Placental haematomas in early pregnancy

A common ultrasound finding in women with threatened miscarriage is a subchorionic bleed or intrauterine haematoma. This review examines the available data on the incidence and clinical significance of these haematomas.

Women presenting with vaginal bleeding in the first trimester are commonly investigated using ultrasonography to assess the viability of the pregnancy and to exclude alternative diagnoses such as ectopic pregnancy. A frequent finding in women with bleeding in the first trimester is the presence of subchorionic bleeding or intrauterine haematoma. The incidence of intrauterine haematoma and their effect on the outcome of the pregnancy has been the subject of much debate over the last two decades and many studies examining outcome are small and uncontrolled (Pearlstone and Baxi, 1993). This review examines the available data on the incidence, associations and outcomes of pregnancies affected by intrauterine haematoma.

Incidence of intrauterine haematoma and pregnancy outcome

An intrauterine haematoma is defined as an echo-free area that lies between the membranes and the uterine wall (Mantoni and Fog Pedersen, 1981) (*Figure 1*). The advent of high resolution ultrasound, and in particular the widespread use of transvaginal ultrasound, has led to more frequent identification of haematomas during routine ultrasound examination, both in women presenting with threatened miscarriage in the first trimester and as an incidental finding. The incidence of intrauterine haematoma is uncertain as reporting the presence and description of such a finding is not part of a routine ultrasound examination in many centres. Studies examining intrauterine haematoma are often small, retrospective and uncontrolled and the incidence varies from three (Nagy et al, 2003) to 18% (Goldstein et al, 1983; Pedersen and Mantoni, 1990b), depending on the definition and inclusion criteria used (*Table 1*).

There has been much debate over the resolution and clinical significance of intrauterine haematoma on ultrasound. The incidence of miscarriage has been variably reported and ranges from 4–33% depending on the gestation at presentation (Pearlstone and Baxi, 1993). A retrospective study of intrauterine haematoma in the first trimester found that the risk of spontaneous miscarriage was significantly increased if the haematoma was diagnosed before 9 weeks (Maso et al, 2005). This is in keeping with the consistent finding that bleeding alone, with or without a haematoma, before 8 weeks results in an increased incidence of miscarriage (Bennett et al, 1996). Other studies have reported no increase in miscarriage in the presence of intrauterine haematoma (Mandruzzato et al, 1989; Stabile et al, 1989; Dickey et al, 1992; Tower and Regan, 2001; Johns et al, 2003). Early reports suggested that large haematomata (>50 ml) may be associated with a much greater risk of spontaneous miscarriage (Mantoni and Fog Pedersen, 1981; Bennett et al, 1996), but more recent reports by the same authors found no association (Pedersen and Mantoni, 1990a,b). More recent data suggest that there is no increased risk of miscarriage irrespective of the volume of the intrauterine haematoma (Kurjak et al, 1996; Tower and Regan, 2001; Sharma et al, 2003; Johns and Jauniaux, 2006).

Intrauterine haematoma have been shown to be associated with an increased incidence of adverse outcome later in pregnancy. They have been associated with abruption (Ball et al, 1996; Nagy et al, 2003), stillbirth (Sauerbrei and Pham, 1986; Ball et al, 1996), pre-eclampsia (Nagy et al, 2003) and fetal growth restriction (Nagy et al, 2003; Maso et al, 2005) but the strength of this association is still debated and the number of studies too small (Mantoni and Fog Pedersen, 1981; Baztofin et al, 1984; Pearlstone and Baxi, 1993; Kurjak et al, 1996; Tower and Regan, 2001; Nagy et al, 2003).

Intrauterine haematomas have also been associated with an increased incidence of pre-term labour and many more studies have found an association with this outcome (Sauerbrei et al, 1986; Ball et al, 1996; Nagy et al, 2003; Sharma et al, 2003). Again, many of these studies are small or retrospective, and more recent prospective, larger studies have not found an association and have suggested that the occurrence of vaginal bleeding and not the presence of the haematoma is responsible for the association with adverse pregnancy outcome (Maso et al, 2005; Johns and Jauniaux, 2006). In the larger study by Nagy et al, where threatened miscarriage was not part of the entry criteria, 71% of the cases in the intrauterine haematoma group had experienced threatened miscarriage before undergoing ultrasound examination. Several of these studies also examined the intrauterine haematoma volume and concluded that volume has no independent association with adverse pregnancy outcome (Pedersen and Mantoni, 1990b; Sharma et al, 2003; Johns and Jauniaux, 2006).

