Maternal serum hormone concentrations for prediction of adverse outcome in threatened miscarriage

Jemma Johns is a year 5 Obstetrics & Gynaecology Specialist Registrar in the London Deanery, currently working at the Whittington Hospital in north London, UK. She has a special interest in early pregnancy scanning and the diagnosis and management of early pregnancy problems, and has undertaken an MD in threatened miscarriage and pregnancy outcome at University College London.

Dr Jemma Johns

J Johns1,2, S Muttukrishna1, M Lygnos1, N Groome2, E Jauniaux1
Academic Department of Obstetrics and Gynaecology, Royal Free and University College London, UCL Campus London, 86–96 Cheries Mews, London WC1E 6HX, UK; 2School of Biological and Molecular Sciences, Oxford Brookes, Oxford OX3 BP, UK
1Correspondence: Tel: +44 207 6796061; Fax: +44 207 3837429; e-mail: j.johns@ucl.ac.uk

Abstract

Many serum markers have been investigated in attempts to predict the outcome of pregnancy in the first trimester, with varying degrees of success. The objective of this study was to investigate whether they can be related to pregnancy outcome in women presenting with first trimester threatened miscarriage. A cohort study of women attending the Early Pregnancy Unit of a London teaching hospital was studied. A total of 122 women presenting with bleeding in the first trimester and an ongoing pregnancy, and 33 women undergoing termination of pregnancy, were recruited. The main outcome measures were gestation at delivery, birth weight and the incidence of adverse pregnancy outcome. Inhibin A, activin A, human chorionic gonadotrophin (HCG), pregnancy-associated plasma protein-A and follistatin concentrations were all significantly lower in women who subsequently miscarried when compared with live births. Serum HCG concentrations were significantly higher in cases of threatened miscarriage compared with controls (P = 0.0009). Logistic regression analysis indicated that inhibin A alone provided the best predictor for first trimester miscarriage. This pilot study suggests that placental hormone concentrations could be useful in predicting adverse pregnancy outcome in women presenting with threatened miscarriage. Inhibin A was best at predicting the likelihood of subsequent miscarriage in this group.

Keywords: adverse outcome, HCG, inhibin, placenta, threatened miscarriage

Introduction

Threatened miscarriage is the commonest gynaecological emergency and occurs with an incidence of 15–20% of ongoing pregnancies (Jouppila, 1985). The authors have previously reported that threatened miscarriage, in addition to a 10% risk of subsequent first trimester miscarriage, is associated with a variety of adverse pregnancy outcomes, and in particular pre-term labour (Johns et al., 2003). These findings are in agreement with the data of other studies (Tongsong et al., 1995; Ball et al., 1996; Farrell and Owen, 1996; Muliket al., 2004; Weiss et al., 2004) that have also suggested an association between first trimester bleeding and pre-term pre-labour rupture of the membranes, fetal growth restriction (FGR) and low birth weight (Mantoni and Fog Pedersen, 1981; Bazzofin et al., 1984; Mulik et al., 2004; Weiss, 2004).

Many maternal serum (MS) markers have been investigated in attempts to predict the outcome of pregnancy in the first trimester and in particular the likelihood of subsequent miscarriage, with varying degrees of success. Many of these studies looked at multiple markers and were conducted after embryonic demise had already occurred (Johnson et al., 1993; Dumps et al., 2002). MS markers, combined with ultrasound parameters, maternal age, smoking habits,
obstetric history and the occurrence of vaginal bleeding, have all been combined in multivariate analyses, with mixed results (Choong et al., 2003; Makrydimas et al., 2003). First trimester human chorionic gonadotrophin (HCG) and more recently progesterone remain the only consistent markers of early pregnancy failure (Hahlin et al., 1991; Banerjee et al., 2001; Dumps et al., 2002), but their predictive value is low (Lower and Yovich, 1992).

The relationship between first trimester MS HCG values and later pregnancy complications is uncertain (Haddad et al., 1999; Yaron et al., 2002) and associations have been made between low concentrations and FGR (Haddad et al., 1999; Ong et al., 2000b) and pregnancy-induced hypertension. Pregnancy-associated plasma protein-A (PAPP-A) has been examined extensively for its role in first and second trimester screening for Down’s syndrome. In addition to this role, it has been found to be low in the first trimester in association with miscarriage, pregnancy-induced hypertension (Ong et al., 2000b) and FGR (Ong et al., 2000b; Yaron et al., 2002).

