The Perinatal Outcome of Pregnancies Complicated by Vaginal Bleeding in First and Second Trimesters

By:

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Dedication

To

My parents
All members of my Family who support and encourage me to do this work,
My merciful wife, who always supports and motivates me for further progress,
My senior and junior colleagues and friends.
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Lastly and not least, my great thanks to the nice lady Fatima Salih Aziz Mohamed and Miss Rania Eltaib who respectively analyzed the data and printed this work.
# Abbreviations

<table>
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<th>Abreviation</th>
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<tr>
<td>KTH</td>
<td>Khartoum Teaching Hospital</td>
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<tr>
<td>SUH</td>
<td>Soba University Hospital</td>
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<tr>
<td>KRT</td>
<td>Khartoum State</td>
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<tr>
<td>APH</td>
<td>Antepartum Hemorrhage</td>
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<td>IUGR</td>
<td>Intra Uterine Growth Restriction</td>
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<tr>
<td>LBW</td>
<td>Low Birth Weight</td>
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<tr>
<td>1st 2nd 3rd trimester</td>
<td>first , second and third trimesters</td>
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<tr>
<td>NCU</td>
<td>Neonatal care unit</td>
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<tr>
<td>Anti-D</td>
<td>Anti-D-immunoglobulin</td>
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<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
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<tr>
<td>HCG</td>
<td>Human Chorionic Gonadotrophin hormone</td>
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<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
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<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
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<tr>
<td>E2</td>
<td>Oestrogen</td>
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<tr>
<td>T4</td>
<td>Thyroxine</td>
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<tr>
<td>T3</td>
<td>Triiodothyronine</td>
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<tr>
<td>HPL</td>
<td>Human Placental Lactogen</td>
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<tr>
<td>SPI</td>
<td>Specific Placental Immunoglobulin</td>
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<tr>
<td>PAPP .A</td>
<td>Placenta Associated Plasma Protein A</td>
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<td>AFP</td>
<td>Alpha Feto Protein</td>
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ABSTRACT

This is a prospective cohort study conducted in the period from June 2003 to June 2004. There were 308 patients attending the outpatient, referred and casualty clinics in KTH and SUH. There were 103 cases and 205 controls.

We studied the effect of bleeding in the 1st and 2nd trimesters on the perinatal outcome. We looked specifically for the risk of prematurity, intrauterine growth restriction, antepartum haemorrhage and the perinatal morbidity and mortality.

Other risks also appeared in the study including the risk of congenital malformations and the association with a previous history of infertility.

Those patients were followed from the time of vaginal bleeding which should be at 24 week gestational age or less.

The pregnancy should proceed to the third trimester.

Patients are seen regularly and at time of complications till delivery and discharge jointly with the neonatologist.

IV
The statistical analysis showed an increased risk of preterm labour and delivery which was statistically significant (P= .003).

It was even more significant for those who had more than one episode of bleeding compared to the control group.

For growth restriction, the study revealed a statistically significant risk of baby born at term with growth restriction compared to the control group.

Also there was an increased risk of perinatal morbidity and mortality among cases with early vaginal bleeding compared to controls (P= .001).

Regarding the risk of antepartum haemorrhage, The P value = .004, showing an increased risk of all forms of APH including unexplained antepartum haemorrhage.

Also there was an association between history of infertility and the risk of bleeding in early pregnancy.

There was no association between previous miscarriages and the occurrence of bleeding in early pregnancy in the future.
لا يمكن قراءة النص بشكل طبيعي.

أ بووش 2003

أبووش وحكي 2004، وهو أول حمل فترته في الرحم في مهبلة نزيف تعرض النسائيات التي حملات بين تقارير دراسة لا تمت، ومتى في الثالثة المراحل في الذكور، وكونها تناسقًا مع الغرض، وأكملت الأوان والنقطة الأولى الحمل فترته في الرحم، والثانية الأخرى، وتنافس أو تحدت، والتي كتبها على الرحم، والتي كتبها على الرحم، ونناولت، والثانية الأولى حمل فترته في الرحم، تركت أثراً ضعيفًا في تأثيرات الفوائد، وربما المضاعفات، وتعرضها للولد، والثانية، والثانية الأولى حمل فترته في الرحم، ونناولت الوالدين، والثانية الأولى حمل فترته في الرحم، ونناولت، والثانية الأخرى، وتنافس أو تحدت، والتي كتبها على الرحم، والتي كتبها على الرحم، ونناولت، والثانية الأولى حمل فترته في الرحم، تركت أثراً ضعيفًا في تأثيرات الفوائد، وربما المضاعفات، وتعرضها للولد، والثانية، والثانية الأخرى.
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Introduction

Human reproduction is a relatively inefficient process. Some investigators demonstrated that 57% of all conceptions advance beyond 20 weeks.\(^{(1)}\) Of those lost 75% occur before implantation, only 25% are clinically recognizable. Recent investigations have found an overall pregnancy loss of 31% with 22% occurring before implantation. Although the number of pregnancies wasted before implantation is very large, most of them are not recognized clinically, and in practice the problem of early pregnancy loss is limited to those pregnancies aborted after implantation.

