Placental pathology of recurrent spontaneous abortion: the role of histopathological examination of products of conception in routine clinical practice: a mini review

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BACKGROUND: Histopathological examination of products of conception from miscarriages is part of routine clinical practice. The extent of additional clinically relevant information provided by this investigation in the setting of recurrent spontaneous abortion remains uncertain. METHODS: Review of the literature was performed to identify studies reporting on findings of histological examination of routinely obtained products of conception in the setting of recurrent spontaneous abortion. The initial search identified 312 potential references, but 300 were excluded on further examination due to lack of data on specific histopathological findings in routine products of conception specimens from patients with recurrent spontaneous abortion. The 12 included studies indicated that such examination may identify hydatidiform moles, villous dysmorphic features suggesting fetal aneuploidy, chronic histiocytic intervillositis (CHI) and massive perivillous fibrin deposition and impaired trophoblast invasion. However, in most cases, morphological assessment cannot reliably determine the cause of the miscarriage or distinguish recurrent from sporadic miscarriage. Studies reporting on the use of additional immunohistochemical methods do not currently provide additional clinically useful diagnostic or prognostic information. CONCLUSION: Routine histological examination of products of conception in the setting of recurrent spontaneous abortion can provide important clinical information in a minority of cases.

Key words: histopathology/products of conception/recurrent spontaneous abortion/review

Introduction

Histopathological examination of products of conception is an integral and a routine component of the management of patients with early pregnancy failure (Hinshaw and Fayyad, 2000). Two important primary reasons for such an examination are to confirm the presence of an intrauterine gestation and to exclude gestational trophoblastic disease in the form of partial or complete hydatidiform mole. In addition, particularly in the clinical setting of recurrent spontaneous abortion, it is hoped, and often assumed, that further diagnostic information regarding the underlying cause of the pregnancy failure may be gained from such examination. However, although there are reports of specific placental pathological findings associated with recurrent spontaneous abortion (Fox, 1997), there has been no systematic examination of the usefulness of routine examination of products of conception in this clinical context.

The aims of this study were, first, to review previous publications that have reported on the histopathological findings of routine examination of products of conception following uterine evacuation in the clinical setting of recurrent spontaneous abortion; second, to determine whether clinically useful information can be provided by such examination and how often such information is found; and finally, to provide evidence-based directions for future investigation in this area.

Search methods

A search of multiple computerized medical literature databases [PUBMED, SCIENCE CITATION INDEX (ISI), EMBASE and COCHRANE COLLABORATION] was undertaken in November 2005 to identify all studies across all years which reported the results of routine histopathological findings in the setting of recurrent spontaneous abortion using the following search terms with no language restrictions [(miscarriage AND recurrent) AND (pathology* OR histopatholog* OR histol*) NOT placenta*[ti]]. The titles and abstracts of retrieved studies
were screened to identify those potentially fulfilling the selection criteria of clinical utility of histopathological examination of products of conception in the setting of recurrent spontaneous abortion. The full text of studies potentially suitable for inclusion was further examined, and the results from these studies were tabulated and summarized. Because of the nature of the studies and their findings, mathematical pooled analysis was not possible. Studies were broadly categorized into those reporting on routine histopathological examination [haematoxylin and eosin (H&E)-stained slides of paraffin-embedded material] and those in which additional techniques applicable to routinely collected material (such as immunohistochemical staining) had been undertaken. Studies performed using specific methodologies or sampling protocols not applicable to routine evacuated products of conception specimens handled in clinical practice were not included.

Search results

The initial search identified 312 potential references but screening of abstracts excluded 296 due to lack of data on specific histopathological findings in routine products of conception specimens from patients with recurrent spontaneous abortion. Of the remaining 16 studies, four were also excluded after examining the full text due to lack of inclusion of an appropriate recurrent spontaneous abortion study group or appropriate histopathological data on, therefore, leaving 12 studies for inclusion (Tables I and II).

Studies reporting on routine morphological examination of products of conception in recurrent spontaneous abortion demonstrate that hydatidiform moles are reliably detected, villous dysmorphic features may suggest fetal aneuploidy and rare specific conditions such as chronic histiocytic intervillositis (CHI) may be diagnosed. There is morphological evidence that impaired trophoblast invasion may be a common mechanism in first-trimester miscarriage, especially in antiphospholipid antibody (aPL)-associated loss (Figure 1), but morphological assessment alone cannot reliably distinguish recurrent from sporadic miscarriage or provide data to determine the underlying aetiology. Studies reporting on the use of additional immunohistochemical methods suggest that in some cases of recurrent spontaneous abortion, there may be abnormal patterns of decidual lymphocyte/natural killer (NK) cell infiltration, with or without alterations in HLA-G expression or immunoglobulin (Ig) deposition. However, there are currently no reliable criteria to provide clinically useful diagnostic or prognostic information using such techniques.

