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Expectant management of miscarriage—prediction of outcome using ultrasound and novel biochemical markers

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BACKGROUND: The aim of this study was to examine the value of various ultrasound and biochemical parameters for the prediction of successful expectant management of miscarriage. METHODS: This was a prospective observational study. Clinically stable women with an ultrasound diagnosis of miscarriage were offered expectant management. In all cases, gestational age, size of retained products of conception, serum HCG, progesterone, 17-hydroxyprogesterone, insulin growth factor-binding protein 1 (IGFBP-1), inhibin A and inhibin pro α-C RI levels were recorded. Follow-up continued until resolution of the pregnancy. Clinical data, ultrasound findings and biochemical markers were analysed using univariate analysis and decision tree analysis. RESULTS: Fify-four women underwent expectant management of miscarriage. Thirty-seven (69%) had successful expectant management and 17 (31%) required surgery. The size of retained products, serum HCG, progesterone, inhibin A and inhibin pro α-C RI were all significantly different in those pregnancies that resolved spontaneously ($P < 0.05$). Serum inhibin A was the best predictor of a complete miscarriage. CONCLUSION: This study shows that novel biochemical markers may be used to predict the likelihood of successful expectant management of miscarriage.

Key words: expectant management/IGFBP-1/inhibin A/inhibin pro α-C RI/miscarriage

Introduction

Surgical evacuation of retained products of conception has been the standard treatment of first trimester miscarriage over the last 60 years. Although relatively safe, surgical treatment is costly and it carries a risk of haemorrhage, infection and anaesthetic complications. Medical management of miscarriage has been described using antiprogestins and prostaglandins as an alternative to surgery. However, the efficacy and cost effectiveness of medical treatment have been questioned (Nielsen *et al.*, 1999). Expectant management follows the natural history of miscarriage and it is an attractive option to many women who wish to avoid all forms of medical interventions in treatment of miscarriage. Expectant management is relatively inexpensive and safe, but its failure rate varies between 10 and 75% (Nielsen and Hahlin, 1995; Jurkovic *et al.*, 1998). One of the difficulties with expectant management of miscarriages is the lack of selection criteria which could reliably predict the likelihood of a complete spontaneous resolution of pregnancy.

Over the last decade, several new biochemical markers of the luteal–trophoblastic axis have been described (Irwin and Guidice, 1998; Glennon Phipps *et al.*, 2000). However, their potential clinical applications have not been studied extensively so far.

The aim of this study was to investigate the potential value of various novel biochemical markers in combination with clinical and ultrasound findings for the prediction of successful expectant management of first trimester miscarriage.

Materials and methods

This was an observational study of women who were referred to our dedicated early pregnancy unit because of suspected early pregnancy complications. All clinically stable women with history of mild lower abdominal pain and bleeding and a conclusive ultrasound diagnosis of miscarriage were offered expectant management. A diagnosis of missed miscarriage was made if the size of gestational sac was >20 mm in diameter with no visible embryo; if the fetal crown–rump length was >5 mm with no detectable fetal heart rate; or if the gestational sac had failed to develop on a follow-up scan >6 days after the initial examination. An incomplete miscarriage was diagnosed in women with a history of bleeding, who had no visible gestational sac on ultrasound scan, but there was clear evidence of retained trophoblast tissue within the uterine cavity. A complete miscarriage was defined as an empty uterine cavity in women with conclusive evidence of intrauterine pregnancy on previous scans.

All women who opted for expectant management had a blood sample taken for serum HCG, progesterone levels and 17-hydroxyprogesterone (17-OHP) (DRG diagnostics, Germany), and the new

serum markers inhibin A (Oxford Bio-innovation, Oxford, UK), inhibin pro α-C RI (Oxford Bio-Innovation, Oxford, UK) and insulin growth factor-binding protein-1 (IGFBP-1) (Oxy Medix Biochemica Ab, Finland). The serum markers chosen were those that previous studies had been shown to play a role in the dynamics of the corpus luteal–placental–decidual axis. HCG production is known to relate directly to the amount of trophoblast present (Zegers-Hochschild *et al.*, 1994). Progesterone has been shown to play a crucial role in pregnancy maintenance (Sitteri *et al.*, 1977) and 17-OHP is produced by the corpus luteum and has been shown to be lower in non-viable pregnancies (Check *et al.*, 1990). Of the newer serum markers, inhibin A is also known to reflect both the trophoblast amount and the dynamics of the corpus luteum (Muttukrishna *et al.*, 1994; Lahiri *et al.*, 2003) and inhibin pro α-C is a product of the corpus luteum (Lockwood *et al.*, 1997). Irwin and Guidice (1998) demonstrated that IGFBP-1 was associated with the placental–decidual interface, with high levels thought to protect the endometrium from invasion.