Threatened miscarriage - vaginal bleeding before 20 gestational weeks - is the commonest complication in pregnancy, occurring in about a fifth of cases.\(^{(2)}\) Miscarriage is 2.6 times as likely, and 17% of cases are expected to present complications later in pregnancy. 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. However, two thirds of the general practitioners recommending this do not believe it affects outcome.

Threatened miscarriage occurs often and is a serious emotional burden for women.\(^{(2)}\) 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%, whereas an empty large gestational sac or a discrepancy between menstrual and sonographic age of more than a week indicates a poor prognosis. Advanced maternal
age and increasing number of previous miscarriages deteriorates prognosis.

All forms of APH were significantly higher in term deliveries complicated by threatened miscarriage. (3) Pregnancies presenting with threatened miscarriage should be highlighted as 'high risk'.
Literature review

Definition:

The clinical diagnosis of threatened abortion is presumed when any bloody vaginal discharge or vaginal bleeding appears during the first half of pregnancy. It is an extremely commonplace occurrence, because one out of four or five pregnant women has vaginal spotting or heavier bleeding during early gestation. The bleeding and pain that accompany threatened abortion are not usually intense. Threatened abortion rarely manifests with severe vaginal bleeding. Often, the bleeding is temporary and self-limited and probably due to trophoblastic implantation within the decidualized endometrium. Threatened abortion is defined by the absence of passing/passed tissue and the presence of a closed cervical os. These findings differentiate threatened abortion from later stages of abortion.

Risk factors:

Maternal Age:

Older women are at increased risk of miscarriage in the general population. 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)
Previous miscarriage:

Having had previous miscarriages is also associated with increased risk in future pregnancies, especially in older women, whereas data from the general population show that the rate of fetal loss declines with advancing gestational age.\(^7\)

Aetiology:

Subchorionic haematoma:

A relatively common cause of bleeding in the first half of pregnancy, but an uncommon cause of pregnancy loss, is the separation of foetal membranes.\(^1\) The bleeding may occur between the chorion and amnion (chorioamniotic separation) or between the chorioamnion and the decidua (subchorionic haematoma). Patient with these abnormalities have first trimester bleeding that may vary in severity. Usually they have minimal or no cramping. Ultrasound shows a normal active foetus and an area of membrane separation usually opposite to the placental implantation site. Often a thin membrane can be seen floating between the uterus and the foetus in cases of chorioamniotic separation. In subchorionic haematomas the membrane is thick and has limited mobility.

The cause of such bleeding and membrane separation is unknown. The course of the problem is not related to the severity of the initial bleeding episode. However, estimation of the haematoma size by ultrasound seems to be of prognostic value.

There are some other etiological factors operating in spontaneous miscarriage:
**Genetic causes:**

Genetic causes of miscarriage include chromosomal abnormalities, single gene defects and polygenic multifactorial conditions. (8) Snijders et al. estimated the prevalence of a range of chromosomal abnormalities at different gestations in relation to trisomy 21 in live births. For each chromosomal abnormality the authors were able to calculate the rate of intra-uterine lethality. For example, in trisomy 21, the rate of intra-uterine lethality between 12 and 14 weeks is 41% and between 16 and 40 weeks is 32%. The more severe the chromosomal abnormality, the earlier in gestation that lethality will occur. Other abnormalities such as non-immune hydrops, neural tube defects and cardiac defects are associated with second trimester miscarriage.

Chromosome analysis was performed on 1,543 specimens of first trimester miscarriage received between 1982 and 1994. (9) Comparisons with earlier studies show that some findings are absolutely consistent between different years and populations, but some major differences are also found. The results are considered in the light of several recent genetic, environmental and physiological studies. Trisomy 16, and probably trisomy 22, is entirely dependent on maternal age; other trisomies show both maternal age and other environmental or genetic effects. Monosomy X and mosaic aneuploidy arise postzygotically by chromosome loss, a normal control mechanism. Some trisomy, dipaternal triploidy and tetraploidy probably occur because of pre- or postovulatory 'overripeness'; either due to transient or chronic maternal conditions or delayed fertilization. Unbalanced structural abnormalities, most apparently of de novo origin, are markedly increased compared to earlier studies and are possibly due to paternal environmental exposures. It is concluded that when considering histories of abortion, studies of the
chromosomes of the aborted products are much more informative and cost-effective than studies of parental bloods. Where available, studies of products should be undertaken for preference, but only by experienced and committed laboratories.

**Serum factors:**

The effect of serum from patients with threatened abortion on in vitro development of two-cell mouse embryos was evaluated. Embryos were cultured for 72 hours in 7.5% serum supplement from patients with threatened abortion and from women with normal pregnancies and in Ham's F-10 medium with no serum supplement. Significantly fewer embryos developed to the blastocyst stage at 72 hours in the threatened abortion group as compared with the normal pregnancy group and Ham's F-10 (P < .001). These results suggest the presence of serum factors that are toxic to early embryonic development and thus may play a role in the pathogenesis of threatened abortion.

**Endocrine abnormalities:**

The role of producing progesterone in early pregnancy is handled by the corpus luteum in response to stimulation by human chorionic gonadotropin (hCG) and is then taken over by the placenta by the end of the first trimester. A defect in corpus luteum function results in decreased progesterone production and a higher likelihood of spontaneous abortion. Consequently, there has been much interest in the use of hCG to treat women with recurrent abortion but the results to date have been conflicting. The data from a randomized, placebo-controlled trial showed that hCG treatment was efficacious only in women with oligomenorrhea.
The trend of inhibin and relaxin concentrations closely parallels rises in progesterone during early pregnancy. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are suppressed very early in pregnancy. The suppression of LH and FSH in hyperstimulated cycles is more governed by E2 than inhibin in stimulated cycles. Some subjects destined to miscarry exhibit abnormal endocrine changes very early in the luteal phase.