Pathophysiology of adverse

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pregnancy outcome with intrauterine haematoma

The mechanism by which intrauterine haematoma and bleeding in the first trimester can affect pregnancy outcome is uncertain. Despite the many studies linking intrauterine haematoma and threatened miscarriage with adverse pregnancy outcome, little work has been done to investigate why such a link occurs. One suggestion has been that the presence of an intrauterine haematoma results in increased production of harmful free radicals. The role of oxidative stress in the pathogenesis of pre-eclampsia has been extensively investigated and there is good evidence supporting increased levels of lipid peroxidation and reduced antioxidant activity in pre-eclampsia (Mikhail et al, 1994; Walsh and Wang, 1995; Myatt et al, 1996; Poranen et al, 1996; Hubel, 1999; Staff et al, 1999; Wang and Walsh, 2001; Zusterzeel et al, 2001) and a study using the antioxidants vitamins C and E have shown that supplementation is beneficial in the prevention of pre-eclampsia in women at risk (Chappell et al, 1999). Supplementation of these women also showed a reduction in maternal markers of oxidative stress and placental dysfunction.

Evidence for a role for increased free radical production in pre-term pre-labour rupture of membranes (PPROM) is becoming apparent (Woods, 2001; Woods et al, 2001). Epidemiological evidence for a link with rupture of the membranes is well established. Cigarette smoking, which is a potent inducer of free radicals, increases the risk of PPROM 2–4-fold compared with non-smokers (Harger et al, 1990) and maternal smoking increases the risk of spontaneous miscarriage by 33% compared with non-smoking controls (Cnattingius et al, 1985; Economides and Braithwaite, 1994; Ananth et al, 1996; Andres, 1996; Wang et al, 1997). Bleeding in the second trimester of pregnancy is also associated with PPROM (Ekwo et al, 1993). Red blood cell haemolysis results in the release of free iron, which can catalyse the generation of the highly damaging OH• radical via the Fenton reaction; potentially damaging the placental membranes and causing premature rupture. The presence of infection is a well recognized cause of PPROM and activated macrophages and neutrophils generate increased levels of superoxide free radicals such as hypochlorous acid during phagocytosis (Winterbourne and Essman, 1990). This in combination with the proteases produced by bacteria including group B streptococcus (McGregor et al, 1986) may impair membrane integrity and result in PPROM.

In-vitro evidence suggests that vitamin C is involved in several biochemical processes involved in collagen synthesis and maintenance (Chojkier et al, 1989; Tejero et al, 2003). Collagen provides strength to the placental membranes and at least five different types can be found within them (Woods, 2001). The main component of amnion is type III collagen and a reduction has been associated with PPROM (Barrett et al, 1994). Culturing amnion cells and

Table 1. Studies examining the outcome of pregnancies complicated by intrauterine haematoma

Reference	Study type	Entry criteria	N	Outcome	Comments
Mantoni and Fog Pedersen (1981)	Observational	TM	10	3 patients with IUH >50 ml miscarried or PTL	
Goldstein et al (1983)	Prospective observational	TM	10	20% loss rate	
Sauerbrei and Pham (1986)	Prospective observational	TM	30	23% PTL, 13% SB, 10% miscarriage	
Stabile et al (1989)	Prospective observational	TM	22	No increase in miscarriage	5.4% incidence of IUH
Mandruzzato et al (1989)	Unclear	TM	?	No increased incidence of miscarriage (12.9%)	11% incidence of IUH
Pedersen and Mantoni (1990a)	Prospective observational	TM	23	No increased risk of miscarriage or PTL	IUH ≥ 50 ml only
Pedersen and Mantoni (1990b)	Prospective observational	TM	62	11% miscarriage, 11% PTL (similar to those without IUH)	18% incidence of IUH No correlation between volume of IUH and outcome
Dickey et al (1992)	Retrospective	Routine US	230	No increase in miscarriage	Assisted conception
Kurjak et al (1996)	Case-control	IUH on US	59	Significantly increased risk of miscarriage (17%)	Site but not size of IUH affected outcome
Ball et al (1996)	Retrospective case-control	IUH on US	?	Increased risk of miscarriage (OR 2.8), SB (OR 4.5), abruption (OR 11.2) and PTL (OR 2.6)	1.3% incidence of IUH Bleeding alone also increases risk of miscarriage
Bennett et al (1996)	Retrospective	IUH on US	516	9.3% miscarriage (13.7% if bleeding< 8 weeks)	Large IUH – 3-fold increase in miscarriage
Tower and Regan (2001)	Prospective	IUH on US	41	No increase in miscarriage or LB rate APL antibodies more common in IUH group	Recurrent miscarriage population 12% incidence of IUH
Nagy et al (2003)	Prospective case-control	IUH on US	187	Increased incidence PIH (RR 2.1), PET (RR 4.0), abruption (RR5.6), PTL (RR 2.3), FGR (RR 2.4)	3% incidence, retroplacental IUH associated with worse outcome
Johns et al (2003)	Retrospective case-control	TM	51	IUH not associated with adverse pregnancy outcome	TM independently associated with adverse pregnancy outcome
Sharma et al (2003)	Retrospective	IUH on US	129	18.6% PTL	No correlation between volume of IUH and outcome
Maso et al (2005)	Unclear	IUH on US	182	14.3% miscarriage, 7.7% FGR, 6.6% PTL	2.4-fold increase risk of adverse outcome if IUH detected <9 weeks gestation
Johns and Jauniaux (2006)	Prospective case-control	TM	184	IUH not associated with adverse pregnancy outcome	TM independently associated with adverse pregnancy outcome