Women were then followed-up in line with the unit policies for expectant management of miscarriage. They were all asked to attend 7 days later for a urinary pregnancy test. If this was positive or if there was continued bleeding, then a further transvaginal ultrasound was carried out. A complete miscarriage was diagnosed if the pregnancy test had become negative and the bleeding had settled. Follow-up continued until the miscarriage was completed or women opted for surgical removal of retained products because of worsening of clinical symptoms or for practical reasons because of prolonged follow-up. Expectant management was classified as successful if a complete miscarriage occurred without the need for surgical intervention. The study protocol was approved by the Research Ethics Committee for King's College Hospital, London, and all women gave their informed consent.

A database was established and the data recorded included maternal age, date of last menstrual period, the presence or absence of vaginal bleeding (expressed as bleeding score 0 or 1), mean diameter of products of conception (calculated from measurements taken in three orthogonal planes) and the serum levels of progesterone, HCG, 17-OHP, inhibin A, pro α-C inhibin and IGFBP-1. As no previous studies existed using these markers, the sample size was calculated on the assumption that the study would detect a difference between the groups of 1 SD. This, therefore, gave a sample size of 45 at the 5% significance level with 90% power.

All statistical analyses were carried out using SPSS version 10 (SPSS Inc., Chicago, IL). The outcomes were dichotomized into successful and failed expectant management categories. Comparison of means of continuous variables was performed using Mann–Whitney or Student's *t*-tests depending on data distribution. Proportions were compared using the Yates corrected χ^2 test. A value of $P < 0.05$ was considered statistically significant.

Data were analysed using decision tree analysis. This tree-based analysis was carried out using SPSS answerTree version 2.1 (SPSS Inc., Chicago, IL). Twelve independent variables were used for construction of the decision tree and these included maternal age, gestational age, diameter of products of conception, serum progesterone level, serum HCG level, serum inhibin A level, serum 17-OHP level, serum pro α-C inhibin level, serum IGFBP-1 level, pregnancy type, presence or absence of pain and presence or absence of bleeding. All except the last three were entered as continuous variables.

A decision tree was developed using the Classification and Regression Trees (C&RT) method. The stopping rules for the iterative process were that the tree should have a maximum of five levels, a minimum of five cases were to be present for a split to be calculated and any given split should not generate a group with less than two cases. This allows sequential analysis of variables to predict whether the final management would be expectant or surgical.

Results

Fifty-eight women with an ultrasound diagnosis of miscarriage were included in the study. Four women were lost to follow-up and were excluded from further analysis. Of the remaining 54 women, 32 (59%) women had an initial diagnosis of an incomplete miscarriage and 22 (41%) of a missed miscarriage. Expectant management was successful in 37 (69%) women, whilst 17 (31%) required surgery. The median time to pregnancy resolution for those with expectant management was 7 days (range 1–17), and for those with surgical management was 7 days (range 1–30) ($P > 0.05$). None of the women suffered any significant complications during expectant management or following surgery and none of them required blood transfusion.