The adverse effect of a high prepregnancy LH concentration on fertility and outcome of pregnancy was seen in primigravidae, women with previously successful pregnancies, and women with a history of recurrent miscarriage. These data indicate an important role for hypersecretion of LH before conception in miscarriage. This finding offers the possibility of a simple predictive test for women before pregnancy, and could also be used to identify patients with an endocrine abnormality that can be remedied.

Lejeune B et al, found that elevated antithyroperoxidase (TPO-Ab) and antithyroglobulin (TG-Ab) antibody titres are associated with an increased miscarriage rate. Also, asymptomatic thyroid abnormalities, mainly abnormal echo-structure but not antithyroid antibodies, are associated with pregnancy induced hypertension. He concluded that the presence of thyroid auto-antibodies during pregnancy constitutes a marker of increased risk of miscarriage and poor obstetric prognosis. However, Harger JH et al, found that thyroid function profiles provided no significant information in the evaluation in these couples.
Corpus luteum insufficiency:

So far the question as to whether deficient luteal steroidogenesis is the cause or the result of an abnormal pregnancy remains unanswered. The classic hypothesis put forth by diZerga and Hodgen states that corpus luteum insufficiency is a result of aberrant folliculogenesis. Therefore, the gestational corpus luteum is unable to respond adequately to the hCG signal from the implanting pregnancy. Ottobre and Stouffer also imply that gestational corpus luteum insufficiency can result from a delay in initiation of hCG rescue. Using their Macaque primate model the authors were able to experimentally induce luteal insufficiency by delaying hCG rescue by 4 days beyond the normal postovulatory day 7. This opens up the possibility that a delay in implantation outside a narrow range of no more than 4 days could be a cause of deficient luteal progesterone production in pregnancy. Interestingly, transperitoneal and transuterine embryo migration have been cited as possible explanations for the occurrence of ectopic pregnancies located in the tube contralateral to the corpus luteum. It is attractive to postulate that the extended course of embryo migration in such cases could cause a delay in implantation and corpus luteum rescue and thus explain the low progesterone levels frequently seen in ectopic pregnancy. Indeed, to validate this hypothesis in future studies, one would need to determine, prospectively, the day of implantation and correlate its timing with steroid production in the ensuing gestational corpus luteum. It is also interesting to note that based on data compiled from the embryological collection of the Carnegie Institution, Iffy inferred that the majority of pathological intrauterine, as well as extrauterine, pregnancies exhibited evidence supporting a delay in the timing of implantation.
**Infections:**

Colonization of the lower genital tract with a variety of organisms has been associated with pre-term delivery and pre-term premature rupture of the membranes. \(^{(8)}\) The risk of pre-term delivery is increased in women with *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Trichomonas vaginalis* and bacterial vaginosis. It is proposed that ascending infection stimulates a local inflammatory response which may in turn trigger a cascade of changes leading to cervical change and uterine contractions.

Grnroos MHonkonen *et al*, found no clear association between *Chlamydia trachomatis* (CT) and abortion, but an association between herpes simplex virus (HSV) and abortion is possible. \(^{(17)}\) The incidence of raised levels of both CT and HSV IgA antibodies in the cervix was surprisingly high in both groups and the significance of this finding remains to be investigated.

In a prospective study, Hay *et al*. screened 783 women at low risk for pre-term delivery and found that the presence of bacterial vaginosis in early pregnancy was associated with second trimester miscarriage and pre-term delivery. \(^{(18)}\) Hauth *et al*. screened a group of 624 women at high risk of pre-term delivery for bacterial vaginosis at a mean gestation of 22.9 weeks. \(^{(19)}\) The authors randomized patients to treatment with metronidazole and erythromycin or placebo. The authors found that treatment with erythromycin and metronidazole reduced the rate of pre-term delivery in women with bacterial vaginosis. These findings were confirmed by Morales *et al*. \(^{(20)}\) A similar study of screening at an earlier gestation performed on women with a history of previous second
trimester miscarriage would provide important information on the value of antibiotic treatment in this group.

**Incompetent cervix:**

Cervical incompetence (cervical weakness) classically presents as painless dilatation of the cervix resulting in the rupture of the membranes and second trimester miscarriage or early pre-term delivery. \(^{(21)}\) Gaillard *et al.* suggested that cervical incompetence was a factor in 10% of second trimester miscarriages.

