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ARTICLE

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

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Abstract 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.

KEYWORDS: C-reactive protein, first-trimester, maternal serum, miscarriage, pregnancy

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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

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