Management of first trimester miscarriage

This article summarizes current knowledge about first trimester miscarriages from the clinician's perspective. The epidemiology of spontaneous miscarriage, its natural course and clinical findings are discussed together with the diagnostic management and therapeutic options, which include expectant, medical and surgical management.

From a biological perspective, mankind has been quite successful in inhabiting the globe, resulting in overpopulation being one of today's major challenges. In contrast to the booming success as a species, the efficiency of human reproduction at the individual level is rather poor. Of all successfully fertilized ova, only about 30% will result in a living child. Approximately 60% do not even reach the stage of a clinically recognized pregnancy: so-called 'occult' miscarriages resulting from immediate demise or failed implantation. Another 10–15% of conceptuses are bound to miscarry after the missed period in the first trimester (Chard, 1991; Wilcox et al, 1988; Macklon et al, 2002). This article summarizes current knowledge of the epidemiology, diagnosis and treatment of first trimester miscarriages.

Epidemiology

First trimester miscarriage is a common event, experienced by about 25% of all women during their reproductive years. The vast majority of first trimester miscarriages are sporadic events, half of which are accounted for by cytogenetic abnormalities, i.e. numerical or structural chromosomal anomalies and mosaicism as demonstrated by classical techniques. With improving cytogenetic techniques, the unexplained other half might also turn out to represent hitherto unrecognized, more subtle, chromosomal anomalies.

In daily practice it is generally acknowledged that parental cytogenetic screening is unnecessary in sporadic miscarriages, and should be restricted to couples with recurrent miscarriages, a topic beyond the scope of this article.

Because the occurrence of miscarriages is a highly age-dependent phenomenon, incidence rates vary widely from 10% for women aged 20–24 years, to a staggering 90–100% for those between 45 and 50 years of age (Nybo-Andersen et al, 2000). Increased age is not only associated with an elevated risk of Down syndrome, as is generally known and acknowledged, but also predisposes to other chromosomal anomalies which explain the increased risk of (repeated) miscarriages in these women (Goddijn and Lesschot, 2000; Heffner, 2004; Franssen et al, 2006).

Dr Willem M Ankum *is Gynaecologist in the Department of Obstetrics and Gynecology (H4-205), Academic Medical Centre, University of Amsterdam, 1100 DE Amsterdam, The Netherlands*

Natural course and clinical findings

Vaginal bleeding is the first clinical symptom of impending miscarriage in the majority of cases. This symptom is by no means specific, since about 50% of these pregnancies will prove to be viable on sonographic examination, and progress without serious consequences. In these women, the exact origin of bleeding usually remains unknown. When other causes, especially cervical Chlamydial infection, cervical carcinoma or a bleeding ectropion, have been ruled out, this type of bleeding is ascribed to the process of placental invasion of the endometrium. Straightforward evidence to substantiate this origin, although plausible from a biological viewpoint, is lacking.

Sooner or later, women with first trimester miscarriages will experience uterine cramps as an accompanying symptom. During the process of expulsion which follows – i.e. the actual miscarriage or spontaneous abortion – vaginal bleeding increases and blood clots may be lost. The cervix gradually dilates to allow passage of the non-vital pregnancy. This is usually passed as a complete gestational sac, which can be distinguished easily from accompanying blood clots. If the miscarriage is complete, pain and bleeding decrease promptly to the level of a regular menstrual period (Ankum et al, 2001).

Some bleeding may persist for several weeks, and is followed by a normal period some 4–7 weeks after the actual miscarriage (Wieringa-de Waard et al, 2003).

In case of an incomplete miscarriage, where a portion of the gestational sac is retained in the uterus, persistent cramping pain and excessive bleeding indicate the need for surgical evacuation, rather than mere sonographic findings.

Knowledge about the natural course of miscarriages is important whenever expectant management is aimed for. If patients have not been informed about what will happen, they may easily be alarmed by the natural course of events and end up undergoing unnecessary surgical evacuation in the final stages of the process. Lack of awareness of these matters can lead to an unsatisfactory experience for both patient and physician.