APL = antiphospholipid; FGR = fetal growth restriction; IUH = intrauterine haematoma; LB = live birth; OR = odds ratio; PIH = pregnancy-induced hypertension; PET = pre-eclampsia; PTL = pre-term labour; RR = relative risk; SB = stillbirth; TM = threatened miscarriage; US = ultrasound

amnion in hydrogen peroxide has been shown to induce apoptosis, cytokine and prostaglandin production (Kumar et al, 2004), and pre-treatment of placental membranes with vitamin C and E protects against oxidative damage in vitro (Plessinger et al, 2000). It has also been shown that women with PPROM have lower levels of vitamin C than controls, suggesting a possible preventative role for antioxidants in those at risk (Casanueva et al, 1991, 1995).

It can be seen that threatened miscarriage and intrauterine haematoma could affect pregnancy outcome in several ways. Theoretically, a large haematoma could be a threat to the continuance of the pregnancy by a direct volume pressure effect. This may well depend upon the site of the haematoma and its distance from the placental site, or the volume of the haematoma. This is not borne out by the observational evidence described above, although Nagy et al (2003) suggested that a retroplacental haematoma was associated with a worse outcome.

Subchorionic bleeding could cause a chronic inflammatory reaction in the decidua and consequent persistent myometrial activity and expulsion of the pregnancy. If the pregnancy continues, subchorionic bleeding will result in an increase in the amount of both oxygenated blood and free iron available, potentially increasing the production of reactive oxygen species with subsequent damage to the placental membranes and eventual rupture. Studies examining maternal serum placental hormones in the presence of intrauterine haematoma have found no increase in placental hormone production and no association with intrauterine haematoma volume, suggesting first that trophoblast dysfunction or failure is not the primary mechanism for the appearance of intrauterine haematoma and second that there appears to be minimal disruption to trophoblast function in the presence of intrauterine haematoma (Stabile et al, 1989; Pedersen et al, 1995; Johns et al, 2003).

There are a small number of studies suggesting an association between threatened miscarriage with intra-uterine haematoma and maternal thrombophilias. The first report of an association described five cases of intrauterine haematoma of which three had antinuclear antibodies and two had anticardiolipin antibodies (Baxi and Pearlstone, 1991) and a larger more recent study also reported an association with antiphospholipid antibodies although this was in a tertiary referral recurrent miscarriage population where the incidence of antiphospholipid antibodies is likely to be higher (Tower and Regan, 2001). Haematomas have also been associated with maternal hyperhomocysteinaemia (Khong and Hague, 1999), protein S deficiency and homozygosity for the methylene-tetrahydrofolate reductase gene (Heller et al, 2003).

Conclusions

Threatened miscarriage is the commonest complication of pregnancy, occurring in 15–20% of ongoing pregnancies (Farrell and Owen, 1996). Detection of an intrauterine haematoma may just be a coincidental finding in these cases. Recent large prospective studies examining outcomes after threatened miscarriage in women with and without intrauterine haematoma have shown no increase in adverse pregnancy outcome in those with an intrauterine haematoma, but have reported an increase in adverse outcome overall. It seems likely that the occurrence of vaginal bleeding in itself increases or is associated with an increased risk of adverse pregnancy outcome. Irrespective of this, women presenting with threatened miscarriage, whether or not they also present with intrauterine haematoma on ultrasound, may well be at increased risk of adverse pregnancy outcome and these cases may require increased antenatal surveillance. Although data are still inconclusive, knowledge of this possible increased risk may facilitate decision making when women present with symptoms and signs of either miscarriage or later pregnancy complications. **BJHM**

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Figure 1. Transvaginal ultrasound image of an intrauterine haematoma.

KEY POINTS

- The incidence of intrauterine haematoma varies from 3–18%.
- The incidence of miscarriage has been variably reported and ranges from 4–33% depending on the gestation at presentation.
- Intrauterine haematoma have been associated with an increased incidence of pre-term labour.
- Intrauterine haematoma volume has no independent association with adverse pregnancy outcome.
- Knowledge of this possible increased risk may facilitate decision making when women present with symptoms and signs of miscarriage or later pregnancy complications.