Cervical incompetence has been considered an all-or-nothing phenomenon. \(^{(22)}\) It has been shown that the length of the cervix is inversely related to the risk of pre-term delivery throughout the range of lengths supporting the concept of a spectrum of cervical competence.
Pregnancy outcome:

Hertz JB et al, collected a group of 93 pregnancies complicated by threatened abortion and carefully monitored them throughout pregnancy, during birth and in the perinatal period, and any deviation from a completely uneventful course was registered. (23) Comparison was made with a selected group of 282 non-risk pregnant women. A significant association was found between threatened abortion and the overall number of complications in the second half of pregnancy requiring medical intervention and/or admission to hospital, impending pre-term birth requiring betamimetics, pre-term birth, retention of the placenta, birth weight below 2000 g, light-for-dates infants in case of pre-term birth or birth weight below 2000 g, and hyperbilirubinemia in infants with birth weight below 2000 g. The incidences of perinatal mortality and congenital malformations did not differ significantly from those of the control group. Pregnancies complicated by threatened abortion constitute a risk group requiring careful obstetric and perinatal supervision and follow-up.

Miscarriage:

Bleeding occurred in one fifth of recognised pregnancies before the 20th week and over half of these miscarried. (24) However, the rate of miscarriage is influenced to a greater extent by the detection of a positive foetal heart activity. Everett CB et al, concluded that, If fetal heart movement is detected at the initial scan, approximately 19 out of every 20 viable pregnancies (those in which the fetus appears normal) will not miscarry before the 20th week. (25) Using ultrasound in general practice it was possible to identify promptly those women with bleeding whose fetus was alive. Where fetal heart movement was detected, there was a good
prognosis and thus women could be given strong reassurance. Maruo et al, found a possible role of thyroid hormones in maintaining early pregnancy, and suggest that maternal serum level of thyroid hormone may be one of the endocrine factors responsible for the outcome of threatened abortion. To evaluate a possible role of thyroid hormones in maintaining early pregnancy, serum levels of thyroid hormones, TSH and thyroxine-binding globulin (TBG) in 32 patients with a clinical diagnosis of threatened abortion were compared between two groups of patients with favorable and unfavorable pregnancy outcome. Serum levels of T4, T3, free T4 and free T3 levels determined at the onset of clinical signs of threatened abortion were found to be significantly lower in patients (N = 11) who subsequently aborted compared to patients (N = 21) who did not. Serum TSH levels did not differ between the two groups. Serum TBG levels in the patients who subsequently aborted were lower compared to patients with favorable pregnancy outcome. Furthermore, serum levels of T4 and T3 at the onset of threatened abortion in patients who subsequently did not abort were significantly higher compared to levels before pregnancy, whereas little increase in serum T4 and T3 levels relative to the pregnant levels was observed at the onset of clinical signs in the patients who subsequently aborted.

**Preterm labour:**

Williams MA et al, assessed the association between first-trimester vaginal bleeding and singleton infant outcomes in a hospital-based population of 11,444 non-diabetic women, he found that shortened gestation occurred more often in women reporting first-trimester bleeding than in those who never bled. These relationships remained statistically significant after adjusting for confounding factors. Women who
experienced vaginal bleeding limited to the first trimester (N = 1174) had double the risk of delivering a preterm infant compared with those experiencing no bleeding (adjusted risk ratio = 2.0; 95% confidence interval 1.6-2.5). Current pregnancy symptoms, including vaginal bleeding, symptomatic contractions within 2 weeks, and acute or chronic lung disease were variably associated with spontaneous preterm delivery in nulliparous and multiparous women. The association between early pregnancy vaginal bleeding and preterm delivery is also confirmed by Meis PJ et al(29).

**Foetal growth:**

Das AG et al, conducted a study to find out the effect of threatened abortion in the current pregnancy on the subsequent perinatal outcome and follow the growth pattern of the fetuses of such complicated pregnancies. The study group consisted of 55 women with threatened abortion and 55 women with normal pregnancies formed the control group. Most of the patients presented at 6-12 weeks' gestation. The fetal growth was monitored by both clinical as well as ultrasound (USG) parameters. The mean growth rates were almost identical throughout gestation. The mean values of each parameter of the study group were found lying with 95% confidence limit values of their control group. In contrast to this, Williams MA et al, found that LBW occurred more often in women reporting first-trimester bleeding than in those who never bled. Bleeding limited to the first trimester was associated with a 1.6-fold risk of delivery of a term LBW infant (95% confidence interval 1.3-2.0). In a population based study, Mulik V et al, found that the incidence of low and very low birth weight deliveries, although significantly higher compared with the control population, was not affected independently by
this early pregnancy complication on logistic regression (OR 1.3, 0.8 - 1.9). (3)

**Antepartum haemorrhage:**

Threatened miscarriage was associated independently with an increased incidence of abruption (OR 2.8, 2.0 - 3.7), unexplained antepartum haemorrhage (APH) (OR 2.3, 1.1 - 5.1). (3) All forms of APH were significantly higher in term deliveries complicated by threatened miscarriage.

**Foetomaternal hemorrhage:**

Von Stein GA *et al* compared the incidence of Foetomaternal hemorrhage between patients with threatened abortion and a control population of similar gestational age. (31) The amount of Foetomaternal hemorrhage was evaluated using the Kleihauer-Betke acid elution assay. A positive result in his laboratory, as determined by a nonpregnant control group, was a value of 0.07% or more fetal cells. Using this criterion, 11% of the study population had a positive Kleihauer-Betke test, compared with 4% in the pregnant control group. Anti-(D) immunoglobulin may be indicated in Rho(D)-negative patients who present with threatened abortion.