Another problem arises when a spontaneous miscarriage simply does not happen within a reasonable period of time, a situation which occurs in about half of the cases. After 2 weeks of waiting in vain, even well-motivated women lose faith, change their minds, and tend to ask for surgical evacuation. These matters should be addressed when counselling women about treatment options.

Diagnostic management

Clinical characteristics of women presenting with first trimester bleeding are of little value in correctly predicting a miscarriage, and cannot be relied upon in daily practice (Wieringa-de Waard et al, 2002a). The only exception is the presence of an expelled gestational sac on vaginal examination. This is a highly specific finding, but because of its rarity (4%), the sensitivity is low (Buckley et al, 1999; Chung et al, 1999). There is no doubt that transvaginal sonography is the most reliable tool in the diagnosis of first trimester miscarriages at present. Sonographic equipment and expertise, therefore, are absolute prerequisites for any unit providing care for women with first trimester pregnancies and their complications.

The most constant sonographic findings indicative of a miscarriage are those of an empty gestational sac, where no yolk sac and no embryonic pole are present, or the finding of an embryo or fetus without cardiac activity. There are caveats in the interpretation of these findings, and both need further specification especially if one relies on information obtained from a single scan. First, a gestational sac can only be called empty with acceptable certainty whenever its mean diameter exceeds 15 mm. Second, the absence of fetal cardiac activity can only be diagnosed with certainty if the fetal crown–rump length exceeds 5 mm. If these criteria are not met, the pregnancy may turn out to be viable when sonography is repeated after a week (Schouwink et al, 2000).

Some authors have advocated the additional use of serum progesterone measurements in differentiating between viable and non-viable pregnancies in these cases with encouraging results (Mol et al, 1998). The usefulness of a single progesterone measurement without further sonographic evaluation, however, is limited.

Apart from sonographic observations indicative of a miscarriage or a vital pregnancy, another sonographic finding deserves attention, namely when sonography fails to show any signs of an intrauterine gestation. In the absence of a clear history of a recent spontaneous miscarriage, this finding suggests an ectopic pregnancy. Since, obviously, the absence of a gestational sac also complies with the non-pregnant state, a pregnancy test should be done immediately to rule out this possibility. Many ectopic pregnancies are easily detected by transvaginal sonography and should be looked for carefully. A gestational sac outside the uterus is a very specific finding, but some free fluid in the cul-de-sac and an ectopic mass are less reliable. The addition of serum human chorionic gonadotrophin (hCG) measurements is useful when sonography fails to identify an intrauterine gestation, or whenever no ectopic pregnancy is detected or findings are dubious, i.e. in case of a pregnancy of unknown location. In these circumstances, hCG levels >1500–2000 IU/litre, or plateauing hCG concentrations at a lower level on follow up, are indicative of ectopic pregnancy (Ankum et al, 1993a,b, 1995; Ankum, 2000; Condous et al, 2004, 2006; Elson et al, 2004). Both serum hCG and progesterone measurements may be used to monitor the expectant management of self-limiting ectopic pregnancies which resolve spontaneously in the majority of cases, without any need to perform a laparoscopy or uterine curettage for either diagnostic or therapeutic purposes.