Discussion

This review highlights the paucity of data addressing the clinical value of routine histopathological examination of products of conception in cases of recurrent spontaneous abortion, a common and clinically significant problem. Presently available data indicate that a small subgroup of women with recurrent

### Table I. Studies reporting on the findings of routine histopathological examination of products of conception from patients with recurrent miscarriage

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van horn et al. (2004)</td>
<td>Histopathological review of tissues</td>
<td>Decidua from aPL+ and aPL-like more necrosis, inflammation and vascular thrombosis. More villous infarction, fibrin deposition, syncytiot knots and fibrosis</td>
</tr>
<tr>
<td>Seibert et al. (2002)</td>
<td>Histopathological review of tissues</td>
<td>Reduced endovascular TB invasion in aPL+. aPL– as controls. No intervillosous thromboses</td>
</tr>
<tr>
<td>Boyd and Redline (2000)</td>
<td>Histopathological review of tissues</td>
<td>CHI associated with recurrent miscarriage, recurrence risk 60–70%</td>
</tr>
<tr>
<td>Redline et al. (1999)</td>
<td>Histopathological review of tissues</td>
<td>Increased CHI, perivillous fibrin, chronic villitis and plasma cell deciduitis in chromosomally normal miscarriages. Most with known autoimmune condition no specific features</td>
</tr>
<tr>
<td>Houwert-de Jong et al. (1990)</td>
<td>Villous morphology review (Rushton classification)</td>
<td>No difference in villous features between control and RM groups</td>
</tr>
</tbody>
</table>

| aPL syndrome, antiphospholipid antibody syndrome; CHI, chronic histiocytic intervillositis; RM, recurrent miscarriage; TB, trophoblast; ToP, social termination of pregnancy. |

### Table II. Studies reporting on the findings of immunohistochemical techniques applicable to routinely collected and processed histopathological specimens of products of conception from patients with recurrent miscarriage

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Askeland et al. (2004)</td>
<td>CD83</td>
<td>No significant differences in decidual CD83+ dendritic cell density between groups</td>
</tr>
<tr>
<td>Quack et al. (2001)</td>
<td>CD56, CD25, CD3, CD68</td>
<td>Reduced decidual CD56+ NK cells and increased CD25+–activated lymphocytes in RM</td>
</tr>
<tr>
<td>Emmer et al. (2002)</td>
<td>CD56, HLA-G</td>
<td>Persistent increased CD56+ cells and reduced HLA-G expression in RM</td>
</tr>
<tr>
<td>Kwak et al. (1999)</td>
<td>CD57</td>
<td>Increased decidual CD57+ cells in RM</td>
</tr>
<tr>
<td>Lea et al. (1997)</td>
<td>TNFβ</td>
<td>Reduced TB expression of TNFβ in RM</td>
</tr>
<tr>
<td>Zhao et al. (1997)</td>
<td>IgM, IgG, C3</td>
<td>Increased C3 and IgM deposition in RM</td>
</tr>
<tr>
<td>Lea et al. (1995)</td>
<td>TGFβ2</td>
<td>Reduced TGFβ expression in RM</td>
</tr>
</tbody>
</table>

| aPL syndrome, antiphospholipid antibody syndrome; CHI, chronic histiocytic intervillositis; IgG, immunoglobulin G; IgM, immunoglobulin M; NK, natural killer; RM, recurrent miscarriage; TB, trophoblast; TGF, transforming growth factor; TNF, tumour necrosis factor; ToP, social termination of pregnancy. |

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spontaneous abortion may show evidence of CHI or massive perivillous fibrin deposition, both of which are histopathological diagnoses which may influence future reproductive management but which affect only around 1 in 200 to 1 in 2000 pregnancies, respectively (Jacques and Qureshi, 1993; Katzman and Genest, 2002), with no reliable data on their prevalence in the setting of miscarriage specifically. An additional minority will miscarry due to hydatidiform mole, which is of major clinical significance because the patient requires both surveillance for the detection of persistent gestational trophoblastic neoplasia and may also be at risk for recurrent mole in future pregnancies. Rarely, recurrent pregnancy losses may be due to familial hydatidiform mole syndrome in which there are recurrent, usually complete, hydatidiform moles of biparental rather than androgenetic origin, which is probably a consequence of dysregulation of imprinting (Fisher et al., 2004). A further subgroup, most notably those with aPL syndrome, may demonstrate abnormalities of trophoblastic invasion indicating the possible mechanism of the loss (Figure 1). However, this information may not alter further management because the aPL status is usually determined on clinical screening as part of the assessment for recurrent spontaneous abortion.