Several studies have investigated inhibin A and activin A in early pregnancy loss, and MS concentrations of inhibin A have been found to be lower in miscarriages when compared with gestation-matched control pregnancies (Phipps et al., 2000; Muttukrishna et al., 2002; Luisi et al., 2003; Wallace et al., 2004). A recent study (Wallace et al., 2004) on asymptomatic women with ongoing pregnancies showed that MS concentrations of inhibin A, pro-α C and HCG were significantly lower in women who subsequently suffered a first trimester miscarriage compared with controls, but that it was less useful than HCG or progesterone. Preliminary work on women with a history of recurrent miscarriages has shown that inhibin A concentrations are lower in women who go on to miscarry (Muttukrishna et al., 2002; Al-Azemi et al., 2003) and that inhibin may predict those women who are destined to miscarry after IVF (Lockwood et al., 1997; Treetampinich et al., 2000), but studies are small and larger studies are needed to confirm this observation. A recent study found inhibin A concentrations four times lower in pregnancies destined to miscarry, and that these concentrations correlated with MS HCG concentrations (Muttukrishna et al., 2002). Inhibin A has been used to assess the likelihood of miscarriage in early pregnancies, where viability is uncertain, or after IVF prior to the onset of clinical symptoms (Lockwood et al., 1997). Overall, inhibin A concentrations, although decreased in early spontaneous miscarriage, appear to add little to progesterone and HCG measurements for the prediction of miscarriage in asymptomatic women, and the role of these hormones in predicting the likelihood of first trimester miscarriage in confirmed ongoing pregnancies after threatened miscarriage is even less clear. It has been shown that inhibin A, in combination with other serum markers, may be useful in determining those pregnancies presenting with threatened miscarriage that are destined to fail (Florio et al., 2004). Few studies have examined the role of a combination of MS markers in the prediction of miscarriage and longer-term complications in this group of women.

The objectives of this prospective pilot study were to investigate: (i) if the serum concentrations of inhibin A, activin A, follistatin, HCG, PAPP-A, oestradiol and progesterone in women who present with first trimester threatened miscarriage are related to the outcome of the pregnancy; and (ii) to study the relationship between these hormones in first trimester threatened miscarriage patients compared with gestation-matched control pregnancies with no history of first trimester bleeding.

Materials and methods

Participants

Women referred to the Early Pregnancy Unit by their family doctor or from the emergency department with a clinical diagnosis of threatened miscarriage were recruited into the study after written consent and followed up prospectively until the end of the pregnancy. Threatened miscarriage was defined as a history of vaginal bleeding in an ongoing pregnancy of less than 14 completed weeks of gestation. All studies on women presenting with threatened miscarriage have been reviewed by the Joint University College London and University College London Hospitals (UCL/UCLH) Committees on the Ethics of Human Research.

At recruitment, blood samples were taken for hormone analysis. Exclusion criteria included multiple gestations, congenital uterine anomalies and the presence of large fibroids distorting the uterine cavity. Pregnancy outcome data collected included gestation at delivery, birth weight and the incidence of adverse pregnancy outcomes, including pre-eclampsia, FGR, stillbirth and pre-term pre-labour rupture of the membranes.

Gestation-matched control samples were collected after informed consent prior to therapeutic termination of pregnancy. Exclusions included a history of vaginal bleeding in the index pregnancy, multiple gestations, abnormal karyotype and large uterine fibroids. Demographic data in both groups were examined including maternal age, gestation at recruitment, previous obstetric history and smoking habits.

Ultrasound data

Pregnancies were dated from the last menstrual period and confirmed on ultrasound using the crown–rump length. Pregnancies were re-dated if there was a discrepancy between the last menstrual period and crown–rump length of ≥7 days. All scans on women in the threatened miscarriage group were performed by the same operator using an Acuson 128/XP with a 7-MHz transvaginal probe.

Sample collection and storage

Maternal blood was collected during morning clinics into plain tubes and centrifuged for 10 min at 3000 g within 2 h of collection. Serum samples were stored at –20°C until analysis.

