation, progesterone is secreted in increasing amounts by the trophoblasts and can be detected in the maternal circulation in about 10 days at a gestational age of 2.5 weeks. β hCG doubles every 2 days following a linear trajectory, whereas progesterone remains relatively constant. Hence a single serum measurement of serum progesterone as opposed to serial β hCG is sufficient. In failing pregnancies (miscarriage and ectopic pregnancies), the rate of increase of β hCG is lower than that for a normal pregnancy, and since the production of progesterone is dependent on stimulation by β hCG, progesterone level is therefore reduced (Tay et al. 2000).

The use of progesterone was introduced into the authors' department 3 years ago in the management of patients presenting with signs and symptoms suggestive of ectopic

pregnancy. This was to reduce the number of β hCGs performed to reach a diagnosis of ectopic pregnancy. An audit of managing women with suspected ectopic pregnancy has revealed that some patients had up to six serial β hCG measurements to reach a diagnosis, which instigated altering existing protocols. This study aims at detecting whether a protocol combining serum progesterone and a maximum of two serial measurements of β hCG helps in the diagnosis of ectopic pregnancy. There have been many studies addressing the use of single measurement of progesterone in managing women with suspected ectopic pregnancy, as will be fully mentioned in the discussion but there is no significant evidence in the literature on its use in conjunction with β hCG levels in a combined protocol.

Material and methods

This is a retrospective study of 357 women presenting to the University Hospital of North Durham with signs and symptoms suggestive of ectopic pregnancy. All patients had detailed history taking and examination. They all had ultrasound examination, where a diagnosis of ectopic pregnancy, intrauterine pregnancy or miscarriage was reached and the patients were managed accordingly. In 126 patients, the scan results were inconclusive and therefore the levels of β hCG and progesterone were measured by radioimmunoassay. Depending on the results, they were managed as per protocol (Table I). Only patients with inconclusive scans were included in the study, women where scans confirmed the presence of intrauterine gestational sac/fetal pole were excluded. In women where the scans confirmed the presence of ectopic pregnancy they were managed accordingly and thus there was no indication for serum progesterone measurement.

Table I. Protocol for managing women with inconclusive scans and possible ectopic pregnancy.

Progesterone (nmol/l)	β hCG (IU/l)	Management
<16	>25	Failing pregnancy, repeat pregnancy test after 1 week unless clinically indicated*
16–80	>25	Likely an ectopic pregnancy, repeat β hCG in 48 h if not increasing adequately [†] , for laparoscopy
>80	<1,000	Likely intrauterine pregnancy repeat scan in 48 h
>80	>1,000	Likely ectopic pregnancy, repeat β hCG in 48 h if not increasing adequately, for laparoscopy

*Patients were aware of the possibility of ectopic pregnancy with low progesterone levels and thus advised to report earlier if they developed certain symptoms.

[†] β hCG is expected to increase by at least 65% in healthy intrauterine pregnancy.

The age of the women ranged from 20–40 years. Some 84 of the patients were primiparous the remaining were multiparous, 31% of the patients had previous risk factors (previous ectopic pregnancy, tubal surgery, pelvic infection, IVF, IUCD), while 69% had no previous risk factors. Seven (13.5%) of women with progesterone levels <16 nmol/l and 12 (18.8%) of women with progesterone 16–80 nmol/l had risk factors, while none of the women with progesterone >80 nmol/l had any previous risk factors. There was no significant difference as regards gestational age, based on last menstrual period between women with progesterone <16 nmol, between 16 and 80 nmol/l and >80 nmol/l (see Table V).

All patients were monitored until a criterion standard diagnosis of intrauterine pregnancy, ectopic pregnancy or miscarriage was confirmed.

The data was analysed using the McNemar test to determine their statistical significance.

Results

The level of serum progesterone ranged from 2–151 nmol/l; mean 32.6; standard deviation (SD) 30.2. The level of β hCG ranged between 19 and 155,370 IU/l; mean 12,773; standard deviation 26,846.

A total of 52 (41.3%) patients had a progesterone level of <16 nmol/l, the level ranged 2–15 nmol/l. In this group of women, 35 women suffered a miscarriage, 16 women had ectopic pregnancies, and one a viable intrauterine pregnancy (Table II). Using progesterone <16 nmol/l as a predictor of an ectopic pregnancy, the sensitivity is 44.4% (95% CI: 28.2–60.7%) and the specificity is 60.0% (95% CI: 49.9–70.1%). Women with low progesterone were informed that the pregnancy was failing but rupture ectopic pregnancy can still occur at low levels, thus they were advised to report back earlier than in 1 week's time if they developed any worrying symptoms, such as pelvic pain, bleeding, shoulder pain or feeling unwell.