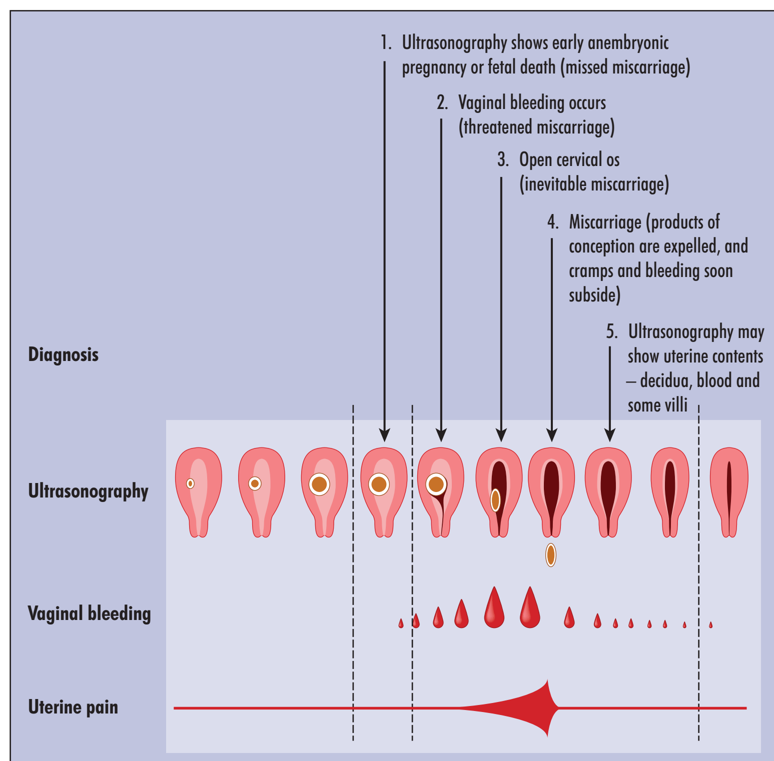

Figure 1. Natural course of miscarriage with clinical and sonographic findings. From Ankum et al (2001).

Therapeutic management

At present, three different treatment options are being used in managing first trimester miscarriages: expectant, surgical, and medical management.

Expectant management, i.e. awaiting the natural course as described earlier, represents the oldest type of managing first trimester miscarriages. Obviously, expectant management originates from a time when no other options were available, circumstances which still apply for less privileged parts of the world. During the first half of the 20th century, surgical evacuation became the preferred treatment option for managing miscarriages in many parts of the Western world. This strategy was

prompted by the high incidence of septicaemia and mortality in cases of retained products of conception. Many complicated cases resulted from criminal attempts to terminate unwanted pregnancies, rather than being complications of spontaneous miscarriages (Irving, 1985; Balagh et al, 1998).

Expectant management remained in use, albeit modestly, in some Western societies where general practitioners were routinely involved in providing obstetric care (Ambulatory Sentinel Practice Network, 1995; Ankum and van der Veen, 1995; Chipchase and James, 1997). During the last decade, expectant management of spontaneous miscarriages has seen a revival in many Western countries which earlier had abolished its use. Ironically, again terminations of pregnancies played a pivotal role in this process of change. The renewed interest in non-surgical management of miscarriages followed the promising experiences with medical termination of pregnancies by the combined administration of the anti-progestagen mifepristone and the prostaglandin misoprostol (Henshaw et al, 1993).

The available knowledge from randomized controlled trials comparing various treatment options for miscarriages has been systematically reviewed by Graziosi et al (2004a). According to this review, aspiration curettage results in the highest complete evacuation rate in comparison to non-surgical management options.

Medical management (i.e. misoprostol administered orally or vaginally) reduces the need for curettage by 81–99%, whereas expectant management reduces this need by 28–94%, depending on whether miscarriages were either incomplete or those with a still present gestational sac. The vast majority of incomplete miscarriages were managed safely without the need for additional surgical interventions. The incidence of pelvic inflammatory disease as a complication of treatment was evenly distributed among women undergoing curettage and those managed non-invasively.

In studies comparing medical with expectant management, misoprostol was more effective in reaching complete evacuation of the uterus, at the expense, however, of minor gastrointestinal side effects and increased need of analgesics. These findings were confirmed in a later article comparing expectant and medical treatment in a randomized placebo controlled trial (Bagratee et al, 2004). In that study, a regimen of daily misoprostol 600 μg administered vaginally up to two doses, had similar side effects compared to placebo.

More recently the MIST trial, a large randomized study, compared all three available options: expectant, medical (misoprostol 800 μg vaginally), and surgical management (Trinder et al, 2006). No difference was found in infection rates between the three (2–3%), nor in the need for blood transfusions (0–1%). More women undergoing expectant management (50%) than those treated medically (38%) needed a curettage. The risk of unplanned hospital admission was highest with expectant management.

Despite this, the net societal costs were lowest in the expectantly managed group at £1086 *vs* £1410 in the medical group, and £1585 in the surgery group (Petrou et al, 2006).

An interesting delayed management option has also been reported; in a randomized trial comparing the vaginal administration of misoprostol with curettage after a week of failed expectant management, the non-invasive strategy was found to be more cost-effective (Graziosi et al, 2004b, 2005).