Hormone assays

Activin A was measured using a two-site enzyme-linked immunosorbent assay (ELISA) specific for ‘total’ activin A, as described previously (Muttukrishna et al., 1996). The detection limit of this assay for human recombinant activin A
Inhibin A was measured using a two-site in-house ELISA that has previously been validated for human serum (Muttukrishna et al., 1994). The minimum detection limit of this assay for human recombinant inhibin A (National Institute for Biological Standards, Potters Bar, Hertfordshire, UK) was 2 pg/ml. Intra- and inter-assay variations were less than 10% respectively.

Follistatin was measured using a two-site ELISA, as described elsewhere (Evans et al., 1998). The sensitivity of this assay was 20 pg/ml. Intra- and inter-assay variations were less than 10% respectively.

PAPP-A was measured using a commercial ELISA kit (IBL Hamburg, Germany) with a sensitivity of 1 μg/ml. HCG was measured using a commercial ELISA kit with a sensitivity of 5 mIU/ml (DRG Instruments GmbH, Germany). Intra- and inter-assay variations were less than 10% respectively. The cross-reactivity of the HCG ELISA with LH, FSH and TSH was less than 1%. Oestradiol and progesterone were also measured using a commercial ELISA kit (IBL Hamburg, Germany) with sensitivities of 4.6 pg/ml and 0.05 ng/ml, respectively.

Statistical analysis

Student’s $t$-tests were performed using GraphPad Prism Version 4, and Stata Version 8 was used for logistic regression analysis. Maternal serum hormone concentrations were log-transformed to obtain normal distribution and compared using Student’s $t$-test. Maternal ages and gestations were compared using Student’s $t$-test. To control for gestation related differences in hormone concentrations found in the first trimester, the logistic regression analysis was performed on multiples of the median (MoM) for HCG using median values for our obstetric population at UCLH and inhibin A values from published medians (Wallace et al., 2004). MoM were calculated using the formula: study value/median value for given gestation.

### Table 1. Demographic details and pregnancy outcomes of 122 cases presenting with threatened miscarriage and 33 controls (where applicable).

<table>
<thead>
<tr>
<th>Cases (n = 122)</th>
<th>Controls (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (years)</td>
<td>31.8*</td>
</tr>
<tr>
<td>Median maternal age (years)</td>
<td>32.5</td>
</tr>
<tr>
<td>Mean gestation (weeks)</td>
<td>9.29</td>
</tr>
<tr>
<td>Range (weeks)</td>
<td>5–16</td>
</tr>
<tr>
<td>Total live births (%)</td>
<td>111 (91.0)</td>
</tr>
<tr>
<td>Term births (%)</td>
<td>99 (81.1)</td>
</tr>
<tr>
<td>Pre-term births (%)</td>
<td>12 (9.8)</td>
</tr>
<tr>
<td>First trimester miscarriages (%)</td>
<td>8 (6.6)</td>
</tr>
<tr>
<td>Second trimester miscarriages (%)</td>
<td>3 (2.5)</td>
</tr>
</tbody>
</table>

NA = not applicable.

*Statistically significant ($P < 0.001$).
those pregnancies that ended in pre-term and those that ended in term delivery. Activin A concentrations were 93% lower in the cases that ended with first trimester miscarriage than in the pre-term labour subgroup ($P = 0.018$). They were not significantly different from the term labour subgroup but were significantly lower than the control group ($P = 0.012$).

Follistatin

Follistatin concentrations were 69% lower in pregnancies ending in first trimester miscarriages than the term labour subgroup ($P = 0.016$) and 69% lower than the controls ($P = 0.003$).

Human chorionic gonadotrophin and PAPP-A

The trend of the HCG concentrations was similar to that of inhibin A. The concentrations were significantly lower in cases of threatened miscarriage that subsequently ended in a first trimester miscarriage when compared with the pre-term labour subgroup, where they were 40% lower ($P = 0.017$), and the term labour subgroup, where they were 64% lower ($P = 0.0001$).

HCG concentrations were significantly higher (195%) when all cases of threatened miscarriage were combined and compared with the control pregnancies ($P = 0.0009$); the pre-term labour subgroup (127% increase) and the term labour subgroup (212% increase) had significantly higher HCG concentrations than the control pregnancies individually ($P = 0.032$ and $P = 0.0001$, respectively). There were no differences between HCG concentrations in pregnancies ending in pre-term labour when compared with term labour. PAPP-A concentrations in the threatened miscarriage group were 70% lower in pregnancies ending in first trimester miscarriage ($P = 0.033$) when compared with the term labour subgroup.