**Perinatal morbidity and mortality:**

The early neonatal mortality rates were significantly higher in the threatened miscarriage group, which on logistic regression was due independently to preterm delivery, placental abruption and low birth weight deliveries. (3)
Outcome prediction in threatened miscarriage:

**CA-125**

CA-125 may serve as an accurate predictor of the outcome in early pregnancies with demonstrable fetal heartbeat, which are complicated by bleeding. In the five patients who eventually aborted, the values of CA-125 were > 125 U/mL, whereas none of the successful pregnancies had a value > 93 U/mL. (32) The mean values were 133 +/- 4.85 versus 36.95 +/- 23.1 U/mL for miscarriages and successful pregnancies, respectively. In normal pregnancies the respective value was 32.3 +/- 4.3 U/mL. No statistically significant difference was observed with respect to the duration of vaginal bleeding between the aborters and the patients with a favorable outcome. Nevertheless, when vaginal bleeding had been present for 3 days or more and there was high maternal serum CA125 activity, the abortion risk was found to be 100%. These findings suggest that the maternal serum CA125 measurement in threatened abortion can be useful to determine the extent of decidual destruction which is directly related to the outcome of pregnancy.

**Pregnancy-associated plasma protein A (PAPP-A):**

Depressed pregnancy-associated plasma protein A (PAPP-A) concentrations have been found in patients with threatened abortion, often weeks before spontaneous abortion while the fetus was still alive. (33) In order to extend these findings Ruge S et al, developed a highly sensitive PAPP-A radio-immunoassay and have established a reference range in early pregnancy for PAPP-A between week 7 and week 20 of pregnancy,
the serum values of PAPP-A were significantly lower (p = 0.002) in the group of women with vaginal bleeding than in the group of normally pregnant women. However, with regard to abortion later on, the predictive value of an abnormal blood test on admission was only 18.7%. Serial determinations showed increased PAPP-A values corresponding to the centile expected in women who aborted, as well as in women who gave birth. Consequently, the test is of no clinical value in the assessment of the prognosis in patients with symptoms of threatened abortion.

**Immunoglobulins IgG, IgA and IgM:**

Mean values of IgG, IgA and IgM of serum and uterine blood were significantly higher in women with spontaneous abortion than in women with delivery. Prognosis of threatened abortion is more unfavourable, if concentrations of immunoglobulins in serum and especially in uterine blood increase.

Hertz JB, Schultz & Larsen P estimated the predictive value of HPL, SP1 and AFP in serum of women admitted to hospital because of vaginal bleeding in the 6th to 19th gestational week. The prediction of abortion based on the initial analysis from the day of admission was found to be 91.7%, 75.9% and 81.8% for HPL, SP1 and AFP, respectively. The corresponding values for prediction of successful outcome were 68.7%, 73.6% and 65.4%. The HPL and AFP determinations were, however, found to be valid only after the 9th and 12th gestational week, respectively. A highly significant positive correlation (r = 0.84, P less than 0.001) was demonstrated between HPL
and SP1 suggesting that SP1 measurements might replace HPL in the evaluation of the prognosis in threatened abortion.

**Diagnosis:**

Bleeding in the first trimester can originate from the uterus, cervix, or vagina, or it can be extragenital. (1) Thorough physical examination is essential to differentiate between genital and extragenital causes. Extragenital causes should be ruled out by speculum examination. Bimanual examination of the uterus will determine whether the uterine size is consistent with the clinical dating. A large uterus may indicate hydatidiform mole, whereas a small uterus suggest a blighted ovum. The presence of a tender adnexal mass suggests an ectopic pregnancy.

**Sonographic evaluation:**

Sonography can usually differentiate between an intrauterine pregnancy (viable or non-viable), a molar pregnancy, or an inevitable abortion. (2) 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. 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%. Fetal heart activity should be visible with transvaginal sonography once the fetal pole is at least 5 mm long. Most prospective series report a loss rate of 3.4-5.5% if bleeding occurs after fetal heart activity starts, and identification of fetal heart activity by ultrasound in primary healthcare settings carries a 97% likelihood for the pregnancy continuing beyond 20 weeks. However, this favourable effect
has not been universally repeated, as miscarriage rates of 20-30% have been reported. [http://bmj.bmjjourrnals.com/cgi/content/full/329/7458/152 - FIG1]

Fetal bradycardia and discrepancy between gestational age and crown to rump length are adverse prognostic factors. 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.

The prognostic value of a subchorionic haematoma in ultrasound has been disputed. (2) Although a large separation has been associated with about a threefold increase of risk of miscarriage (19% v 71%) in women with bleeding, the presence or the size of haematoma did not affect miscarriage rate (10% v 11%) in another prospective series, and other studies reported similar findings. 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. However, the presence of a haematoma did not influence the risk for subsequent complications in a smaller study of symptomatic women.

**Management:**

Because most physicians consider any bleeding in early pregnancy to be a sign of threatened abortion, any treatment of so-called threatened abortion has a considerable likelihood of success. (4) Most women who actually are threatening to abort progress normally no matter what is done. If, however, bleeding is attributable to one of the unrelated causes mentioned above, it is likely to disappear, regardless of treatment.
**Insitu IUCD:**

If an intrauterine device is still present and the “string” is visible, the device should be removed for reasons cited in. \(^{(4)}\)

**Bed rest:**

Bed rest is used in nearly 20% of all pregnancies to prevent or treat a wide variety of conditions, including spontaneous abortion, preterm labor, fetal growth retardation, edema, chronic hypertension, and preeclampsia. There is little evidence of effectiveness. \(^{(36)}\)

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. \(^{(37)}\) Only one randomised controlled trial considers the impact of bed rest on the course of threatened miscarriage. \(^{(38)}\) 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). 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). 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, thus providing emotional relief.

