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Maternal serum markers in predicting successful outcome in expectant management of missed miscarriage

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KEY MESSAGE

Using patient age and easily accessible serum markers enables identification of patients whose miscarriage could be managed expectantly. This could allow patients to choose a treatment option with a greater chance of success, thus reducing the distress the patient is already going through.

A B S T R A C T

The aim of this study was to evaluate the use of biological serum markers, available routinely in most hospital clinical laboratories, in predicting successful outcomes of expectant management in women presenting with a missed miscarriage. This is a single centre observational prospective study over a 16-month period. Among the 490 women who consented to the study protocol, 83 presented with missed miscarriage during the first trimester of pregnancy and opted for expectant management. The mean gestation sac diameter and volume of the gestation sac were recorded during ultrasound examination. Maternal serum samples were obtained in each case and assayed for human chorionic gonadotrophin, progesterone, pregnancy associated plasma protein A (PAPP-A) and high-sensitivity C-reactive protein using commercial assays. When examined individually, maternal age (P = 0.01), progesterone (P = 0.03) and PAPP-A (P = 0.02) were all significantly associated with successful expectant management. Increased maternal age was associated with an increased chance of success with the odds of success increased by around 75% for a 5-year increase in age. Higher values of progesterone and PAPP-A were associated with a reduced chance of successful management. Low maternal serum progesterone concentration was the strongest parameter associated with a successful spontaneous completion of miscarriage.

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Introduction

Between 12 and 24% of women with a missed menstrual period and positive urine pregnancy test will present with a miscarriage or early pregnancy failure (Nybo Andersen et al., 2000). It is estimated that around 125,000 miscarriages occur annually in the UK (Knez et al., 2014). Miscarriages result in 42,000 hospital admissions and are considered the most common clinical complication of human pregnancy. Access to transvaginal ultrasound by trained staff has considerably improved the management of early pregnancy loss (Jurkovic et al., 2013).

A missed miscarriage corresponds to an early embryonic demise and refers to the early stage in the natural history of a miscarriage. Missed miscarriages have been referred to in the medical literature as an empty sac (anembryonic), blighted ovum, delayed or silent miscarriage. A missed miscarriage is diagnosed on ultrasound when there is no embryo within a gestational sac or when there is a visible embryo with no cardiac activity (Jurkovic et al., 2013; Knez et al., 2014). A missed miscarriage must be differentiated from an incomplete miscarriage, which is defined by the presence of retained intrauterine products of conception without a well-defined gestation sac. The ultrasound diagnosis of incomplete miscarriage can be difficult and there is no consensus on the best diagnostic criteria (Jurkovic et al., 2013).

Surgical management under general anaesthesia used to be the only option for women presenting with a missed miscarriage on the basis that it decreases the risk of haemorrhage and subsequent gynaecological infection. Over the past two decades, the management of miscarriage has radically changed and has moved towards individualized treatment and patient choice between expectant, medical and semi-elective surgical treatment. Improved access to specialized Early Pregnancy Units and increasing awareness amongst women of their choices in the management of early pregnancy complications have led to an increasing demand for more conservative management of early miscarriage (Jurkovic et al., 2013).

Expectant management is now regularly chosen by women presenting with first trimester missed and incomplete miscarriage to avoid a surgical evacuation. In one observational study, it was found that 70% of women opted to wait for the pregnancy to resolve spontaneously (Luise et al., 2002). Medical management by means of prostaglandin has also become an option, chosen as the primary treatment option by 20–30% of women (Shankar et al., 2007). A recent meta-analysis of randomized trials comparing expectant care and surgical treatment has shown that the risks of infection and psychological outcomes are similar for both groups and that the costs are lower for expectant management (Nanda et al., 2012). However, expectant management is associated with a higher risk of incomplete miscarriage, need for unplanned or additional surgical evacuation of the uterus, bleeding and need for transfusion (NICE, 2012). The main issue with expectant management has been the lack of ultrasound and/or biological criteria that can accurately predict the likelihood of a successful spontaneous completion of miscarriage (Elson et al., 2005).