There was significant correlation between the concentrations of inhibin A, HCG, PAPP-A and activin A for each of the outcome groups, in particular between HCG and inhibin A ($r = 0.6194$, $P < 0.001$). When IUH (intrauterine haematoma) volume was examined, no correlation could be found between bleed volume and the level of any of the hormones measured.

Progesterone and oestradiol

Progesterone concentrations were 48% lower in the cases of threatened miscarriage that went on to miscarry when compared with pregnancies that delivered at term (Figure 2; $P = 0.03$). There were no other statistically significant differences in progesterone concentrations between the subgroups. In cases that went on to miscarry, oestradiol and progesterone were positively correlated ($r = 0.932$, $P < 0.007$). Overall, oestradiol concentrations were 39% lower in the threatened miscarriage group when compared with the controls (not significant). The concentrations were 42% and 41% lower than the pre-term and the term labour subgroups, respectively, but again these differences were not statistically significant. There was no difference in the oestradiol concentrations between the pre-term and term birth subgroups.

Predicting outcome

Logistic regression of inhibin A and HCG MoM found that inhibin A in isolation provided the best predictor for miscarriage in the first trimester after threatened miscarriage, with areas under the receiver operator curve (ROC) of 0.6916 and 0.6088 respectively (Table 3). In fact the addition of HCG weakened the predictive power of the inhibin A results with a combined area under the ROC curve of 0.6810.

<table>
<thead>
<tr>
<th></th>
<th>Term birth</th>
<th>Pre-term birth</th>
<th>First trimester miscarriage</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibin A (pg/ml)</td>
<td>252.2 (161.1)</td>
<td>227.4 (92.8)</td>
<td>148.1 (153.1)</td>
<td>211.8 (105.2)</td>
</tr>
<tr>
<td>Activin A (pg/ml)</td>
<td>339.6 (571.0)</td>
<td>377.8 (432.1)</td>
<td>26.2 (23.8)</td>
<td>356.5 (359.2)</td>
</tr>
<tr>
<td>HCG (mIU/ml)</td>
<td>157617.4 (117323.3)</td>
<td>94826.4 (30318.9)</td>
<td>57218.75 (53432.7)</td>
<td>74491.3 (22459.3)</td>
</tr>
<tr>
<td>PAPP-A (μg/ml)</td>
<td>8.2 (11.3)</td>
<td>8.4 (17.1)</td>
<td>2.5 (4.7)</td>
<td>8.4 (13.6)</td>
</tr>
<tr>
<td>Follistatin (pg/ml)</td>
<td>822.4 (1090.8)</td>
<td>1661.9 (3408.7)</td>
<td>256.7 (153.3)</td>
<td>820.5 (577.6)</td>
</tr>
<tr>
<td>Oestradiol (pg/ml)</td>
<td>2484.0 (1043.9)</td>
<td>2525.4 (894.6)</td>
<td>1475.0 (1179.9)</td>
<td>2403.2 (1450.2)</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>62.7 (45.3)</td>
<td>38.3 (17.1)</td>
<td>35.5 (23.2)</td>
<td>54.6 (20.1)</td>
</tr>
</tbody>
</table>

HCG = human chorionic gonadotrophin; PAPP-A = pregnancy associated plasma protein-A.
Values in parentheses are SD.
Figure 1. Mean (SD) human chorionic gonadotrophin (HCG) (a), serum inhibin A (b), activin A (c), follistatin (d), and pregnancy associated plasma protein-A (PAPP-A) (e) concentrations for each outcome group. Term = term labour; PTL = pre-term labour; M/C = first trimester miscarriage. Asterisks indicate significantly different results; individual $P$-values are presented in the Results section of the text.
Discussion

The results of this study demonstrate that after threatened miscarriage in the first trimester, maternal serum hormone concentrations, in particular inhibin A and HCG, are altered in women who subsequently have a first trimester miscarriage. This study also demonstrates that changes in maternal serum hormone concentrations at this stage, and in particular inhibin A, could be used to predict pregnancy outcomes in the second half of pregnancy. The differences in maternal ages between the cases and controls clearly demonstrate the general demographics of our local population; however data from established international serum screening programmes suggest that there is little or negligible maternal age effect for the hormones measured (Wald and Watt, 1996).