Progestogen therapy:

Two recently published meta-analyses of controlled trials of a wide variety of progestational agents, used in pregnancy (Daya 1989; Goldstein et al. 1989), prompted this third meta-analysis of placebo-controlled trials involving the prophylactic use of a single agent, 17 alpha-hydroxyprogesterone caproate. Of seven relevant published reports of controlled trials, six had involved women considered to be a high risk of miscarriage or preterm birth. This analysis provides no support for the view that 17 alpha-hydroxyprogesterone caproate protects against miscarriage, but suggests that it does reduce the occurrence of preterm birth. The latter effect was reflected in a reduced rate of low birthweight babies, but not in a statistically significant reduction in perinatal mortality and morbidity. The difference between this meta-analysis and the two earlier meta-analyses illustrates the problems both of selective sub-grouping and of comprehensive pooling of data from small trials.
The continued use of progestational agents in attempts to achieve a normal outcome of pregnancy in women with a 'high-risk' pregnancy (previous miscarriage, stillbirth or present preterm labour) prompted this meta-analysis of randomized control trials of such therapy.\(^{(42)}\) Of 20 trials of a progestogen 15 had combinable data. Combined comparisons, using odds ratios with confidence intervals, were made of the rates of livebirths at term or preterm and the sum of term and preterm deliveries, miscarriages, stillbirths and neonatal deaths. All but one comparison failed to show a significant benefit.

Progesterone is prescribed in 13-40% of women with threatened miscarriage, according to published series.\(^{(3)}\) Progesterone is the main product of the corpus luteum, and giving progestogen is expected to support a potentially deficient corpus luteum gravidarum 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 settings however, it did not provide a separate analysis for progesterone in threatened miscarriage. Four published papers in the meta-analysis were assessing this relationship, one of them including three different regimens of progestogen, 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. 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.

**Buphenine hydrochloride:**

Buphenine hydrochloride a vasodilator and muscle relaxant as well was used by Soltan MH in a placebo controlled study, in women with threatened miscarriage.\(^{(43)}\) Pregnancy continuation was 90.6% in the Buphenine group and 62.3% in the placebo group. He concluded that Buphenine hydrochloride was better than placebo

**Rh prophylaxis:**

Dayton VD *et al*, described a patient whose history suggests development of an anti-D antibody after first-trimester bleeding.\(^{(44)}\) To his knowledge, that was the first such case reported in the English literature. Women who are D negative with a threatened abortion probably should receive anti-D immunoglobulin. Von Stein and associates (1992) reported that more than 10 percent of their patients had significant fetomaternal hemorrhage.\(^{(4)}\)
Objectives:

This study was conducted to address the effects of bleeding in early pregnancy regarding the followings:

1. The association between bleeding in early pregnancy and risk of preterm labour.
2. The association between bleeding in early pregnancy and risk of intrauterine growth restriction (IUGR).
3. The effects of bleeding in early pregnancy on the perinatal morbidity and mortality.
4. The association between bleeding in early pregnancy and bleeding in 3rd trimester (APH).
Patients and Methods:

This is a hospital based prospective cohort study conducted on patients with bleeding in early pregnancy (1st and 2nd trimesters) in Khartoum teaching hospital (KTH) and Soba University hospital (SUH). In the period from June 2003 to June 2004.

Study area:

This study was carried out in KTH and SUH. KTH is the biggest governmental hospital that belongs to ministry of health. It serves a large area including KRT state and wide area surrounding it. It accepts booked, referred and casualty patients. It consists of six units shared by ministry of health (3 units) and faculty of medicine, university of KRT (3 units). Each unit is covered by a senior consultant and two specialist, registrars and house officers working 24 hours.

SUH is one of the specialized hospital in Sudan which belongs to university of KT, it serves Khartoum and Gesira states, it is the only hospital which has a specialized foetal unit and received high risk patients from all over Sudan.

Study population:-

The study population includes 103 cases with bleeding in early pregnancy attending KTH casualty and SUH referred clinic and labour room, and 205 control patients. Every case was matched with two controls of same age group and parity.

The cases and controls were followed up regularly in antenatal clinics and in the wards wherever a complication occurred. All patients were followed during labour and early postnatal period till time of discharge in collaboration with the neonatologist.
Inclusion criteria:

1. Patient should be pregnant < 24 weeks at time of presentation.
2. The viability of the baby at the time of presentation should be confirmed.
3. Singleton pregnancies were included.

Exclusion criteria:

1. Patients with missed abortion, multiple pregnancy and molar pregnancy (Partial mole) were excluded.
2. Patient with Inevitable and complete abortion were also excluded.

Data collection:

Data were collected by questionnaire at the time of presentation which was filled by resident registrar in casualty and labour room after checking that the patients were fulfilling the inclusion and exclusion criteria.

Data analysis

Information were entered in computer system for analysis using SPSS software.
The Results

103 patients with bleeding in early pregnancy (1\textsuperscript{st}, 2\textsuperscript{nd} trimesters) attended to SUH, were enrolled in the study after fulfilling the inclusion and exclusion criteria.