Comparison of the initial findings in women with successful and failed expectant management showed significant differences in the size of retained products of conception, serum HCG, progesterone, inhibin A and inhibin pro α-C RI (Table I)

Serum inhibin A levels were the most powerful predictor of successful expectant management of miscarriage. Twenty

Table I. Comparison of measured variables in miscarriages requiring surgery and those resolving spontaneously

Variable	Expectant ($n = 37$)	Surgical ($n = 17$)	*P*-value
Maternal age (years)[a]	32.3 (7.8)	32.2 (5.25)	>0.05
Gestational age (days)[a]	74 (13.6)	67.2 (26.2)	>0.05
Vaginal bleeding (%)[b]	95	76	>0.05
Diameter of products of conception (mm)[c]	18.6 (16–44)	24.7 (22–35.5)	<0.05
βHCG (IU/l)[c]	918 (254–2755)	5290 (2070–11 742)	<0.001
Progesterone (nmol/l)[c]	7 (5–16)	18 (9–39)	<0.05
17-αOH progesterone (ng/l)[c]	1.6 (0.9–2.1)	2.5 (1–2.9)	>0.05
IGFBP-1 (μg/l)[c]	30.9 (2.9–23.9)	29.2 (6.8–23.9)	>0.05
Inhibin A (pmol/l)[c]	24.6 (5.8–21.1)	74.8 (7.1–47.3)	<0.001
Inhibin pro α C-RI (pmol/l)[c]	259 (139–192)	499 (168–419)	<0.05

[a]Data distributed normally with values given as the mean and SD.
[b]Discrete data given as a percentage of a feature for each final outcome.
[c]Data distributed non-parametrically with values given as the median (25th to the 75th interquartile range).

out of 21(95%) miscarriages with unmeasurable inhibin A (≤3.9 pmol/l) resolved spontaneously compared with 17 out of 33 (51.5%) with detectable serum inhibin A. In the latter subgroup of women, successful expectant management was more likely if IGFBP-1 was high (>15 μg/l) and pro α-C inhibin was low (≤400 pmol/l) (Figure 1).

Discussion

This study showed significant differences in the ultrasound and biochemical parameters between those miscarriages undergoing spontaneous resolution and those requiring surgery. There was a resolution rate of 69% for a combined group of missed and incomplete miscarriages. The type of pregnancy was shown to be significant, with fewer pregnancies with an intact gestation sac resolving spontaneously. Other studies have shown success rates of 25–65% for missed miscarriage (Jurkovic *et al.*, 1998) and 79–91% for incomplete miscarriage alone (Nielsen and Hahlin, 1995; Schwarzler *et al.*, 1999, Luise *et al.*, 2002). The amount of retained products of conception was also found to be significant, with those pregnancies with less trophoblastic tissue more likely to resolve spontaneously. This agrees with studies by Nielsen and Hahlin (1995) looking at expectant management of incomplete miscarriage and Jurkovic *et al.* (1998) in their study of missed miscarriage.