Inhibin A, activin A and follistatin are present at high concentrations in maternal serum in normal human pregnancy (Muttukrishna, 1995; Fowler et al., 1998). Initially, in early pregnancy, inhibin A is produced by both the fetoplacental unit (Muttukrishna et al., 1997) and the corpus luteum (Treetampinich et al., 2000); later the fetoplacental unit continues to be a source of inhibin A, activin A, follistatin and activin receptors throughout pregnancy (Petraglia et al., 1991; Petraglia, 1997; Peng et al., 1999; Debieve et al., 2000; Manuelpillai et al., 2001). The exact role of these proteins and their receptors remains unclear. Inhibin A has been shown to have autocrine and paracrine effects on placental hormone production, and has been shown to reduce the secretion of HCG and progesterone from cultured placental trophoblasts (Petraglia et al., 1989; Mersol-Barg et al., 1990; Steele et al., 1993). Activin A has been shown to promote cytotrophoblast invasion (Bearfield et al., 2005) and follistatin to induce angiogenesis (Kozian et al., 1997) in vitro. Increased maternal concentrations of inhibin A and activin A can be found in women suffering from such pregnancy complications as pre-eclampsia (Petraglia et al., 1995; Muttukrishna et al., 1997, 2000) and FGR (Bobrow et al., 2002). Decreased concentrations of inhibin A have been found in women who subsequently miscarry in an IVF population, although it was not useful for predicting ongoing pregnancy (Hauzman et al., 2004). Alterations in gene and protein expression of inhibin/activin subunits have been demonstrated in placetas complicated by pre-eclampsia (Silver et al., 2002); in miscarriages, there is a decrease in the expression of the HCG-α and -βA subunit gene in villous tissue of miscarriages compared with controls, suggesting that down-regulation occurs in the HCG gene after embryonic demise. In the case of inhibin, activin and follistatin however, reduced concentrations of these proteins appears to be related to a decrease in trophoblastic mass or reduced trophoblast secretion prior to embryonic demise rather than an alteration in gene expression (Muttukrishna et al., 2004).

HCG is widely used in the diagnosis and management of early pregnancy complications, including ectopic pregnancy, gestational trophoblastic disease and early pregnancy failure. A single serum HCG measurement has a sensitivity of 88% in determining between viable and non-viable pregnancies (Al-
Sebai et al., 1996) (including ectopic pregnancies) and several studies have reported low initial HCG concentrations in non-viable pregnancies (Dumps et al., 2002; Urbancsek et al., 2002) but its use in predicting subsequent loss after the confirmation of a viable pregnancy is still being evaluated (Ong et al., 2000a; Yaron et al., 2002). PAPP-A concentrations also decrease in miscarriage but they have a low predictive value for fetal demise (Westergaard et al., 1985; Ruge et al., 1990; Dumps et al., 2002; Tong et al., 2004). Inhibin A concentrations have also been found to be lower in miscarriages when compared with gestation matched viable pregnancies (Wallace and Healy, 1996; Phipps et al., 2000; Luisi et al., 2003).

The mechanism by which threatened miscarriage alters maternal serum hormone concentrations is uncertain. Vaginal bleeding in the first trimester has been associated with increased concentrations of free serum β-HCG in maternal serum (De Biasio et al., 2003) and it has been suggested that this increase is related to an increase in HCG transfer into the maternal circulation due to disruption of the materno-fetal interface after vaginal bleeding (De Biasio et al., 2003). It has also been suggested that weakening of the membranes occurs due to thrombin generation and a subsequent proteolytic process leads to membrane weakness and eventual premature rupture (Ellovitz et al., 2001), but evidence for these mechanisms is lacking. Subchorionic bleeding will result in an increase in the amount of free iron available, catalysing the generation of the extremely damaging hydroxyl radical and subsequent free-radical damage to the membranes causing disruption to the materno-fetal interface. During normal pregnancy development, two-thirds of the developing placenta degenerates to form the chorion laeve. It has been shown that in the peripheral developing placenta, there is increased oxygen free-radical formation, correlating with the increase in maternal blood flow between 8 and 12 weeks of gestation (Jauniaux et al., 2003), and it has been suggested that this is a normal physiological process required for villous regression and the formation of the chorion laeve. In threatened miscarriage, it is possible that maladaptation to this process results in free-radical damage to the developing placenta and membranes, resulting in an increase in placental hormone production and subsequent release into the maternal circulation.