A total of 64 (50.8%) of the women had progesterone levels ranging 16–80 nmol/l. In this group, 20 women suffered a miscarriage, 19 women had an ectopic pregnancy and 25 women had a viable intrauterine pregnancy (Table III).

Using progesterone to differentiate between ectopic and non-ectopic pregnancy (16–80): sensitivity = 52.8% (95% CI: 36.5–69.1%); specificity = 50.0% (95% CI: 39.7–60.3%). Using progesterone \geq 16 nmol/l to predict between viable/non-viable gestation: sensitivity = 97.1% (95% CI: 85.0–99.93%); specificity = 56.0% (95% CI: 45.9–66.2%) and to differentiate between ectopic and non-ectopic pregnancies: sensitivity = 55.6% (95% CI: 39.3–71.8%); specificity = 40.0% (95% CI: 29.9–50.1%). There

Table II. Correlation between progesterone levels <16 nmol/l and outcome of pregnancy.

	β hCG (IU/l)	Progesterone level <16 nmol/l		
		Miscarriage	Viable pregnancy	Ectopic
No. patients	52	35	1	16
Maximum	40,229	14	14	15
Minimum	19	2	14	3
Mean	2,017	7.9	14	10.1
SD	5,705.6	3.8	0	3.8

Table III. Correlation between progesterone levels 16–80 nmol/l and outcome of pregnancy.

	β hCG (IU/l)	Progesterone level 16–80 nmol/l		
		Miscarriage	Viable pregnancy	Ectopic
No. patients	64	20	25	19
Maximum	155,370	67	79	64
Minimum	86	18	28	16
Mean	13,104.2	25.45	55.75	33.5
SD	16,609.25	8.3	16.8	9.4

were nine (7.1%) women with progesterone >80 nmol/l in that group; one patient had an ectopic pregnancy, and in the other eight women, the pregnancy was confirmed to be intrauterine (Table IV). To differentiate between ectopic and non-ectopic with progesterone >80 nmol/l: sensitivity = 2.8% (95% CI: 0.07–15.0%); specificity = 90.0% (95% CI: 83.8–96.2%); to predict between viable and non-viable gestation: sensitivity 25.7%, (95% CI: 11.2–40.2%) and specificity 98.9%, (95% CI: 94.0–99.97%) and to predict between ectopic and viable >80 nmol/l: sensitivity = 2.8% (95% CI: 0.0–8.1%); specificity = 90.0% (95% CI: 83.8–96.2%).

In general, there were more viable pregnancies with higher progesterone levels and more miscarriages with lower progesterone levels (Table V). Most of the ectopic pregnancies were between 16–80 nmol/l and also a significant number with progesterone <16 nmol/l (Figure 1).

Discussion

This study examines the value of single measurement of serum progesterone in women with pregnancy of unknown location, in conjunction with β hCG levels. In failing pregnancies, whether ectopic or miscarriage, the

progesterone levels are expected to be low as compared with healthy on going pregnancies (Hahlin et al. 1990).

Subnormal values were first reported in association with ectopic pregnancy by Radwanska et al. 1978, and this observation raised the possibility that a single progesterone measurement could be of diagnostic value in cases of suspected ectopic pregnancy and would not incur the delay associated with serial β hCG assays.

The protocol used in the authors department was designed and introduced 3 years ago. The cut-off levels for progesterone are based on the available evidence (Sau and Hamilton-Fairley 2003; Mathews et al. 1986), as most studies reported failing pregnancy with progesterone levels < 16 nmol/l and healthy on going pregnancies with levels > 80 nmol/l. Thus, levels between 16 and 80 nmol/l were considered more likely to be an ectopic pregnancy. When combining these levels with β hCGs level, 25 was used as the lowest cut-off, below which the test was considered negative. The cut-off level used in the department to pick up intrauterine pregnancy on transvaginal scanning is 1,000 and therefore levels above 1,000 were more likely to be ectopic since the gestational sac should have been identified on scanning, and levels below 1,000 were more likely intrauterine pregnancy as the gestational sac would not be expected to be visualised at this stage in addition to the high progesterone levels.