In the absence of clinically relevant differences in safety, non-invasive treatment modalities can now be offered with confidence to women with first trimester miscarriages who wish to avoid surgery. This is important, since freedom of treatment choice improves quality of life in these women (Wieringa-de Waard et al, 2002b,c).

KEY POINTS

- Miscarriage is experienced by about 25% of women during their lifetime.
- The incidence increases with maternal age from 10% (20–24 years) to 90–100% (45–50 years).
- First trimester bleeding is indicative of a miscarriage in about half of cases.
- Transvaginal sonography is required to diagnose miscarriage with certainty by showing an empty gestational sac >15–20 mm in diameter, a persisting empty gestational sac <15 mm during sonographic follow-up or absence of cardiac activity in a fetus >5 mm.
- An empty uterus on ultrasonographic examination, i.e. absence of a gestational sac, is indicative of an ectopic pregnancy, a complete miscarriage, or the non-pregnant state, and needs further evaluation.
- Surgical management is the most effective treatment, but may be avoided if women prefer other treatment options. These have been proven to be safe.
- Expectant management takes time and results in a spontaneous complete miscarriage in about 50% of women within 2 weeks, thus avoiding the need for surgery.
- Medical therapy (i.e. misoprostol administered vaginally or orally) further reduces the need for curettage by 28–94%. Medical treatment can also be started after failed expectant management, e.g. after 1 week.
- Patients should be well informed about the course of miscarriage when non-surgical options are preferred.

Conclusions

First trimester bleeding is a common event, indicative of a miscarriage in about half of women presenting with this symptom. Careful sonographic evaluation is required to confirm the diagnosis. For women with a confirmed miscarriage, three different treatment options are now available: surgical treatment, i.e. vacuum curettage, expectant management, and medical treatment with misoprostol. The treatment choice should be individualized and can be based on patients' preferences with safety. **BJHM**