Several biochemical markers and algorithms have been trialled over the last decade in an attempt to guide clinicians and women in the decision-making process with varying success due mainly to small numbers, different populations studied and different methodologies used. Unlike, human chorionic gonadotrophin (hCG) and progesterone assays, the assays for new proteins are not available routinely in most hospital clinical laboratories. Maternal serum pregnancy-associated protein A (PAPP-A) is now widely used to predict adverse pregnancy outcomes (Wells et al., 2015; Yliniemi et al., 2015) and high-sensitivity C-reactive (hsCRP) protein is routinely used in cardiovascular disease risk stratification and management (Kalogeropoulos et al., 2014).

The aim of this study was to evaluate the role of biochemical markers available in routine clinical laboratories in predicting successful expectant management of first trimester missed miscarriage and incomplete miscarriage.

Materials and methods

The early pregnancy assessment unit (EPAU) at University College London Hospital (UCLH) is part of the Emergency Gynaecological service, which provides daily ultrasound and biological investigations to all women presenting with pelvic pain and/or bleeding in early pregnancy. All pregnant women presenting with bleeding and or pain have routine blood investigations including blood group and full blood count. Women with suspected ectopic pregnancy are routinely tested for hCG serum and progesterone concentrations. In addition, blood samples were collected as part of a prospective cohort study on the diagnosis and management of early pregnancy disorders. Maternal serum and plasma were separated and frozen at –80°C until analysis.

The patients for this study were recruited prospectively from a cohort of 523 pregnant women consecutively attending the EPAU over a 16 month-period. There were 490 women who consented to the study protocol, including women diagnosed with threatened (n = 111), complete (n = 52), incomplete (n = 22) or missed miscarriage (n = 99), women with an ectopic pregnancy (n = 54) or a pregnancy of unknown location (n = 67) and women with an uncomplicated singleton pregnancy referred for a reassurance scan because of a previous history of pregnancy loss or pelvic pain (n = 85).

Women with multiple pregnancies, women with pregnancies resulting from assisted reproductive technologies and women who were on supplemental hormonal treatment were excluded from the study group. Demographic data including maternal age, ethnicity, parity, cigarette smoke exposure, age and body mass index (BMI) were collected from questionnaires completed at the time of the first appointment. Pregnancy outcome information was collected from the medical case notes and hospital electronic patient records. The study was approved by the Joint University College London (UCL)/UCLH Committees on the Ethics of Human Research on 3 December 2007 (Reference Number: 07/Q0512/41). All women received information about the study and written consent was obtained prior to the ultrasound examination.

The study group included women diagnosed with a missed miscarriage during the first trimester of pregnancy and opting for expectant management. The diagnosis of missed miscarriage was defined as a gestational sac size >20 mm in diameter with no evidence of an embryo or yolk sac; or as fetal crown-rump length (CRL) >6 mm with no fetal heart rate, or in case of no evidence of fetal development and/or no fetal heart activity during a follow-up scan performed ≥7 days since the initial examination (Association of Early Pregnancy Units, 2007).

All examinations were carried out by an experienced operator using a high-resolution transvaginal probe (Voluson 730 and E8 expert, GE, USA). Pregnancies were dated according to the last menstrual period (LMP). Other measurements obtained during the scan and collected for the study were the mean gestation sac diameter (MSD) and the volume of the gestation sac.

Women were then followed-up in line with the EPAU guidelines for expectant management of missed miscarriage. Their pain and bleeding levels (none, mild, moderate and heavy) were recorded at the time of the first consultation. Women were asked to attend the unit 7 days post-diagnosis for a urinary pregnancy test, and a subsequent ultrasound examination was performed if the pregnancy test was positive or if women experienced continuous vaginal bleeding. Follow-up was completed if the pregnancy test was negative and the bleeding had settled (successful outcome of expectant management). Women who opted for surgical management either due to worsening symptoms or personal choice (e.g. prolonged follow-up) were included in the failed outcome group. In all cases, the pregnancy outcome was confirmed by telephone follow-up or through the UCLH maternity database. Only cases with a full set of data including demographic information, serum biomarkers results and clinical outcomes were included in the final analysis.