Our results confirm that serum progesterone can differentiate between healthy on-going pregnancy and failing pregnancy with a sensitivity 25.7%, (95% CI: 11.2–40.2%) and specificity 98.9 %, (95% CI: 94.0–99.97%). Phipps et al. (2000) on studying multiple markers to differentiate between viable and non-viable pregnancy concluded that progesterone was the most specific biomarker for distinguishing viable from non-viable pregnancies. They concluded as well that on combining serum progesterone with β hCG the specificity improved significantly. A meta analysis of 26 studies (Mol et al. 1998) evaluating performance of serum progesterone to diagnose pregnancy failure from viable pregnancy showed 95%

sensitivity with a specificity of 40%, and to differentiate between ectopic and non-ectopic pregnancy; sensitivity was 95% with a specificity of <40%. Concluding a single measurement of serum progesterone is insufficiently sensitive and specific to allow a definite diagnosis of ectopic pregnancy, however it is valuable in the immediate diagnosis of early pregnancy failure and long-term prognosis of viability (Al-Sebai 1995).

Many studies showed no discriminatory threshold separating viable from pathological pregnancies – at best it can be said that high progesterone concentrations suggest on-going normal pregnancies and vice versa, with a large grey area in between (Condous et al. 2004). Even this general rule may not hold true for pregnancies that follow ovulation induction and assisted reproduction (Perkins et al. 2000).

The main difficulty in terms of management is the differentiation of ectopic pregnancy from early miscarriage, and here serum progesterone is of minimal help (Kuscu et al. 1994).

Unless the threshold value for progesterone is set at a sufficiently low level, there is a danger that a viable pregnancy may be interrupted inadvertently. A low threshold in turn excludes a large proportion of the at-risk population from this line of investigation. Studies performed in the past used various cut-off levels 22 ng/ml by Buckley et al. (2000) and Daly et al. (1994), while McCord et al. (1996) used 55.7 nmol/l as their cut-off value. These studies reported varying sensitivity and specificity.

If serum progesterone is to be considered in the diagnosis of ectopic pregnancy, the optimal threshold must be validated by each institution. Stovall et al. (1990, 1992) reported that a serum progesterone value of <5.0 ng/ml (16 nmol/l) rules out a viable pregnancy, but in view of the variations in assay methods, suggested a departmental protocol to establish its own normal range. In our unit, we used 16 nmol/l as the lower limit of viable pregnancy. Out of 47 patients with progesterone <16 nmol/l, there was one viable pregnancy; 16 had ectopic pregnancies and 30 had miscarriages. The patients were informed of the possibility of ectopic pregnancy with low progesterone levels; they were aware as well that tubal rupture can occur with low progesterone levels. The patients were advised to report earlier than 1 week to the gynaecology ward if they developed any pain, bleeding, shoulder pain, fainting attacks, feeling unwell or in cases of any other worrying symptoms. Despite the low progesterone levels, all 16 women with ectopic pregnancies required active intervention, where 15 had laparoscopic salpingectomy and one patient who became haemodynamically unstable required a laparotomy. This is in contrast to earlier reports by Mathews et al. (1986) as they found no ectopic pregnancies in patients with serum progesterone levels <15 ng/ml,

Table IV. Correlation between progesterone levels >80 nmol/l and outcome of pregnancy.

	β hCG (IU/l)	Progesterone level >80 nmol/l		
		Miscarriage	Viable pregnancy	Ectopic
No. patients	10	0	9	1
Maximum	150,119	–	151	86
Minimum	784	–	82	86
Mean	29,698	–	107.1	86
SD	46,934	–	26.1	0.0

Table V. Correlation between progesterone levels and outcome of pregnancy.