The remainder of patients, the majority, may simply have intrauterine products of conception confirmed. In these cases, the products may be further morphologically classified to suggest possible fetal aneuploidy or estimate the timing of intrauterine death using previously suggested histopathological classifications (Rushton, 1978), but both of these issues can be more reliably determined by other means, karyotyping and serial sonography, respectively. Additionally, there are practical issues that make specific interpretation of such routine histopathological samples problematic, including the limited and fragmented nature of the tissues, and the difficulty in determining which events, if any, are primary aetiological factors and are simply consequences of the pregnancy failure (Jauniaux and Burton, 2005). At present, therefore, routine histopathological examination of products of conception in patients with recurrent spontaneous abortion only rarely provides significant additional specific information in determining the cause of the recurrent loss or influencing future management.

Several studies have attempted to supplement routine morphological examination with immunohistochemical markers of infiltrating cells, usually leukocyte subpopulations; however, at present, these have no direct implications for clinical practice (Table II). In addition, further studies have used specialist research techniques not applicable to routine practice, such as the detection of auto-antibodies to adhesion molecules which may interfere with anchoring villi formation (Aplin et al., 1998), testing sera from recurrent spontaneous abortion patients in trophoblast adhesion assays (Bulla et al., 1999) and in vitro detection of persistent NK cell expression of CD56 and reduced expression of trophoblast HLA-G in recurrent spontaneous abortion (Emmer et al., 2002). However, these data are inconsistent and, until further studies have been undertaken, are unlikely to affect clinical management.

There is now a growing body of evidence, based on pathological data, that many miscarriages may be associated with impaired early trophoblastic invasion, premature intervillous space blood flow, fragmentation of the trophoblastic shell and subsequent oxidative damage (Khong et al., 1987; Michel et al., 1990; Jauniaux and Burton, 2005), although not all studies support these findings (Ball et al., 2006). However, despite these general findings, there remains poor correlation between specific histological features and the aetiology of the miscarriage (Jauniaux and Burton, 2005), and recurrent spontaneous abortion cannot be reliably distinguished from sporadic losses on this basis. Furthermore, the identification of many such pathological features requires placental bed biopsies, an additional sampling technique not used as part of routine therapeutic uterine evacuation. Although implantation site fragments may be present in routinely evacuated material and can provide some information regarding trophoblastic invasion, extrapolation of events deeper in the placental bed from superficial decidual fragments may be misleading (Sebire et al., 2002; Ball et al., 2006).

Acquired and inherited thrombophilic conditions are associated with an increased risk of recurrent pregnancy failure, including primary antiphospholipid syndrome (PAPS) and
activated protein C resistance (Rey et al., 2003; Kujovich, 2004). In pregnancies complicated by late fetal loss, intrauterine growth restriction or pre-eclampsia, in association with thrombophilia, uteroplacental vascular disease with intervillous hypoperfusion appears to be a common mechanism. Despite their apparently prothrombotic nature, in miscarriage, there appears to be little, if any, histopathological evidence that intervillous or placental thrombosis is an important mechanism (Salafia and Cowchock, 1997; Blumenfeld and Brenner, 1999; Sebire et al., 2002, 2003), and it is likely that such ‘thrombophilic’ factors may modulate the decidual environment to impair trophoblastic invasion, leading to both early loss and later obstetric complications (Sebire et al., 2003).

We have demonstrated that there is a relative paucity of data examining the role of routine histopathological examination of evacuated products of conception in recurrent spontaneous abortion. Such examination remains clinically indicated because it may allow the identification of important specific aetiological entities in a minority of cases but, for most patients, clinical management will not be influenced by the histopathological findings. We suggest that an optimized protocol should be developed for the histopathological evaluation of products of conception in recurrent spontaneous abortion based on currently available evidence, and prospective efforts should be made to use new technologies such as RT–PCR and micro-array profiling to maximize the future clinical information yield from these specimens.

References


