

Clinical review

Threatened miscarriage: evaluation and management

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Threatened miscarriage—vaginal bleeding before 20 gestational weeks—is the commonest complication in pregnancy, occurring in about a fifth of cases.^{w1} Miscarriage is 2.6 times as likely,¹ and 17% of cases are expected to present complications later in pregnancy.² Although general practitioners and gynaecologists often see this condition, management of threatened miscarriage is mostly empirical. Bed rest is routinely recommended, and about a third of women presenting with threatened miscarriage are prescribed drugs.^{w2} However, two thirds of the general practitioners recommending this do not believe it affects outcome.³

In this review, we present available evidence on the initial evaluation and management of threatened miscarriage, focusing mainly on the first trimester of pregnancy and primary healthcare settings.

Sources and selection

We searched literature in English with Medline (January 1965 to April 2004), Embase (January 1980 to April 2004), and the Cochrane database using the keywords “threatened” and “abortion” or “miscarriage” and “pregnancy” and “first trimester” or “early” and “bleeding”. We scanned abstracts and got the full text of relevant articles. We also scanned the references of retrieved articles. The more recent or randomised, prospective, or large studies focusing on women with symptoms of threatened miscarriage were primarily cited; we excluded studies on recurrent pregnancy loss or women without symptoms, unless otherwise stated.

Evaluation

Bleeding in the first trimester can originate from the uterus, cervix, or vagina, or it can be extragenital. Thorough physical examination is essential to differentiate between genital and extragenital causes. After exclusion of extragenital causes, several parameters have been associated with prognosis (table 1).

History

Older women are at increased risk of miscarriage in the general population.^{w3} A prospective study on women with threatened abortion reported that women older than 34 years had an odds ratio of 2.3 for miscarriage, however, the 95% confidence interval was wide (0.76 to 7.10), and the contribution of maternal age in regression analysis was not significant ($P=0.13$).⁴ Having had previous miscarriages is also associated with increased risk in future pregnancies, especially in older women,^{w4} whereas data from the general population

Summary points

One in five pregnancies is complicated by vaginal bleeding before 20 weeks' gestation

A large empty gestational sac, discrepancy between gestational age and crown to rump length, fetal bradycardia or absence of fetal heart activity at presentation, advanced maternal age, history of recurrent pregnancy loss, a maternal serum progesterone <45 nmol/l or low maternal serum hCG or inhibin A are adverse prognostic factors

Fetal heart activity and lack of adverse prognostic factors conveys a favourable prognosis

Although bed rest and progesterone supplements are often advised, little evidence supports their effectiveness

Give anti-Rh D immune globulin to non-sensitised women with symptoms near, at, or after 12 gestational weeks

show that the rate of fetal loss declines with advancing gestational age.¹

Sonographic evaluation

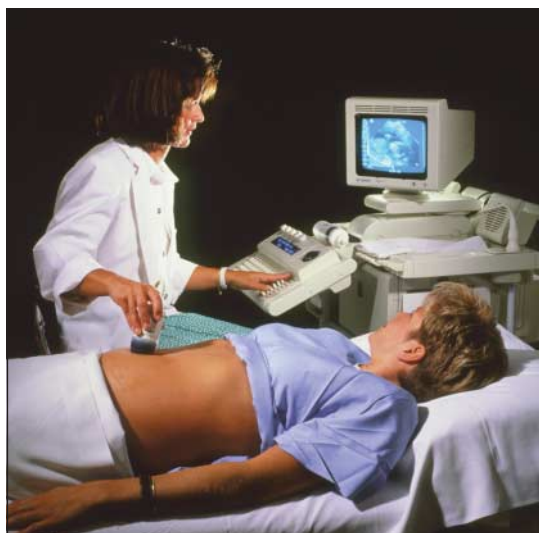
Sonography can usually differentiate between an intrauterine pregnancy (viable or non-viable), a molar pregnancy, or an inevitable abortion. Furthermore, sonographic features of pregnancy have been proposed as predictors.