Bioassays

All maternal serum samples were assayed for hCG, progesterone, PAPP-A and hsCRP using commercial assays. Maternal serum progesterone and hCG assays were performed on a Modular E170 Analyser (Roche Diagnostics, Vilvoorde, Belgium) with an electrochemiluminescence competitive method. hsCRP assay was performed using an immunoturbidimetric method on a Modular P Analyser (Roche Diagnostics) with a quantitation limit of 0.5 mg/l. Maternal serum PAPP-A assay was performed on a IMMULITE 2000 immunoassay system (Siemens, Brussels, Belgium) with an enzyme-labelled chemiluminescent immunometric method.

Statistical analysis

The data were analysed using data analysis and statistical software package Stata 13.1 (StataCorp, Texas, US). The outcome variable was the success of the expectant management, which was considered as a binary variable (success or failure), and the analysis was performed using logistic regression. The association between each variable and outcome was first assessed separately using a univariate analysis. The joint association on the outcome was assessed with a multivariate analysis. A backwards selection procedure was used to retain only the statistically significant variables in the final model removing non-significant variables, one at a time, until all remaining variables were significant.

For the categorical variables, data are displayed as odds of success in each category relative to the odds in a baseline category. For the continuous variables, the relative change in the odds of success for a one-unit increase in the corresponding variable is presented. Variables that presented with skewed distributions were transformed using a logarithmic transformation before analysis. Results were considered statistically significant at $P < 0.05$.

Results

The study group consisted of 83 women with a full set of data who opted for an expectant management including 64 (77.1%) women who had successful expectant management and 19 (22.9%) who required a surgical procedure. In five cases, the smoking status was not provided ($n = 3$) or uncertain ($n = 2$) due to passive smoking. Detailed information on the bleeding and pain at the time of the ultrasound examination was missing in two cases. The average maternal age of the study group was 33.4 years with 32 women of advanced maternal age (AMA) (>35 years old). A total of 58 women (70%) completed the follow-up in two weeks or less.

A summary of the univariate analysis results is presented in **Table 1**. This analysis indicated that, when examined individually, maternal age ($P = 0.01$), progesterone ($P = 0.03$) and PAPP-A ($P = 0.02$) were all significantly associated with successful expectant management. Increased age was associated with an increased chance of success with the odds of success increased by around 75% for a 5-year increase in age. Higher values of both progesterone and PAPP-A were associated with a reduced chance of successful management. A one-unit increase in progesterone on the log scale (equivalent to a 10-fold increase in progesterone) was associated with a 50% lower chance of successful expectant management. The study has an 80% power to detect a difference of 25% in outcome between groups, and over 90% to detect a difference of 30% between groups.

The multivariate analysis (**Table 2**) indicated that both age ($P = 0.01$) and progesterone ($P = 0.03$) were significantly associated with successful management. After adjusting for these variables, there was no longer a significant effect of PAPP-A on the outcome. Older women were more likely to have successful management. A 5-year increase in age was associated with the odds of success increasing by 82%. Conversely, higher concentrations of progesterone were associated with lower levels of success. A one-unit increase on the log scale (equivalent to a 10-fold increase in progesterone) was associated with a 50% drop in the odds of successful management.

Progesterone and age were combined in a logistic regression model to predict the probability (P) of successful management using the following equation:

$$P = e^{y}/(1+e^{y}) \text{ where}$$
$$y = 0.356 + 0.078\,\text{age} - 0.917\,\text{logprogesterone}$$

Discussion

The results of this study indicate that low maternal serum progesterone concentration is the strongest parameter associated with a successful spontaneous completion of miscarriage in cases of missed miscarriage. Combined with maternal age in a logistic regression model it may be used to determine the likelihood of successful expectant management. The data also indicate that the role of maternal serum hsCRP and PAPP-A is limited and that routine measurement of the concentration of these proteins does not provide additional information for the management of missed miscarriage.

The success of expectant management within two weeks is variable across observational studies (Casikar et al., 2010; Jurkovic et al., 2013; Knez et al., 2014). It is generally accepted that the likelihood of completion after two weeks is low and evacuation of the uterus should be offered. Completion rates are higher in incomplete miscarriages (80–96%) at two weeks with lower low complication rate than in missed miscarriage. In controlled trials of medical management, expectant management (placebo arm) was successful in 29–42% of women with missed miscarriage and 55–86% of women with incomplete miscarriage (Bagratee et al., 2004; Blohm et al., 2005; Kovavisarach and Sathapanachai, 2002; Lister et al., 2005; Luise et al., 2002; Wood and Brain, 2002). The Royal College of Obstetricians and

Table 1 – Results of the univariate analysis of the different variables investigated in successful expectant management (*n* = 64).