These cases were followed throughout pregnancy and labour and delivery and early postnatal period. These patients were compared with 205 controls with same parity and age. Of these 103 patient with bleeding in early pregnancy, 17 cases (16.5\%) had bleeding in early in 1\textsuperscript{st} trimester and the rest (86 cases (63.5\%) had their first episode of bleeding in 2\textsuperscript{nd} trimester Fig(7). The majority of patients had one episode of vaginal bleeding (72.8\%) in comparison to (18.4\%) which had two episodes and (7.8\%) which has three or more episodes.

37 patients of cases (35.9\%) delivered prematurely in comparison to 16 patients in the controls (7.81\%) which delivered premature labour (P=.003) which was statistically significant in patient with bleeding in early pregnancy in comparison with the controls.

22 patients out of 75 patients with one episode of vaginal bleeding delivered prematurely (29.3\%).

Ten patients out of 19 patients with two episodes delivered prematurely (52.6\%).

Five patients out of nine with three or more episodes delivered prematurely (55.6\%) fig 8.

Out of 66 patients who reach term in patients with bleeding in early pregnancy (9\%) have birth wt < 2.5kg in comparison to (4\%) out of 189 patients who reach term in the control group.

The perinatal outcome in 90 patients (87.4\%) delivered alive and well babies in comparison to 199 (97.1\%) in control groups. The fresh stillbirth in cases were 9(8.7\%) in comparison to 2 on the control groups (1\%).
The macerated still-birth were 4(3.9%) and 4(2%) respectively in cases and control. These differences were statistically significant (P=0.001).

Regarding the risk of antepartum haemorrhage 7 out of 103 cases (6.8%) developed APH in comparison to 2 out of 205 (1%) of the control group. This difference is statistically significant (P=0.004).

Considering the risk of congenital malformations 5 patients out of 103 cases (4.9%) delivered a congenitally malformed baby in contrast to 4 patient out of 205 (2%) on the control group. This difference is not statistically significant (P=0.154).

- Concerning infertility, there were 19 cases with a history of infertility (18.4%) compared to 11 cases in the control groups (5.4%) making a significant association between a history of infertility and early pregnancy bleeding (P=0.001).

- There was no association between history of previous miscarriage and the occurrence of bleeding in early pregnancy (P=0.68).
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Table (1): Gestational age at time of delivery

<table>
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<th>Gestational age</th>
<th>Cases</th>
<th>Control</th>
<th>Total</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Term</td>
<td>66 (64.1%)</td>
<td>189 (92.2%)</td>
<td>255</td>
<td>(82.8%)</td>
</tr>
<tr>
<td>Preterm</td>
<td>37 (35.9%)</td>
<td>16 (7.8%)</td>
<td>53</td>
<td>(17.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>(103)100%</td>
<td>205 (100%)</td>
<td>308</td>
<td>(100%)</td>
</tr>
</tbody>
</table>
Table (2): Perinatal Outcome In The study Population

<table>
<thead>
<tr>
<th>Perinatal Outcome</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive &amp; well</td>
<td>90 (87.4%)</td>
<td>199 (97%)</td>
<td>289</td>
<td>93.8%</td>
</tr>
<tr>
<td>Fresh still birth</td>
<td>9 (8.7%)</td>
<td>2 (1%)</td>
<td>11</td>
<td>3.6%</td>
</tr>
<tr>
<td>Macerated still birth</td>
<td>4 (3.9%)</td>
<td>4 (2%)</td>
<td>8</td>
<td>2.6%</td>
</tr>
<tr>
<td>Total</td>
<td>103 (100%)</td>
<td>205</td>
<td>308</td>
<td>100%</td>
</tr>
<tr>
<td>Percentage</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Table (4): The Incidence Of Antepartum Haemorrhage:

<table>
<thead>
<tr>
<th>APH</th>
<th>Cases</th>
<th>Control</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>APH +</td>
<td>07 (6.8%)</td>
<td>02 (1%)</td>
<td>9</td>
<td>3%</td>
</tr>
<tr>
<td>No APH</td>
<td>96 (93.2%)</td>
<td>203 (99%)</td>
<td>299</td>
<td>97%</td>
</tr>
<tr>
<td>Total</td>
<td>103 (100%)</td>
<td>205 (100%)</td>
<td>308 (100%)</td>
<td>100%</td>
</tr>
</tbody>
</table>
### Table (5): The Incidence Of Congenital Malformations

<table>
<thead>
<tr>
<th>Congenital Malformations</th>
<th>Cases</th>
<th>Control</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformed</td>
<td>05 (4.9%)</td>
<td>02 (1%)</td>
<td>9</td>
<td>3%</td>
</tr>
<tr>
<td>Not Malformed</td>
<td>98 (95.1%)</td>
<td>201 (99%)</td>
<td>299</td>
<td>97%</td>
</tr>
<tr>
<td>Total</td>
<td>103 (100%)</td>
<td>205 (100%)</td>
<td>308</td>
<td>100%</td>
</tr>
</tbody>
</table>
Fig.1: Age distribution of the study cases