An empty gestational sac with a diameter of at least 15 mm at seven weeks and 21 mm at eight weeks has diagnostic accuracy of 90.8% in predicting miscarriage in women with symptoms.⁵ A mean sac diameter of at least 17 mm without an embryo or 13 mm without a yolk sac can predict non-viable gestation with a specificity and a positive predictive value of 100%.⁶

Fetal heart activity should be visible with transvaginal sonography once the fetal pole is at least 5 mm long.^{w5} Most prospective series report a loss rate of 3.4-5.5% if bleeding occurs after fetal heart activity



References w1-w19 are on bmj.com



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Threatened miscarriage affects one in five pregnancies

starts,^{7 8 w6} and identification of fetal heart activity by ultrasound in primary healthcare settings carries a 97% likelihood for the pregnancy continuing beyond 20 weeks.⁹ However, this favourable effect has not been universally repeated, as miscarriage rates of 20-30% have been reported.^{10 11}

Fetal bradycardia and discrepancy between gestational age and crown to rump length are adverse prognostic factors.^{1 12} Prospective data indicate that the presence of any of three risk factors (fetal bradycardia, discrepancy between gestational sac and crown to rump length, and discrepancy between menstrual and sonographic age by more than one week) increases the rate of abortion from 6% when none are present to 84% when all three are present.⁴

The prognostic value of a subchorionic haematoma in ultrasound has been disputed. Although a large separation has been associated with about a threefold increase of risk of miscarriage (19% *v* 71%) in women with bleeding,¹³ the presence or the size of haematoma did not affect miscarriage rate (10% *v* 11%) in another prospective series,¹⁴ and other studies reported similar findings.^{4 5 15}

A prospective study of 6675 women found that the presence of an intrauterine haematoma in the first trimester of pregnancy increases the risk of severe obstetric complications, irrespective of the presence of symptoms of threatened miscarriage.¹⁶ However, the presence of a haematoma did not influence the risk for subsequent complications in a smaller study of symptomatic women.²

Maternal serum markers

Maternal serum biochemistry has also been proposed as a predictor. Women with threatened miscarriage in their first trimester who eventually miscarried have lower serum hCG values compared with women continuing the pregnancy and asymptomatic pregnant women.¹⁰ A prospective study showed that a free β hCG cut-off value of 20 ng/ml could differentiate between normal (control and threatened continuing) and abnormal (non-continuing threatened miscarriage and tubal) pregnancies, with 88.3% sensitivity and 82.6% positive predictive value.¹¹ The bioactive to immunoreactive ratio

of serum hCG was also higher in symptomatic women who continued with pregnancy than in women who eventually miscarried.^{w7} However, this study included only 24 women with threatened abortion and did not give data on fetal heart activity at presentation.

Progesterone concentrations show a narrow variation in the first trimester. According to data from mixed obstetric populations, the lowest serum progesterone concentration associated with a viable first trimester pregnancy is 5.1 ng/ml,^{w8} and a single serum progesterone measurement of at least 25 ng/ml carries a 97% likelihood for viable intrauterine pregnancy, being more sensitive than two serial hCG measurements.^{w9} Data from 358 women presenting with vaginal bleeding in the first 18 gestational weeks indicated that a single progesterone value of less than 45 nmol/l (14 ng/ml) is able to differentiate between abnormal and normal (ongoing) pregnancies, with a sensitivity of 87.6% and a specificity of 87.5%.¹⁷

In a recent series, women with threatened abortion and fetal heart activity at presentation, serum inhibin A, activin A, and hCG concentrations were much lower in cases in which the women eventually miscarried; inhibin A at the cut-off of 0.553 multiples of median was the best predictor with an area under the curve 0.9856.¹⁸

Women with threatened abortion who eventually miscarried had constant or increasing concentrations of ovarian carcinoma antigen CA125 over 5-7 days, whereas those who continued with pregnancy had a constantly low or steeply declining CA125 concentration.¹⁹ Also, a single CA125 concentration of at least 43.1 IU/ml was associated with a greater risk of miscarriage in 200 women who had had vaginal bleeding in their first trimester.²⁰

Finally, although pregnancy associated placental protein A (PAPP-A) concentrations were much lower in a series of 128 symptomatic women with fetal heart activity at presentation than in normal controls, its predictive value for miscarriage was only 18.7%.²¹

Management

Doctors often prescribe bed rest and progesterone for women with symptoms of threatened miscarriage, but evidence is sparse and of low level (table 2).

Table 1 Prognostic factors in cases of threatened abortion

Favourable prognostic factors	Adverse prognostic factors
History	
Advancing gestational age ^{1*}	Maternal age >34 years ^{4 w3* w4*}
	Increasing number of previous miscarriages ^{w4*}
Sonography	
Fetal heart activity at presentation ⁶⁻⁸	Fetal bradycardia ^{1*}
	Discrepancy between gestational age and crown to rump length ^{4 12}
	Empty gestational sac >15-17 mm ^{5 6}
Maternal serum biochemistry	
Normal levels of these markers	Low β hCG values ¹⁰
	Free β hCG value of 20 ng/ml ¹¹
	β hCG increase <66% in 48 hrs ^{w9*}
	Bioactive/immunoreactive ratio hCG <0.5 ^{w7}
	Progesterone <45 nmol/l in 1st trimester ¹⁷
	Inhibin A <0.553 multiples of median ¹⁸
	CA125 level \geq 43.1 U/mL in 1 st trimester ¹⁹

*Women without symptoms of threatened abortion.

Bed rest

In one study, 1228 out of 1279 (96%) general practitioners prescribed bed rest for heavy bleeding in early pregnancy, although only an eighth of them felt it was mandatory, and only one third felt it could affect outcome.³ Only one randomised controlled trial considers the impact of bed rest on the course of threatened miscarriage²²; 61 women with viable pregnancies at less than eight gestational weeks and vaginal bleeding were randomly allocated into either injections of hCG, injections of placebo, or bed rest. The abortion rates in the three groups were 30%, 48%, and 75%—significant differences between hCG and bed rest groups but not between hCG and placebo groups or between placebo and bed rest groups. Although hCG performed significantly better than bed rest in this study, the lack of profound benefit over placebo, the concern about potential development of ovarian hyperstimulation syndrome, and the fact that threatened miscarriage may be the result of various conditions, irrelevant to luteal function, prevented further testing and application of hCG treatment in general obstetric practice.

In a retrospective study of 226 women who were hospitalised for reasons related to their pregnancy and previous threatened miscarriage, 16% of 146 women who were bed resting eventually miscarried, compared with a fifth of women who did not follow this option (not significant; $P=0.41$).²³ In contrast, a recent observational cohort study of 230 women with threatened miscarriage who were recommended bed rest showed that women who adhered to this suggestion had a miscarriage rate of 9.9%, compared with 23.3% of women who continued their usual activities ($P=0.03$).²⁴ The duration of vaginal bleeding, haematoma size and gestational age at diagnosis did not influence miscarriage rate. Although there is no definite evidence that bed rest can affect the course of pregnancy, abstinence from active environment for a couple of days may help women feel safer,^{w10} thus providing emotional relief.

Progesterone

Progesterone is prescribed in 13-40% of women with threatened miscarriage, according to published series.^{3 w2} Progesterone is the main product of the corpus luteum, and giving progestogen is expected to support a potentially deficient corpus luteum gravi-

darum and induce relaxation of a cramping uterus. The evidence on progesterone is of low quality. Recently, a meta-analysis assessed the impact of progesterone supplementation on miscarriage rate in various clinical settings²⁵; however, it did not provide a separate analysis for progesterone in threatened miscarriage. Four published papers in the meta-analysis were assessing this relationship,^{w11-w14} one of them including three different regimens of progestogen,^{w11} and those data were reanalysed. Having miscarriage as outcome, random effects risk ratio was 1.10 (95% confidence interval 0.92 to 1.31) for progestogens group. In the only studies that provided sonographic evidence of fetal heart activity at presentation, the relative risk for miscarriage was 1.09 (90% confidence interval 0.90 to 1.33) for the progestogen group.^{w14} Thus, given the poor quality of the data, progesterone does not seem to improve outcome in women with threatened miscarriage. However, local application of a progestogen was found to subjectively decrease uterine cramping more rapidly than bed rest alone in one small study.^{w15}

Other regimens

Buphenine hydrochloride (a vasodilator that is also used as a uterine muscle relaxant) was better than placebo in a randomised controlled trial. But the method of randomisation in this trial was unclear, and no other studies consider tocolysis in early threatened miscarriage.^{w16}

Apart from its effectiveness, the extent of active support is generally questionable in cases of threatened miscarriage, since most pregnancies resulting in early fetal loss are chromosomally abnormal.^{w17}

Rh prophylaxis

Vaginal bleeding in early pregnancy raises the question of whether to give anti-D immunoglobulin in Rh D negative women. Unfortunately, there are no conclusive data on this topic, and all evidence comes from expert or panel opinions (level C). According to the guidelines of the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynaecologists, although Rh D alloimmunisation attributable to first trimester threatened miscarriage is rare, giving anti-D globulin should be considered for non-sensitised Rh D negative women

Table 2 Pregnancy outcome in studies with various therapeutic regimens

First author	Design	N	Sonography at presentation	Intervention	Successful continuation of pregnancy		
					Intervention group	Controls	P value
Moller ^{w11}	Randomised controlled trial	260	No	Medroxyprogesterone (three regimens)	60/123	71/137	0.62
Tognoni ^{w12}	Randomised controlled trial	145	No	Hydroxyprogesterone caproate	49/74	50/71	0.58
Berle ^{w13}	Randomised controlled trial	300	No	Hydroxyprogesterone caproate	96/154	100/146	0.26
Gerhard ^{w14}	Randomised controlled trial	52	Yes	Progesterone	23/26	21/26	0.44
Soltan ^{w16}	Randomised controlled trial	35	Yes	Buphenine	19/23	4/12	<0.01
Harrison ²²	Randomised controlled trial	61	Yes	hCG	14/20	11/21	0.24
Harrison ²²	Randomised controlled trial	61	Yes	Bed rest	5/20	11/21	0.07
Giobbe ²³	Retrospective	226	Yes	Bed rest	123/146	64/80	0.41
Ben-Haroush ²⁴	Prospective observational	230	Yes	Bed rest	180/200	23/30	0.03

Additional educational resources

Websites for doctors

www.update-software.com/Cochrane—The home page of Cochrane Library, where registered users can reach a large number of meta-analyses of therapeutic interventions in obstetrics

www.rcog.org.uk/mainpages.asp?SectionID=5—The good practice page of the Royal College of Obstetricians and Gynaecologists has many evidence based clinical guidelines of obstetric interest, including that on Rhesus prophylaxis

www.earlypregnancy.com—Page of the Special Interest Group Early Pregnancy of ESHRE including useful links and updated scientific information on early pregnancy

Websites for patients

<http://health.allrefer.com/health/abortion-threatened.html>—Gives information on several health issues; an introduction to threatened miscarriage and miscarriage

www.emedicine.com/med/topic3308.htm—Gives useful information on threatened miscarriage and miscarriage; suitable for doctors and patients

with a threatened miscarriage after 12 weeks of pregnancy, or in cases of heavy or repeated bleeding or where there is associated abdominal pain, particularly as gestation approaches 12 weeks.^{w18 w19} In contrast, anti-D Ig is not considered necessary in women with threatened miscarriage with a viable fetus and cessation of bleeding before 12 weeks' gestation.^{w19}

Conclusions

Threatened miscarriage occurs often and is a serious emotional burden for women. Sonographic evaluation at presentation can usually differentiate between intrauterine and extrauterine pregnancy and offer some prognostic clues. Demonstration of fetal heart activity is generally associated with a successful pregnancy rate of 85-97%,^{4 7-9 w6} whereas an empty large gestational sac or a discrepancy between menstrual and sonographic age of more than a week indicates a poor prognosis.^{4-6 12} Advanced maternal age and increasing number of previous miscarriages deteriorates prognosis.^{1 4 w4}

Serum β hCG, progesterone, inhibin A, and CA125 concentrations may be helpful as predictors; however, these tests may not be useful in primary care settings.

Although many women with threatened miscarriage are given progestogens and are prescribed bed rest, little evidence supports these policies. There are only four old randomised controlled trials on progestogens,^{w11-w14} and their cumulative results show that they do not improve outcome. Data on bed rest are of even lower quality, as there is only one small randomised controlled trial,²² one observational,²⁴ and one retrospective study,²³ yielding conflicting results. Although no evidence based suggestions can be made, short term abstinence from usual activity may be feasible for women if it is likely to relieve their stress.

Rhesus sensitisation is rare after first trimester threatened miscarriage; however, consensus suggests that anti-D immune globulin should be given in cases

with bleeding after 12 gestational weeks or cases with heavy symptomatic bleeding near 12 weeks.^{w18 w19}

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