Variable	Category	Success number (%)	Odds ratio (95% CI)	*P*-value
Age[a]	–	–	1.77 (1.13, 2.76)	0.01
Ethnicity	Caucasian	37/52 (71)	1	NS
	South Asian	13/15 (87)	2.64 (0.53, 13.1)	–
	Afro-Caribbean	6/7 (86)	2.43 (0.27, 22.0)	–
	Other	8/9 (89)	2.43 (0.27, 22.0)	–
BMI[a]	–	–	1.07 (0.62, 1.84)	NS
Smoker[b]	No	56/71 (79)	1	NS
	Yes	5/7 (71)	0.79 (0.14, 4.43)	–
Parity	0	34/47 (72)	1	NS
	1	14/18 (78)	1.33 (0.37, 4.82)	–
	2 +	16/18 (89)	3.06 (0.62, 15.2)	–
Pain[a]	None	38/52 (73)	1	NS
	Mild/Moderate	24/29 (83)	1.77 (0.56, 5.54)	
Bleeding[b]	None/Mild	38/50 (76)	1	NS
	Moderate	17/22 (77)	1.07 (0.33, 3.52)	
	Heavy	7/9 (78)	1.11 (0.20, 6.05)	
Sac diameter[c]	–	–	0.81 (0.50, 1.31)	NS
Sac volume[d]	–	–	0.80 (0.49, 1.31)	NS
Gestational age (weeks)	–	–	0.99 (0.72, 1.34)	NS
β-hCG[d]	–	–	0.73 (0.49, 1.08)	NS
Progesterone[d]	–	–	0.46 (0.23, 0.91)	0.03
CRP[d]	–	–	1.14 (0.70, 1.87)	NS
PAPP-A[d]	–	–	0.62 (0.41, 0.94)	0.02

[a] Odds ratios given for a 5-unit increase in predictor variable.
[b] Missing data in some cases.
[c] Odds ratios given for a 10-unit increase in predictor variable.
[d] Variable analysed on log scale.
BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; hCG = human chorionic gonadotrophin; NS = not statistically significant; PAPP-A = pregnancy-associated protein A.

Gynaecologists (RCOG) evidenced-based guidelines on the care of women requesting induced abortion indicates that there is insufficient evidence to imply causality for preterm birth and miscarriage following first trimester surgical abortion when the procedure is carried out in a high standard health care set up (RCOG, 2011). However, several more recent systematic reviews have suggested that surgical management can be associated with increased risks of long-term complications such as preterm birth in subsequent pregnancies (Lemmers et al., 2016) and intrauterine adhesions (Hooker et al., 2016).

A meta-analysis of studies comparing expectant management with active management (medical or surgical) showed a higher rate of unplanned emergency interventions (NICE, 2012). In the present study, the completion rate was 78%, which is higher than in previous observational and cohort studies. This may be due to the fact that this study included only cases of missed miscarriages. By contrast the majority of previous studies included both incomplete and missed miscarriage in their data analysis. The difference in outcome and success rates may also be due to different study populations and changes in maternal parameters over the last decade. In particular, the population in this study includes a high number of women with AMA and in the study group the average maternal age was above the national average of 30.3 years reported recently for England and Wales in 2015 (ONS, 2016). A history of previous miscarriage with different management approaches i.e. expectant, surgical or medical may also influence outcome in large series.

The diameter of retained products of conception as seen on ultrasound examination was assessed and found to be significantly different in women with successful and failed expectant management in a study that included 54 women who were diagnosed either with an incomplete or missed miscarriage (Elson et al., 2005). Ultrasound parameters such as MSD and sac volume have not been routinely evaluated in the successful expectant management of missed miscarriage. In a study of 85 women diagnosed with missed miscarriage, the mean diameter of the gestational sac at the initial ultrasound examination was found to be significantly smaller in women who successfully completed expectant management of missed miscarriage, compared with those who failed expectant management (Jurkovic et al., 1998). In this study, the cumulative success rates were 15%, 20% and 25% after one, two and more than two weeks, respectively. In this study, no difference was observed when evaluating sonographic characteristics such as sac diameter and sac volume and successful outcome of expectant management of missed miscarriage after two weeks. This could be explained by the maximum length of two weeks of follow-up offered to women who opted for expectant management in this study and the fact that it only included women who opted for an expectant management.

