

1 **Maternal Serum Markers in Predicting**  
2 **Successful Outcome in Expectant**  
3 **Management of Missed Miscarriage**

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6 Maria Memtsa<sup>a</sup>, Eric Jauniaux<sup>a,b,\*</sup>, Béatrice Gulbis<sup>c</sup>, Netta C Nyrhinen<sup>b</sup>, Davor  
7 Jurkovic<sup>b</sup>

8

9 <sup>a</sup> Early Pregnancy Assessment Unit (EPAU), Department of Obstetrics and  
10 Gynaecology, University College London Hospital (UCLH), London; <sup>b</sup>  
11 Academic Department of Obstetrics & Gynaecology, UCL Institute for  
12 Women's Health, University College London (UCL), London, UK; <sup>c</sup>  
13 Department of Clinical Chemistry, Erasme Hospital, Université Libre de  
14 Bruxelles (ULB), Brussels, Belgium.

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19 \* Corresponding author. E-mail address: e.jauniaux@ucl.ac.uk.

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21 **Short title:** Predicting Outcome in Expectant Management of Missed Miscarriage

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## 1 **Abstract**

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

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23 **Key words:** Miscarriage, pregnancy, first-trimester, maternal serum, C -  
24 reactive protein.

# 1 Introduction

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

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

22 Surgical management under general anesthesia used to be the only  
23 option for women presenting with a missed miscarriage on the basis that it  
24 decreases the risk of hemorrhage and subsequent gynecological infection.

25 Over the past 2 decades, the management of miscarriage has radically

1 changed and has moved towards individualized treatment and patient choice  
2 between expectant, medical, and semi-elective surgical treatment. Improved  
3 access to specialized Early Pregnancy Units and increasing awareness  
4 amongst women of their choices in the management of early pregnancy  
5 complications have led to an increasing demand for more conservative  
6 management of early miscarriage (Jurkovic et al., 2013).

7         Expectant management is now **regularly** chosen by women presenting  
8 with first trimester missed and incomplete miscarriage to avoid a surgical  
9 evacuation. **In one observational study, it was found that 70%** of women opted  
10 to wait for the pregnancy to resolve spontaneously (Luise et al., 2002).

11 Medical management by means of prostaglandin has also become an option,  
12 chosen as the primary treatment option by 20-30% of women (Shankar et al.,  
13 2007). A recent meta-analysis of randomised trials comparing expectant care  
14 and surgical treatment has shown that the risks of infection and psychological  
15 outcomes are similar for both groups and that the costs are lower for  
16 expectant management (Nanda et al., 2012). However, expectant  
17 management is associated with a higher risk of incomplete miscarriage, need  
18 for unplanned or additional surgical evacuation of the uterus, bleeding and  
19 need for transfusion (NICE, 2012). **The main issue** with expectant  
20 management **has been** the lack of ultrasound and/or biological criteria that  
21 can accurately predict the likelihood of a successful spontaneous completion  
22 of miscarriage (Elson et al., 2005).

23         Several biochemical markers and algorithms have been trialed over the  
24 last decade in an attempt to guide clinicians and women in the decision-  
25 making process with varying success due mainly to small numbers, different

1 populations studied and different methodologies used. Unlike, human  
2 chorionic gonadotrophin (hCG) and progesterone assays, the assays for new  
3 proteins are not available routinely in most hospital clinical laboratories.  
4 Maternal serum pregnancy-associated protein A (PAPP-A) is now widely used  
5 to predict adverse pregnancy outcomes (Wells et al., 2015; Yliniemi et al.,  
6 2015) and high-sensitivity C-reactive (hsCRP) protein is routinely used in  
7 cardiovascular disease risk stratification and management (Kalogeropoulos et  
8 al., 2014).

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

13

## 14 **Materials and methods**

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

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

9           Women with multiple pregnancies, women with pregnancies resulting  
10 from assisted reproductive technologies and women who were on  
11 supplemental hormonal treatment were excluded from the study group.  
12 Demographic data including maternal age, ethnicity, parity, cigarette smoke  
13 exposure, age and body mass index (BMI) were collected from questionnaires  
14 completed at the time of the first appointment. Pregnancy outcome  
15 information was collected from the medical case notes and hospital electronic  
16 patient records. The study was approved by the Joint UCL/UCLH Committees  
17 on the Ethics of Human Research on 3<sup>rd</sup> December 2007 (Reference Number:  
18 07/Q0512/41). All women received information about the study and written  
19 consent was obtained prior to the ultrasound examination.

20           The study group included women diagnosed with a missed miscarriage  
21 during the first trimester of pregnancy and opting for expectant management.  
22 The diagnosis of missed miscarriage was defined as a gestational sac size  
23 >20 mm in diameter with no evidence of an embryo or yolk sac; or as fetal  
24 crown-rump length (CRL) >6 mm with no fetal heart rate, or in case of no  
25 evidence of fetal development and/or no fetal heart activity during a follow-up

1 scan performed  $\geq 7$  days since the initial examination (The association of Early  
2 Pregnancy Units. AEPU organisational, clinical and supportive guidelines,  
3 2007; <http://www.earlypregnancy.org.uk>).

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

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

24

1 **Bioassays**

2 All maternal serum samples were assayed for hCG, progesterone, PAPP-A  
3 and hsCRP using commercial assays. Maternal serum progesterone and hCG  
4 assays were performed on a Modular E170 Analyzer (Roche Diagnostics,  
5 Vilvoorde, Belgium) with an electrochemiluminescence competitive methods.  
6 hsCRP assay was performed using an immunoturbidimetric method on a  
7 Modular P Analyzer (Roche Diagnostics, Vilvoorde, Belgium) with a  
8 quantitation limit of 0.5 mg/L. Maternal serum PAPP-A assay was performed  
9 on a IMMULITE 2000 immunoassay system (Siemens, Brussels, Belgium)  
10 with an enzyme-labeled chemiluminescent immunometric method.

11

12 **Statistical analysis**

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

23 For the categorical variables, data are displayed as odds of success in  
24 each category relative to the odds in a baseline category. For the continuous  
25 variables, the relative change in the odds of success for a one-unit increase in



1 the corresponding variable is presented. Variables that presented with  
2 skewed distributions were transformed using a logarithmic transformation  
3 before analysis. Results were considered statistically significant at  $P < 0.05$ .

4

## 5 **Results**

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

15 A summary of the univariate analysis results is presented in table 1.  
16 This analysis indicated that, when examined individually, maternal age ( $p =$   
17  $0.01$ ), progesterone ( $p = 0.03$ ) and PAPP-A ( $p = 0.02$ ) were all significantly  
18 associated with successful expectant management. Increased age was  
19 associated with an increased chance of success with the odds of success  
20 increased by around 75% for a 5-year increase in age. Higher values of both  
21 progesterone and PAPP-A were associated with a reduced chance of  
22 successful management. A one-unit increase in progesterone on the log scale  
23 (equivalent to a 10-fold increase in progesterone) was associated with a 50%  
24 lower chance of successful expectant management. The study has an 80%  
25 power to detect a difference of 25% in outcome between groups, and over

1 90% to detect a difference of 30% between groups.

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

11         Progesterone and age were combined in a logistic regression model to  
12 predict the probability of successful management ( $p$ ) using the following  
13 equation:

14  $p = e^y / (1 + e^y)$  where  $y = 0.356 + 0.078 \text{ age} - 0.917 \text{ log progesterone}$

15

## 16 **Discussion**

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

1           The success of expectant management within two weeks is variable  
2 across observational studies (Casikar et al., 2010; Jurkovic et al., 2013; Knez  
3 et al., 2014). It is generally accepted that the likelihood of completion after two  
4 weeks is low and evacuation of the uterus should be offered. Completion  
5 rates are higher in incomplete miscarriages (80-96%) at two weeks with lower  
6 low complication rate than in missed miscarriage. In controlled trials of  
7 medical management, expectant management (placebo arm) was successful  
8 in 29 to 42% of women with missed miscarriage and 55% to 86% of women  
9 with incomplete miscarriage (Kovavisarach et al.,2002; Luise et al.,2002;  
10 Wood et al, 2002; Bagratee et al., 2004; Blohm et al., 2005; Lister et al.,  
11 2005). **The Royal College of Obstetricians and Gynaecologists( RCOG)**  
12 **evidenced-based guidelines on the care of women requesting induced**  
13 **abortion indicates that there is insufficient evidence to imply causality**  
14 **for pre-term birth and miscarriage following first trimester surgical**  
15 **abortion when the procedure is carried out in a high standard health**  
16 **care set up (RCOG 2011). However, several more recent systematic**  
17 **reviews have suggested that surgical management can be associated**  
18 **with increased risks of long-term complications such as preterm birth in**  
19 **subsequent pregnancies (Lemmers et al., 2016) and intrauterine**  
20 **adhesions (Hooker et al., 2015).**

21           A meta-analysis of studies comparing expectant management with  
22 active management (medical or surgical) showed a higher rate of unplanned  
23 emergency interventions (NIH, 2012). In the present study, the completion  
24 rate was 78%, which is higher than in previous observational and cohort

1 studies. This may be due to the fact that our study included only cases of  
2 missed miscarriages. By contrast the majority of previous studies included  
3 both incomplete and missed miscarriage in their data analysis. The difference  
4 in outcome and success rates may also be due to different study populations  
5 and changes in maternal parameters over the last decade. In particular, our  
6 population includes a high number of women with AMA and in our study group  
7 the average maternal age was above the national average of 30.0 years  
8 reported recently for England and Wales (ONS, 2014). A history of previous  
9 miscarriage with different management approaches i.e. expectant, surgical or  
10 medical may also influence outcome in large series.

11         The diameter of retained products of conception as seen on ultrasound  
12 examination was assessed and found to be significantly different in women  
13 with successful and failed expectant management in a study that included 54  
14 women who were diagnosed either with an incomplete or missed miscarriage  
15 (Elson et al., 2005). Ultrasound parameters such as mean gestational sac  
16 diameter (MSD) and sac volume have not been routinely evaluated in the  
17 successful expectant management of missed miscarriage. In a study of 85  
18 women diagnosed with missed miscarriage, the mean diameter of the  
19 gestational sac at the initial ultrasound examination was found to be  
20 significantly smaller in women who successfully completed expectant  
21 management of missed miscarriage, compared with those who failed  
22 expectant management (Jurkovic et al, 1998). In this study, the cumulative  
23 success rates were 15%, 20% and 25% after one, two and > two weeks,  
24 respectively. In our study, no difference was observed when evaluating  
25 sonographic characteristics such as sac diameter and sac volume and

1 successful outcome of expectant management of missed miscarriage after  
2 two weeks. This could be explained by the maximum length of two weeks of  
3 follow-up offered to women who opted for expectant management in our study  
4 and the fact that our study only included women who opted for an expectant  
5 management.

6 Maternal serum  $\beta$ -hCG and progesterone are the most commonly used  
7 serum markers in the assessment of pregnancy viability (Chetty et al., 2011).  
8  $\beta$ -hCG levels are directly related to the amount of villous trophoblast whereas  
9 progesterone production in early pregnancy reflects the dynamics of the  
10 corpus luteum-trophoblast axis and the status of the trophoblastic tissue. It  
11 has previously been established that the likelihood of a spontaneous  
12 pregnancy failure declines as the maternal progesterone level rises in both  
13 intrauterine and extrauterine pregnancies (McCord et al. 1996; Verhaegen et  
14 al., 2012). A recent systematic review and diagnostic accuracy meta-analysis  
15 has confirmed that low serum progesterone is strongly associated with a  
16 failing pregnancy and can be used to rule out the possibility of a viable  
17 pregnancy (Pillai et al. 2016).

18 Pregnancy associated plasma protein A (PAPP-A) is mainly produced  
19 by the villous trophoblast and its synthesis is up-regulated by progesterone  
20 during pregnancy (Wang et al., 2014). PAPP-A levels in maternal serum have  
21 been shown to be low in pregnancies with chromosomal abnormalities, like  
22 triploidy, trisomy 21, 18 and 13, and sex chromosome aneuploidy (Spencer et  
23 al., 2008, Suri et al., 2013). Low levels of PAPP-A have also been related to  
24 spontaneous miscarriage (Yaron et al., 2002). Our results confirm these

1 findings with women presenting with lower levels of progesterone and PAPP-  
2 A having a higher rate of successful expectant management.

3         Recent studies have reported a possible role for the measure of  
4 maternal serum hsCRP in the first-trimester screening of pre-eclampsia  
5 (Kashanian et al., 2013), in predicting long-term cardiovascular risks in  
6 women who had hypertensive disorders late in pregnancy (Hermes et al.,  
7 2013) and in the diagnosis of early-onset neonatal infection in cases of  
8 chorioamnionitis (Howman et al., 2012). We recently found that hsCRP levels  
9 do not predict the likelihood of miscarriage in women presenting with  
10 threatened miscarriage (Jauniaux et al., 2015). In the present study, hsCRP  
11 levels were not different between successful and unsuccessful subgroups,  
12 suggesting that this parameter does not contribute to the management of  
13 early pregnancy complications.

14         A mathematical model to predict successful expectant management of  
15 missed and incomplete miscarriages was validated in a recent prospective  
16 study (Casikar et al., 2013). The data were separated in 3 groups, missed  
17 miscarriage, anembryonic sac and incomplete miscarriage and the authors  
18 found that the most independent prognostic variables for their model are the  
19 type of miscarriage at primary scan, vaginal bleeding and maternal age. In our  
20 study, symptomatology at presentation was not recorded and therefore not  
21 included in the analysis. However, maternal age appears to be a common  
22 strong predictor probably due to the relationship between advanced maternal  
23 age (AMA) and aneuploidy rates. In addition, we found that routine  
24 biochemical markers can contribute to the management of missed

1 miscarriage with progesterone being the best biochemical marker to predict  
2 successful outcome.

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

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

3

Variable	Category	Success Number (%)	Odds Ratio (95% CI)	P-value
Age (*)	-	-	1.77 (1.13, 2.76)	<b>0.01</b>
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 (*)	-	-	1.07 (0.62, 1.84)	NS
Smoker <sup>a</sup>	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	None	38/52 (73%)	1	NS
	Mild/Moderate	24/29 (83%)	1.77 (0.56, 5.54)	
Bleeding <sup>a</sup>	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 (**)	-	-	0.81 (0.50, 1.31)	NS
Sac volume (†)	-	-	0.80 (0.49, 1.31)	NS
Gest. age (wks)	-	-	0.99 (0.72, 1.34)	NS
βhCG (†)	-	-	0.73 (0.49, 1.08)	NS
Progesterone (†)	-	-	0.46 (0.23, 0.91)	<b>0.03</b>
CRP (†)	-	-	1.14 (0.70, 1.87)	NS
PAPP-A (†)	-	-	0.62 (0.41, 0.94)	<b>0.02</b>

4 (\*) Odds ratios given for a 5-unit increase in predictor variable

5 (\*\*) Odds ratios given for a 10-unit increase in predictor variable

6 (†) Variable analysed on log scale

7 <sup>a</sup> Missing data in some cases.

8

9

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

3

Variable	Odds Ratio (95% CI)	P-value
Age (*)	1.82 (1.14, 2.91)	0.01
Progesterone (†)	0.44 (0.21, 0.90)	0.03

4 (\*) Odds ratios given for a 5-unit increase in predictor variable

5 (†) Variable analysed on log scale

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