Progesterone (nmol/l)	β hCG (IU/l)	Gestation (LMP) (mean/range)	Risk factor	Outcome of pregnancy			Total
				Ectopic	Miscarriage	Viable	
< 16	>25	6 + 2/5 + 0–8 + 1	7	16 (30.8%)	35 (67.3%)	1 (1.9%)	52
16–18	>25	6 + 5/5 + 1–7 + 6	12	19 (29.7%)	20 (31.3%)	25 (39%)	64
> 80	<1,000	6 + 0	0	0	0	1 (100%)	1
> 80	>1,000	6 + 4/5 + 2–7 + 0	0	1 (11.1%)	0	8 (88.9%)	9
Total				36	55	35	126

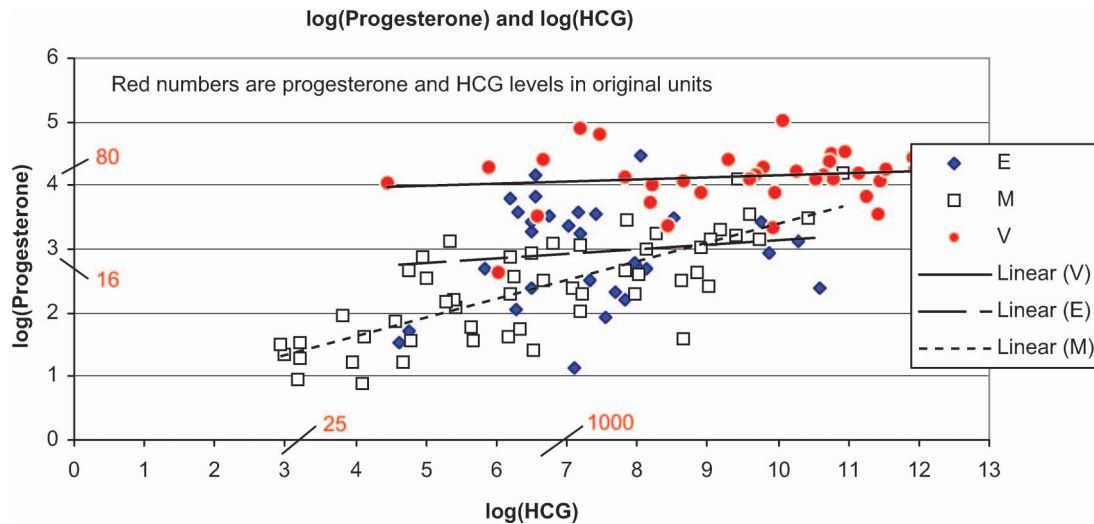


Figure 1. Relationship between progesterone and β hCG levels in patients with ectopic pregnancy (E), miscarriage (M) and viable pregnancy (V).

but the total number of women they studied was limited to 29.

Six diagnostic algorithms involving combinations of clinical examination, transvaginal ultrasound, serum progesterone, serum β hCG and D&C were compared. No ectopic pregnancies were missed with strategies involving only ultrasound and β hCG. Among those strategies, transvaginal ultrasound as the first step led to the fewest interrupted intrauterine pregnancies. Serum progesterone measurement was not favoured because it was associated with missed ectopic pregnancies (2.6%) and required more surgeries than those without progesterone and had the fewest number of interrupted intrauterine pregnancies (Gracia and Barnhart 2001).

This study confirms that a protocol of combining β hCG and progesterone levels is helpful in managing women with suspected ectopic pregnancy when ultrasound examination is inconclusive. Only 14 (11%) patients out of 126 needed more than two serial β hCGs measurement to reach a definite diagnosis. Some 98% of women with progesterone < 16 nmol/l had failing pregnancies whether miscarriage or ectopic pregnancy, thus progesterone < 16 nmol/l is highly sensitive in diagnosing viable from non-viable pregnancies, but does not help in differentiating between miscarriage and ectopic pregnancy. As expected, 90% of women with progesterone > 80 nmol/l had viable pregnancies; again, progesterone is highly sensitive in differentiating between viable and non-viable pregnancies at high levels. With progesterone levels between 16 and 80 nmol/l, the outcome varied: 29.7% had ectopic pregnancies, 31.3% had a miscarriage and 39% had viable pregnancies. The management of women within this range is highly dependant on the levels of β hCG as per protocol.

Conclusion

A protocol combining single serum progesterone measurement and β hCG is helpful in managing women with pregnancy of unknown location when the ultrasound examination is inconclusive. Serum progesterone can differentiate between viable and non-viable pregnancies. High levels of progesterone are reassuring as regards ongoing viable pregnancies and low levels allow a definitive

differentiation between viable and non-viable pregnancies. However, low progesterone could not efficiently differentiate between miscarriage and ectopic pregnancy. The use of β hCG levels in conjunction with serum progesterone is helpful, particularly with serum progesterone levels between 16–80 nmol/l.

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