Figure 1 *is reproduced courtesy of the BMJ Publishing Group.*

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Ambulatory Sentinel Practice Network (1988) Spontaneous abortion in primary care. *J Am Board Fam Pract* **1:** 15–23
Ankum WM, Van der Veen F, Hamerlynck JVThH, Lam-mes FB (1993a) Laparoscopy; A dispensable tool in the diagno-sis of ectopic pregnancy? *Hum Reprod* **8:** 1301–6
Ankum WM, Van der Veen F, Hamerlynck JVThH, Lam-mes FB (1993b) Transvaginal sonography and human chorionic gonadotrophin measurements in suspected ectopic pregnancy; a detailed analysis of a diagnostic approach. *Hum Reprod* **8:** 1307–11
Ankum WM, van der Veen F (1995) Management of first trimester abortion. *Lancet* **345:** 1179
Ankum WM, Van der Veen F, Hamerlynck JVThH, Lam-mes FB (1995) Ectopic pregnancy: what to do when HCG levels are below the Discriminatory Zone? *J Reprod Med* **40:** 525–8
Ankum WM (2000) Editorial: Diagnosing suspected ectopic pregnancy; HCG monitoring and transvaginal ultrasound lead the way. *BMJ* **321:** 1235–6
Ankum WM, Wieringa-de Waard M, Bindels PJE (2001) Management of spontaneous miscarriage in the first trimester. *BMJ* **322:** 1343–6
Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H (2004) A randomised controlled trial comparing medical and expectant management of first trimester miscarriage. *Hum Reprod* **19:** 266–71
Balagh SA, Harris HA, Demasio K (1998) Is curettage needed in uncomplicated incomplete spontaneous abortion? *Am J Obstet Gynecol* **179:** 1279–82
Buckley RG, King KJ, Disney JD, Gorman JD, Klausen JH (1999) History and physical examination to estimate the risk of ectopic pregnancy: validation of a clinical prediction model. *Ann Emerg Med* **34:** 589–94
Chard T (1991) Frequency of implantation and early pregnancy loss in natural cycles. *Baillière's Clin Obstet Gynaecol* **5:** 179–89
Chipchase J, James D (1997) Randomised trial of expectant versus surgical management of spontaneous miscarriage. *Br J Obstet Gynaecol* **104:** 840–1
Chung TKH, Sahota DS, Lau TK, Mongelli JM, Spencer JAD, Haines CJ (1999) Threatened abortion: prediction of viability based on signs and symptoms. *Aust NZ J Obstet Gynaecol* **4:** 443–7
Condous G, Okaro E, Khalid A et al (2004) The use of a new logistic regression model for predicting the outcome of pregnancies of unknown location. *Hum Reprod* **19:** 1900–10
Condous G, Kirk E, Lu C, Van Calster B, Van Huffel S, Timmerman D, Bourne T (2006) There is no role for uterine curettage in the contemporary diagnostic workup of women with a pregnancy of unknown location. *Hum Reprod* **21:** 2706–10
Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D (2004) Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. *Ultrasound Obstet Gynaecol* **23:** 552–6
Franssen MTM, Korevaar JC, van der Veen F et al (2006) Reproductive outcome after chromosome analysis in couples with two or more miscarriages: case-control study. *BMJ* **332:** 759–63
Goddijn M, Lesschot NJ (2000) Genetic aspects of miscarriage. *Baillière's Clin Obstet Gynaecol* **14:** 855–65
Graziosi GCM, Mol BW, Ankum WM, Bruinse HW (2004a) Management of early pregnancy failure. *Int J Gynaecol Obstet* **86:** 337–46
Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW (2004b) Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomised trial. *Hum Reprod* **19:** 1894–9
Graziosi GC, van der Steeg JW, Reuwer PJ, Drogtrop A, Bruinse HW, Mol BW (2005) Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. *Hum Reprod* **20:** 1067–71
Heffner LJ (2004). Advanced maternal age – How old is too old? *N Engl J Med* **351:** 1927–9
Henshaw RC, Naji SA, Russell IT, Templeton AA (1993) Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment. *BMJ* **307:** 714–17
Irving J (1985) *The Cider House Rules*. Black Swan Books, Transworld Publ Ltd, London
Macklon NS, Geraedts JPM, Fauser BCJM (2002) Conception to ongoing pregnancy: the 'black box' of early pregnancy loss. *Hum Reprod* **8:** 333–43
Mol BWJ, Lijmer JG, Ankum WM, Van der Veen F, Bossuyt PMM (1998) The accuracy of single progesterone measurement in the diagnosis of ectopic pregnancy: a meta-analysis. *Hum Reprod* **13:** 3220–7
Nybo-Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M (2000) Maternal age and fetal loss: population based register linkage study. *BMJ* **320:** 1708–12
Petrou S, Trinder J, Brocklehurst P, Smith L (2006) Economic evaluation of alternative management methods of first-trimester miscarriage based on results from the MIST-trial. *Br J Obestet Gynaecol* **113:** 879–89
Schouwink MH, Fong BF, Mol BWJ, van der Veen F (2000) Ultrasonographic criteria for non-viability of first trimester intra-uterine pregnancy. *Early Pregnan Biol Med* **IV:** 203–13
Trinder J, Brocklehurst P, Porter R, Read M, Vyas S, Smith L (2006) Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). *BMJ* **332:** 1235–40
Wieringa-de Waard M, Bonsel GJ, Ankum WM, Vos J, Bindels PJE (2002a) Threatened miscarriage in general practice: diagnostic value of history taking and physical examination. *Br J Gen Pract* **52:** 825–9
Wieringa-de Waard M, Vos J, Bonsel GJ, Bindels PJE, Ankum WM (2002b) Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation. *Hum Reprod* **17:** 2445–50
Wieringa-de Waard M, Hartman EE, Ankum WM, Reitsma JB, Bindels PJE, Bonsel GJ (2002c) Expectant management versus surgical evacuation in first trimester miscarriage: health related quality of life in randomized and non-randomized patients. *Hum Reprod* **17:** 1638–42
Wieringa-de Waard M, Ankum WM, Bonsel GJ, Vos J, Biewenga P, Bindels PJE (2003) The natural course of spontaneous miscarriage: analysis of signs and symptoms in 188 expectantly managed women. *Br J Gen Pract* **53:** 704–8
Wilcox AJ, Weinberg CR, O'Connor JF et al (1988) Incidence of early loss of pregnancy. *N Engl J Med* **319:** 189–94