- 68.00% >34 Years
- 17.50% 19-34 Years
- 14.50% <19 Years

Legend:
- □ <19 Years
- ■ 19-34 Years
- □ □ >34 Years
Fig. 2: Distribution of the study cases according to the working state.
Fig. 3: Distribution of the study cases according to the level of education

- Illiterate: 22.30%
- Basic education: 2.90%
- Secondary education: 38.80%
- Higher education: 35.90%
Fig. 4: Distribution of the study cases according to parity.
Fig. 5: History of subfertility among the study cases

- 81.60% No history of subfertility
- 16.40% History of subfertility

Legend:
- Blue: History of subfertility
- Maroon: No history of subfertility
Fig. 6: Amount of vaginal bleeding among the study cases

- Heavy bleeding: 73.80%
- Light bleeding: 26.20%

Legend: □ Heavy bleeding  ▪ Light bleeding
Fig. 7: Distribution of the study cases according to the time of vaginal bleeding

- First trimester: 83.50%
- Second trimester bleeding: 16.50%
Fig. 8: Frequency of vaginal bleeding in the study cases

- 18.40% Once
- 7.80% Twice
- 72.80% Tries
Discussion

This cohort study was conducted to show the adverse outcomes and the effects of first and 2nd trimesters bleeding on the outcome of pregnancy which proceeds beyond the episode of bleeding.

The results showed that bleeding in early pregnancy was associated with increased risk of preterm labour and delivery over those without any episode of vaginal bleeding in the 1st and 2nd trimester (35.9% Vs 7.8%).

The risk is proportional to the number of bleeding episodes. Hertz JB et al found a significant association between threatened abortion and preterm birth (23). Williams MA et al found that shortened gestation was more often in women reporting 1st trimester bleeding than in those who never bleed (23).

The association between early pregnancy bleeding and preterm delivery was also confirmed by Meis PJ et al (29).

Lastly Everett CB et al, arrived to the same conclusion but linked the final outcome of pregnancy to the viability of the fetus at the time of the bleeding episode (24).

Regarding foetal growth, the study revealed an increased number of babies whose weight was less than 2.5 kg at term compared to those in the control groups (9% Vs 4%).

Das AG et al, found that the mean growth rates were almost identical throughout gestation in the study and control groups (30).

In contrast to this, Williams MA et al, found a significant association between first trimester bleeding and LBW (27).

Mulik V et al, also found an increased risk of LBW in association with early pregnancy bleeding (3).
Our study showed a significant association between antepartum haemorrhage in those cases of early pregnancy bleeding (6.8%Vs 1%).

Mulik V et al found an increased incidence of all forms of APH in term deliveries complicated by threatened miscarriage including unexplained APH (3).

There was a statistically significant difference in the occurrence of FSB between the cases complicated by early vaginal bleeding and those with out in our study (8.7%Vs 1%).

There was no significant difference regarding the occurrence of MSB between the cases and the control group.

Mulik v, Bethes, and Bhal K.A. found a higher rate of perinatal morbidity and mortality in cases complicated by early pregnancy bleeding and attributed that to preterm delivery, placental abruption and low birth weight (3).

In our study there was no effect of bleeding in early pregnancy on the occurrence of congenital malformation.

We found a statistically significant association between the occurrence of bleeding in early pregnancy and history of infertility (18.4% Vs 5.4%), (P=.001).

There was no link between previous miscarriage and the occurrence of bleeding in early pregnancy.

Regarding afeto-maternal haemorrhage, Van Stein GA et al found a significant feto-maternal haemorrhage in cases complicated by early vaginal bleeding compared to control groups (11%Vs +4 %) and recommended anti-D for Rh-(D) negative patient with threatened abortion.
Conclusion:

- Bleeding in early pregnancy is associated with increased risk of preterm delivery.
- Bleeding in the 1st and 2nd trimesters is associated with increased risk of intrauterine growth restriction.
- 1st and 2nd trimester bleeding is associated with increased risk of perinatal morbidity and mortality.
- Bleeding in the 1st half of pregnancy is associated with increased risk of a abruption, placenta previa and unexplained APH.
- There is no increased in congenital anomalies in babies whose mothers were affected by bleeding in the 1st half of pregnancy.
- All these risks are increased in proportion to the number of episodes of vaginal bleeding in the 1st and 2nd trimester.
**Recommendations :-**

- Pregnancy complicated by 1<sup>st</sup> and 2<sup>nd</sup> trimesters bleeding should be considered as a high risk pregnancy and managed accordingly.
- All patients with early pregnancy bleeding should be managed in a center where there are facilities for NCU to deal with the cases of prematurity and intrauterine growth restricted babies.
- Blood bank facilities should be available as there is increased risk of ante-partum haemorrhage.
- We should adopt a programme for delivering anti.D immunoglobulin to those who need it in the proper dose and time as there is a significant risk of feto-maternal haemorrhage in Rh-ve patients.
- Neonatologist supervision of new born babies should be available.
- There should be a reliable method for detection of the outcome of pregnancies complicated by early vaginal bleeding such as CA-125 – PAPP – A and immunological tests.
References


4. (Williams)

5. emedicine


26. Maruo T, Katayama K, Matuso H, Anwar M, Mochizuki M: The role of maternal thyroid hormones in maintaining early pregnancy in


34. Donat H Brüggemann J [Prognostic value of immunoglobulin determination in women with threatened abortion] transliterated:


