

## Predictors of Efficacy of Medical Management of First Trimester Miscarriage: A Prospective Cohort Study in an Early Pregnancy Unit

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### ABSTRACT

Spontaneous miscarriage is the commonest complication of the first trimester of pregnancy. Non-surgical management is both a safe and an acceptable alternative. However, there is a paucity of evidence on factors that influence the success rate and efficacy of medical management of first trimester miscarriage.

This is a prospective cohort study looking at the potential factors that influence the efficacy of medical management of first trimester miscarriage, including clinical factors, ultrasound features and biochemical markers. Cases were recruited from the early pregnancy unit at the Coombe Women and Infants University Hospital (CWIUH) over a period of 18 months [October-2015 to April-2017]. Cases that underwent medical management were analyzed for primary and secondary outcomes. Statistical analysis was used to assess factors influencing the efficacy of medical management.

In total, 186 cases were analyzed. Mean maternal age was 33.5 years and 35.4% were primigravidas. Mean BMI at presentation was 26kg/m<sup>2</sup>. In this study, body mass index was a significant predictor ( $p = 0.005$ ) of efficacy of medical management. The crown-rump length was also a significant predictor ( $p = 0.005$ ) of efficacy of treatment, particularly when combined with HCG levels. Decision tree analysis showed an 81.3% likelihood of non-surgical outcome with serum bHCG levels <26,528. Medical management of miscarriage offers an alternative to women wishing to avoid surgical management. It has relatively low risk of complications. Using biochemical markers can potentially help clinicians in counselling women about the likelihood of success of management.

### Keywords

Miscarriage, Misoprostol, First trimester, Predictors, Medical management.

### Introduction

Spontaneous miscarriage is the commonest complication in the first trimester of pregnancy. It occurs in up to 20% of clinical pregnancies [1]. Traditionally, surgical curettage was the gold standard for the management of first trimester miscarriage [2]. However, the introduction of medical and expectant management has increased options for women as well as clinicians alike for the management of this common condition [3]. A NICE review concluded that non-surgical management is both a safe and acceptable

alternative to surgical evacuation [4]. However, the evidence on clinical factors influencing efficacy of medical management is sparse and occasionally conflicting. Factors studied included obstetric history, ultrasound findings and biochemical markers [5-8].

The main research objectives of this study was to explore clinical, sonographic and biochemical factors that can predict the efficacy of medical management of first trimester miscarriage in the setting of an early pregnancy unit (EPAU).

### Methods

This was a prospective cohort study conducted in the Coombe Women and Infants University Hospital (CWIUH). CWIUH

is a large tertiary maternity hospital with a stand-alone Early Pregnancy Assessment Unit (EPAU) and over 8,000 deliveries per year. Women who presented with a first trimester miscarriage to the EPAU between October 2015 to April 2017 were enrolled at their convenience.

The diagnosis of miscarriage was made using transvaginal ultrasound using the criteria from the Irish clinical guideline [9]. Once the diagnosis was made, women were counselled and offered expectant, medical, or surgical management. At the time of recruitment, BMI was measured, serum blood was obtained, and symptoms diary was given to the participants to fill during the period of their management. Misoprostol, which is a prostaglandin analogue was used for the medical management of both delayed and incomplete miscarriage. Two doses of 600mcg of Misoprostol were administered orally four hours apart (a total of 1200mcg); as per the Irish clinical guideline No. 10, 2014 [10]. A repeat transvaginal ultrasound was performed 10 to 14 days later to assess the resolution of the miscarriage. If the miscarriage was not complete, they were offered further management. If they opted for non-surgical management, further follow-up was organised 10 to 14 days later. A maximum of two trials of medical management was offered (at least 10 days apart). All participants were followed up until complete miscarriage was achieved or surgical intervention was indicated.

Using previous studies on this topic as a guide, several clinical, ultrasound and biochemical factors were explored. The serum markers chosen were those that previous studies had shown to play a role in the dynamics of the corpus luteal-placental-decidual axis and that were readily available in every day practice.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS), version 26. The analysis for predictors of efficacy of medical management was run twice for all variables: first with the outcome at first follow-up (10 to 14 days from diagnosis), and then for the final outcome of management (Complete miscarriage and surgical intervention). Multivariable logistic regression was performed using both Enter and Backward stepwise technique. Explanatory variables were removed from the model if  $P > 0.05$  and the point estimate for odds ratios (ORs) of the other explanatory variables did not change by more than 10%. The study was approved by hospital ethical committee.

## Results

A total of 517 women were enrolled in the study, of whom 203 opted for medical management over a period of 18 months (October 2015 to April 2017). Seventeen women were excluded leaving 186 cases in the analysis group. The analysis group was made up of 169 cases of delayed miscarriages and 17 cases of incomplete miscarriage. Due to the small number of cases in the incomplete group, any separate analysis would yield inaccurate results. Therefore, the analysis focused on the 169 cases in the delayed group, as analysing all miscarriages together would also yield inaccurate results.

Two types of outcomes were used in the analysis. The outcome at first follow-up (10 to 14 days following diagnosis and management) and the final outcome. These outcomes were analysed against several independent variable including: clinical factors, Ultrasound features and biochemical markers

Influence of clinical factors on outcome of management

### Maternal age

Maternal age showed no influence on the outcomes of medical management at either the first follow-up or outcome. The mean age was 33.5 years for complete and incomplete miscarriages at both outcome,  $p=0.9$ .

### Body mass index

BMI had a statistically significant relationship with the outcome of treatment. Interestingly, Women in the Obese BMI group had higher rates of complete miscarriage (69.0%); compared with Normal BMI (36.0%) and overweight BMI (51.1%);  $p=0.008$ . The same trend and relationship was maintained when looking at the final outcome, with non-surgical outcome in the obese group reaching 89.7% compared to 60.8% in the normal BMI and 66.0% in the overweight group, ( $p=0.017$ ).

### Symptoms at diagnosis

Abdominal pain or cramps did not have any significant effect on the outcome of medical management. Women who had bleeding in the 24 hours prior to the diagnosis were more likely to have a complete miscarriage (62.0%, 28/45 compared with 43.0%, 48/112;  $p=0.02$ ). This relationship was only significant when the bleeding occurred in the 24 hours prior to diagnosis

### Ethnicity

There was a trend in the ethnicity showing higher efficacy of management in non-caucasians compared to caucasians; 68.4% (13/19) and 45.1% (65/144) respectively;  $p=0.056$ . However, the number of non-caucasian women was small ( $n=19$ ), and larger numbers would be needed to investigate the true relationship between ethnicity and outcome of management.

### Obstetric history

**Parity:** Parity was divided into categories of (P0, P1,P2+) and analysed against outcome at first follow-up and final outcome. No statistical significance was found between groups.

**Previous vaginal deliveries:** Vaginal deliveries was also not found to have any influence on the outcomes of management,  $p=0.53$ .

**Type of conception:** A small number in this cohort had assisted reproduction ( $n=10$ ). There was a trend for higher rates of non-surgical outcome in the spontaneous conception group compared to the assisted reproduction group; 71% (4/10) and 40% (112/158) respectively;  $p=.04$ .

**Previous medical management of miscarriage:** It appeared to be linked to higher efficacy of medical management; 66.7% (8/12) with previous history compared to 45.2% (19/41) without history.

The number of cases however was small (n=12) and the p-value was not significant (p=.19).

Influence of ultrasound features on outcome of management

#### Midgestational sac diameter (MGSD)

MGSD was analysed as a continuous variable and also divided into categories. There was no significant difference found between the mean of the MGSD with complete miscarriages (mean of 25.4mm, SD 9.1) and incomplete miscarriages (mean 26.9mm, SD 10.3).

#### Presence of fetal pole (embryonic and anembryonic)

There was a higher percentage of non-surgical outcomes in embryonic miscarriages compared to an-embryonic (empty gestational sac); 72.8% (91/125) and 56.8% (25/44) respectively; p=0.049.

#### Crown-rump length

For ultrasound features only the CRL (gestation by ultrasound) was significant (p=0.005). This relationship was only present when the CRL was divided into categories and not as a continuous variable. Specifically, when the CRL was above 20mm (equivalent to approximately 8.5 weeks gestation). The efficacy of management was significantly reduced (24%). The higher rate for the complete miscarriage was for CRL 10-20mm (7 to 8.5 weeks gestation) at 68% (27/40).Table 1

**Table 1:** CRL (mm) and complete miscarriage following medical management at first follow-up.

N=123	CRL (mm)					
	<10mm		10-20mm		>20mm	
	N	N%	N	N %	N	N %
<b>Complete miscarriage at first follow-up</b>	30	48.4%	27	67.5%	5	23.8%
	n= 62		n= 40		n= 21	

p= 0.005; chi-square

#### Presence of a corpus luteum

There was also a significantly higher number of non-surgical outcomes when the corpus luteum was absent at the time of diagnosis of miscarriage (73% versus 50%, p=.01).

#### Other factors

There was no significant relationship between the outcome of miscarriage following medical management and the following clinical factors: gestation at diagnosis (by LMP), planned pregnancy, gravidity, previous caesarean sections, regularity of menstrual cycle, smoking, presenting complaint and pain. There was also no significant relationship between the outcome and the following ultrasound features: uterine position and presence of yolk sac.

Influence of biochemical markers on outcome of management

HCG, progesterone and Rhesus blood group were explored as potential predicting factors of outcome of management. Rhesus blood group showed no relationship with either outcomes investigated in this study.

#### Human chorionic gonadotrophin

Three categories (<10, 10-20, >20 thousand) were considered. Up to 91% of women had a non-surgical outcome when the HCG levels were between 10,000-20,000 IU/l, compared to 55% with HCG levels over 20,000IU/l (p= 0.006). The analysis was repeated with 20,000IU/l as a cut-off point using dichotomous categories. This showed significant results at both first follow-up (.048) and at final outcome (.006). The relationship was stronger between HCG level and the final outcome. Table 2

**Table 2:** HCG level and outcome of medical management.

		βhCG level (IU/l)			
		<20,000		>20,000	
		N	N%	N	N%
<b>Outcome at first follow-up*</b>	Complete	41	53.9%	50	32.1%
	N=104	76		28	
<b>Final outcome**</b>	Non-surgical	62	81.6%	16	55.2%
	N=105	76		29	

\* p= 0.048, \*\*p=.006; chi-square

#### Progesterone

Using the value of 9nmol/l as the cut-off point gave a significant difference with the outcome. 80% (8/10) of women with progesterone less than 9nmol/l had a complete miscarriage, compared to 44% (43/90) with progesterone above 9nmol/l (p= 0.04).

#### Combined clinical factors

Several combinations of the above variables (CRL, BMI, HCG, Progesterone and bleeding) were computed and checked against outcome. Table 1 below summarises the statistically significant combinations and efficacy rates above 80%. A CRL size of 10-20mm (gestational age of 7+0 to 8+4 by Robinsons)<sup>[11]</sup> was the most predictive of efficacy rates, especially when combined with HCG levels less than 20,000 IU/l (89% at first follow-up and 100% at final outcome).

**Table 3:** Combination of clinical factors and efficacy of medical management of miscarriage.

Clinical factors and outcome of management	N	Efficacy rate% (n)	p-value
<b>Outcome at first follow-up</b>			
CRL (10-20mm) + HCG <20,000 IU/l	18	89% (16)	<.001 <sup>a</sup>
CRL (10-20mm) + bleeding 24hours prior to treatment	12	75% (9)	.05 <sup>a</sup>
CRL <20mm + HCG <20,000 IU/l	67	58% (39)	.002 <sup>a</sup>
CRL <20mm + BMI >30	28	71% (20)	.003 <sup>a</sup>
HCG <20,000 IU/l + P4 <9nmol/l	10	80% (8)	.03 <sup>b</sup>

a: chi-square; b: Fisher's exact (1-sided sig.).

#### Discussion and Conclusion

This study aimed to find predictors of effective medical management in first trimester miscarriages. Non-Caucasian women, higher BMI, bleeding in the 24 prior to treatment, gestational age by ultrasound between 7 to 8.5 weeks (CRL 10-20mm), HCG level less than 20,000 IU/l and progesterone level less than 9nmol/l had higher rates of complete miscarriage in the two weeks following oral misoprostol.

In this study, BMI was a significant predictor of efficacy of medical management. To the best of our knowledge only two previous studies looked at BMI as a predictor of outcome of medical management of miscarriage and both found no significant relationship [8,12]. However, both studies were retrospective, had lower sample size and had different treatment protocol and a vague criterion for diagnosing complete miscarriages. In Ireland, the majority of surgical evacuations are done under general anaesthetic. Therefore, this findings can be very useful clinically as it can reduce surgical intervention in women with higher BMI who would be considered high risk patients.

The efficacy of treatment was particularly improved when the CRL was between 10-20mm which would be equivalent to 7+0 to 8+4 weeks [by Robinsons et al [11] and significantly reduced when CRL was over 20mm (approaching 9 weeks' gestation). The response to treatment was best when a CRL of 10-20mm was combined with a HCG level less than 20,000 IU/l, reaching efficacy of almost 90%. This finding was supported by Ehrnsten et al and Odeh et al who found smaller CRL to be associated with better outcome [6,7]. Other studies that looked at CRL found no significant relationship [8-10]. This could be due to the type variable used in the analysis.

Similar to previous studies, we found no relationship between outcome of medical management of first trimester miscarriage and maternal age [8-10], previous miscarriage [3,6,11], gestational age [11-13], MGSD [3,6,10] and uterine position [8]. However, Unlike previous studies, this study showed no relationship between efficacy of medical management and parity or gravidity [3,9,10,11,14]. Previous studies showed parity and previous pregnancies to be negatively correlated with the efficacy of medical management. Our finding however was in agreement with more recent studies by Ehrnsten, 2019; Banerjee, 2013 and Lusink, 2018 [13,15].

Lusink et al and others also showed no significant relationship of efficacy to type of miscarriage, pelvic pain and vaginal bleeding; which was in agreement with some of our findings [3,4,15]. However, we found a significant relationship between outcome at first follow-up and bleeding but only when it occurred in the 24 hours prior to diagnosis ( $p=.028$ ), which was similar to Elkhohi et al and Creinin et al. [6,19].

A novel ultrasound predicting factor, not investigated previously, was the absence of corpus luteal cyst; which we found to be significantly associated with a non-surgical outcome ( $p=.01$ ). The corpus luteum is most prominent early in pregnancy and is critical to sustaining the gestation in the first 8 weeks, during which the maximum progesterone secretion occurs [16]. Therefore, the absence of a corpus luteal cyst is perhaps associated with low progesterone levels, which we also found to be associated with better outcomes of medical management. Progesterone levels below 9nmol/l was found to be correlated to higher efficacy of medical management.

Previous studies on serum markers as predictors show conflicting results. Gronlund, Schreiber and Nielsen found no relationship between outcome of medical management and progesterone level [8,17,20]. On the other hand, Banerjee et al found that a combined mifepristone/misoprostol regimen is less effective with progesterone less than 10 nmol/l [18]. This is contradictory to my findings. However the role of progesterone might be different when using mifepristone as it is an anti-progesterone, while in this study a misoprostol only regimen was used. There is evidence that Mifepristone is a progesterone receptor modulator and can act as an agonist when progesterone levels are low, which could explain the findings by Banerjee [21]. It is also possible that misoprostol alone will be more effective for patients with low progesterone, which would support the findings in this study [18].

The use of bHCG levels as a predictor of treatment efficacy has a similar contradictory pattern in the literature. Again, Gronlund, Nielsen and Creinin found no relationship between bHCG as an independent factor and efficacy of medical treatment [6,17,20]. Gronlund et al however, did find the combination of HCG between 2000-20,000 and gestational age <75 days to predict efficacy up to 90%. This agrees with our finding of bHCG less than 20,000 to be predictive of efficacy and the gestational age <75 days could be linked to a smaller CRL size which I also found to be predictive. Odeh et al also found higher level of bHCG to have a negative effect on treatment efficacy [5]. On the other hand, Schreiber et al found higher levels (above 4000 IU/l) to be predictive of success [8]. They didn't however comment on bHCG levels above 20,000 IU/l. Therefore, one can argue that levels above 20,000 IU/l could still have a negative effect on the efficacy and that all the studies had similar findings that were just reported differently.

Some limitation to our study is the low efficacy rate and the sample size. Perhaps that can explain why factors identified in previous studies, like parity, were not predictive in this study. It would be interesting to do a validation study on a similar cohort of women (same unit) using the predicting factors identified in this study to see if the efficacy rate will improve. The study would also need to be repeated using the combined medical management protocol (Mifepristone along with misoprostol) to see if the same predictors will maintain their predictive relationship with the outcome of treatment.

Our data adds to the existing literature that shows that clinical, ultrasound and biochemical factors can be useful to help guide women and clinicians in choosing the appropriate management option for first trimester miscarriage.

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