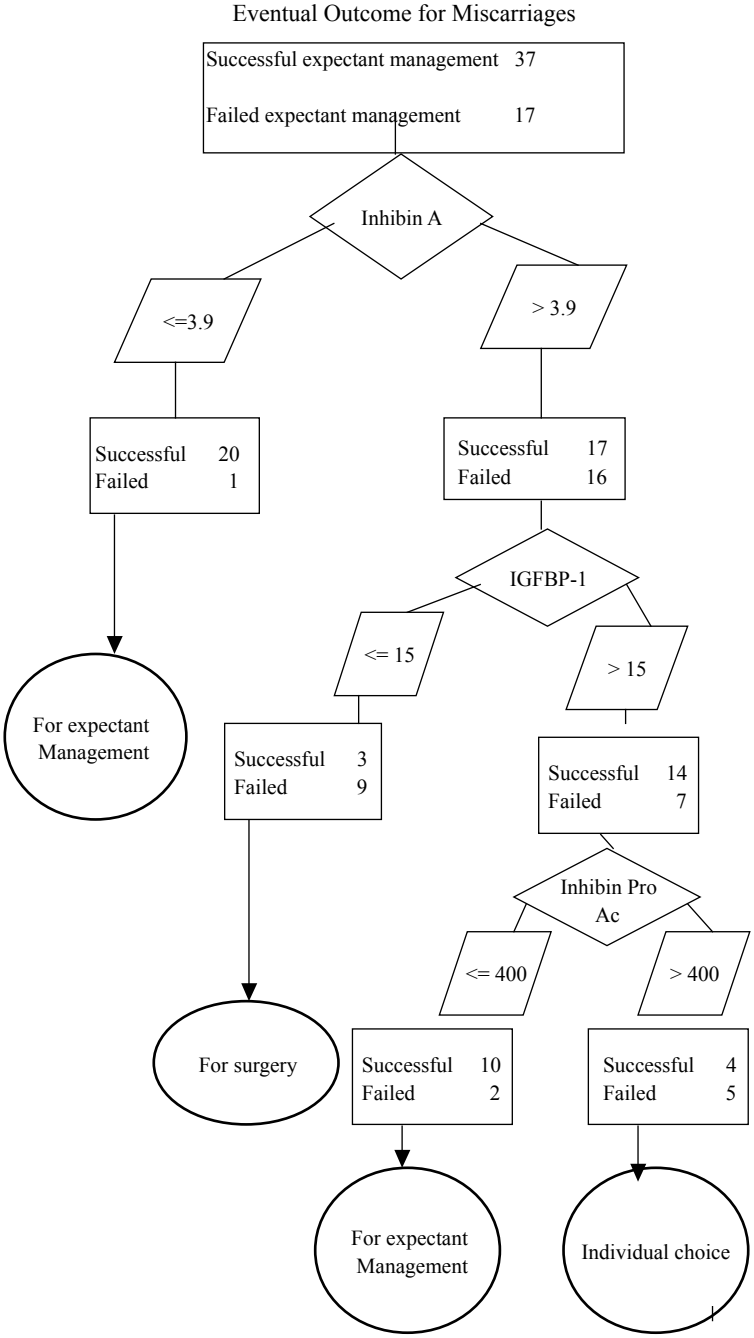

Figure 1. Decision tree analysis for expectant management of miscarriage.

This study has also shown that some of the novel biochemical markers may be used at the initial visit to identify women in whom miscarriage is likely to be completed spontaneously. Undetectable serum inhibin A was strongly associated with successful expectant management, indicating a low amount of retained functioning trophoblast. Persistent functioning trophoblast is probably the main factor leading to failed expectant management and it would seem that serum inhibin A levels reflect the trophoblastic activity more accurately than HCG. Of those pregnancies where the inhibin was still measurable, high concentrations of IGFBP-1 were associated with successful expectant management. Two hypotheses exist for the action of IGFBP-1 in early placentation. One is that higher concentrations of IGFBP-1 are thought to inhibit binding of the trophoblast to the decidual cells (Irwin and Guidice, 1998). The second is that there is overproduction of IGFBP-1 by the decidua response to defective implantation. In this study, the presence of a raised IGFBP-1 concentration was associated with an increased chance of successful expectant management. This is the first time that raised IGFBP-1 concentrations have been described in association with miscarriage. It suggests that high levels reflect a defect in the attachment of the trophoblast to the decidua, thus resulting in an increased chance of the retained products being expelled spontaneously.

In those women with high IGFBP-1, lower levels of inhibin pro α-C RI were associated with an increased success of expectant management. Inhibin pro α-C RI is known to be a product of the corpus luteum and has been shown to drop during termination of pregnancy (Lahiri *et al.*, 2003). It is not known whether the mechanism responsible for lower levels of inhibin pro α-C RI in successful expectant management reflects a poorly functioning corpus luteum or whether inhibin pro α-C RI levels are low in response to feedback from lower levels of HCG. Previous studies have suggested that pro α-C RI may be responsible for maintaining luteal progesterone output that may or may not be HCG mediated (Webley *et al.*, 1994).

Using the decision tree analysis for management of miscarriages alone, successful outcome could be predicted in 81% of the population. This compares favourably with the logistic regression model of Nielsen *et al.* (1996). The use of colour Doppler as advocated by Schwarzler *et al.* (1999) predicts successful outcome with a probability of 80% but only in 54% of the population. Recently Wieringa-de Waard *et al.* (2002) demonstrated that using initial expectant management of miscarriage can reduce the number of surgical procedures required by 37%. The same group has also demonstrated improved mental health scores in women undergoing expectant management. The major limitation with uptake of expectant management is the inability to predict which women are likely to have spontaneous pregnancy resolution. Decision tree analysis as presented in this study could be used for both patient selection and counselling. However, the efficacy and the cost-effectiveness of the proposed model have to be evaluated in a prospective study before it can be recommended for use in clinical practice.

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