Studies examining placental hormone production in anembryonic and missed miscarriages, where hormone concentrations remain in the normal range, suggest that production may be independent of embryonic development (Stabile et al., 1989), although the decrease in the expression of the HCG-α and -β, subunit gene in villous tissue of miscarriages compared with controls suggests that down-regulation occurs in the HCG gene after embryonic demise (Henderson et al., 1992). In the case of inhibin, activin and follistatin however, reduced concentrations of these proteins appears to be related to a decrease in trophoblastic mass or reduced trophoblast secretion prior to embryonic demise rather than an alteration in gene expression (Muttukrishna et al., 2004). In a study of HCG concentrations in missed miscarriages, it has been shown that HCG concentrations are higher than normal controls in cases where fetal demise has been recent, whereas in cases with a larger discrepancy between expected and observed findings the HCG concentrations were lower than normal concentrations (Greenwold et al., 2003) and this could be explained by the trophoblastic regeneration that occurs after necrosis and apoptosis in cases of tissue damage (Jones and Fox, 2005) and oxidative stress (Greenwold et al., 2003). In our study population, those pregnancies that went on to miscarriage showed significantly lower concentrations of all pregnancy-related hormones investigated, with significant correlation between many of the hormones. The most likely explanation for this is decreased placental cell mass resulting from the excessive influx of oxygenated maternal blood into the developing placenta, resulting in irreversible damage to the placenta and subsequent reduction in placental hormone production. If the damage is extensive and involves a significant proportion of the definitive placenta, the fall in progesterone, oestradiol and HCG would result in a complete miscarriage. If the placental damage is limited, and HCG gene expression is not affected, it is possible that increased hormone production and subsequent placental repair will ensue.

In the present study population, the maternal serum concentrations of HCG were considerably higher than the control population. Whilst the authors accept that the control population was relatively small, they provided a useful and valid ‘normal range’ for our population who were known to have a viable pregnancy with no bleeding. In those pregnancies that went on to deliver a live birth, the HCG concentrations were significantly higher, particularly in those pregnancies that resulted in a term birth. It is possible that after the initial insult, it was these pregnancies that were better able to adapt to the trophoblastic stress associated with threatened miscarriage, reflected in the higher HCG concentrations in these cases. These findings are contradictory to the results of the study by Wallace et al. (2004) who found that HCG concentrations were lower in those women who subsequently miscarried. Their study population looked at asymptomatic women however, and there was no assessment of viability at the time of sample collection in their miscarriage cases.

The lower concentrations of activin A and follistatin in those cases that subsequently miscarried, compared with the term labour group, are consistent with the role of these hormones in early pregnancy suggested by in-vitro studies. Activin A has been shown to promote cytotrophoblast invasion (Bearfield et al., 2005) in very early pregnancy and follistatin to induce angiogenesis (Kozian et al., 1997). It is possible that a reduction in production of these hormones secondary to reduced placental mass could impair placental invasion and vascular development, with resulting eventual placental failure and miscarriage.

It has been shown that inhibin A, in combination with other serum markers, may be useful in determining those pregnancies presenting with threatened miscarriage that are destined to fail (Florio et al., 2004); however, the predictive value for subsequent miscarriage is low under these circumstances (Treetanpiminch et al., 2000). The above results suggest that first trimester miscarriage is the most significant pregnancy outcome when examining maternal serum hormone concentrations in this study group, and that the two hormones most likely to be useful for predictive testing for first trimester miscarriage are inhibit A and HCG. As discussed above, it was necessary to use MoM to eliminate the gestation-related changes in hormone concentrations that are found in the first trimester. In this study, inhibin A alone was found to be highly predictive of first trimester miscarriage, without the addition of other markers and its potential for use with other markers such as
Article - Serum markers in threatened miscarriage  J Johns et al.

ultrasound parameters and demographic features requires further investigation. Inhibin A has been shown to clear from the maternal circulation more quickly than HCG, progesterone and oestradiol after termination of pregnancy (Muttukrishna et al., 1997), suggesting that it may be more sensitive than HCG in predicting the outcome of pregnancies in the first trimester.

Acknowledgements

The authors thank Miss Sarah Buckley and Mrs Kris McCann for their help in recruiting for this study.

Declaration

The authors declare no conflict of interest.

References


Revised 10 April 2000

RBMOlne®


Received 31 May 2007; refereed 13 June 2007; accepted 11 July 2007.