Maternal serum β-hCG and progesterone are the most commonly used serum markers in the assessment of pregnancy viability

Table 2 – Significant results of multivariate analysis in successful expectant management (*n* = 64).

Variable	Odds ratio (95% CI)	*P*-value
Age[a]	1.82 (1.14, 2.91)	0.01
Progesterone[b]	0.44 (0.21, 0.90)	0.03

[a] Odds ratios given for a 5-unit increase in predictor variable.
[b] Variable analysed on log scale.
CI = confidence interval.

(Chetty et al., 2011). β-hCG concentrations are directly related to the amount of villous trophoblast whereas progesterone production in early pregnancy reflects the dynamics of the corpus luteum-trophoblast axis and the status of the trophoblastic tissue. It has previously been established that the likelihood of a spontaneous pregnancy failure declines as the maternal progesterone concentration rises in both intrauterine and extrauterine pregnancies (McCord et al., 1996; Verhaegen et al., 2012). A recent systematic review and diagnostic accuracy meta-analysis has confirmed that low serum progesterone is strongly associated with a failing pregnancy and can be used to rule out the possibility of a viable pregnancy (Pillai et al., 2016).

PAPP-A is mainly produced by the villous trophoblast and its synthesis is up-regulated by progesterone during pregnancy (Wang et al., 2014). PAPP-A concentrations in maternal serum have been shown to be low in pregnancies with chromosomal abnormalities, like triploidy, trisomy 21, 18 and 13, and sex chromosome aneuploidy (Spencer et al., 2008; Suri et al., 2013). Low concentrations of PAPP-A have also been related to spontaneous miscarriage (Yaron et al., 2002). Results from this study confirm these findings with women presenting with lower concentrations of progesterone and PAPP-A having a higher rate of successful expectant management.

Recent studies have reported a possible role for the measure of maternal serum hsCRP in the first-trimester screening of pre-eclampsia (Kashanian et al., 2013), in predicting long-term cardiovascular risks in women who had hypertensive disorders late in pregnancy (Hermes et al., 2013) and in the diagnosis of early-onset neonatal infection in cases of chorioamnionitis (Howman et al., 2012). We recently found that hsCRP concentrations do not predict the likelihood of miscarriage in women presenting with threatened miscarriage (Jauniaux et al., 2015). In the present study, hsCRP concentrations were not different between successful and unsuccessful subgroups, suggesting that this parameter does not contribute to the management of early pregnancy complications.

A mathematical model to predict successful expectant management of missed and incomplete miscarriages was validated in a recent prospective study (Casikar et al., 2013). The data were separated into three groups; missed miscarriage, anembryonic sac and incomplete miscarriage, and the authors found that the most independent prognostic variables for their model are the type of miscarriage at primary scan, vaginal bleeding and maternal age. In this study, symptomatology at presentation was not recorded and therefore not included in the analysis. However, maternal age appears to be a common strong predictor probably due to the relationship between advanced maternal age (AMA) and aneuploidy rates. In addition, it was found that routine biochemical markers can contribute to the management of missed miscarriage with progesterone being the best biochemical marker to predict successful outcome.

In conclusion, several novel biochemical markers such as angiogenic factors, macrophage inhibitory endoglin, macrophage inhibitory growth factor, endocannabinoids, cytokines and chemokines have been used to improve prediction of pregnancy outcome in women presenting with early pregnancy complications (Pillai et al., 2016). However, their cost and availability render them impossible to use in everyday clinical practice. By contrast, progesterone assays, are widely available in laboratories and used routinely in the management of ectopic pregnancy. In women diagnosed with a missed miscarriage, combining maternal age and progesterone concentration can aid clinicians and women in making informed decisions about treatment options available. Future research should focus on prospectively evaluating the mathematical model to identify, at an early stage, those women who are more likely to have unsuccessful management and thus avoiding the additional stress of requiring an emergency surgical procedure.

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