Letters to the Editor

The ETEP protocol for recurrent miscarriage

Dear Sir,

As a centre that has assessed and treated over 1500 women with recurrent miscarriage, we were very interested to read the protocol of the Euro-Team for Early Pregnancy (Berry et al., 1995). We would like to commend the authors on publishing guidelines which will certainly gain wide acceptance in the medical community at large. However, because this protocol was published by such a distinguished panel, we feel obliged to clarify and elaborate some of the points made.

The authors list conditions which need to be investigated in order to reach a prognosis. Some of these conditions are extremely rare, e.g. in the 1500 patients who have presented to us, we have found one patient with diabetes, one with thyrotoxicosis, and none with Wilson's disease, hyperhomocysteinaemia nor excess radiation.

In some of the other conditions which are controversial, the authors state one side of the argument and ignore the opposing view. Two examples are alloimmunity and inappropriate luteinizing hormone (LH) secretion as causes of abortion.

The alloimmune section is titled 'Lack of blocking factor and HLA sharing'. It is some years since human leukocyte antigen (HLA) sharing or blocking factors were thought to provide an explanation. Induction of appropriate cytokines or neutralization of embryotoxic factors are more likely explanations.

The numerous publications on immunopotentiation are summarized in one sentence as questionable. No mention is made that this is the only therapy which has been investigated in double-blind randomized trials. Most trials are too small for the reported benefit to reach statistical significance, and no trial has controlled for predictive features (number of previous miscarriages, previous live birth, time to conceive or maternal age). Hence the 'Recurrent Miscarriage Immunotherapy Trialsists Group' (RMITG, 1994), set up an international register of 1753 patients from double-blind randomized and non-randomized trials. They reported that when all patients with three or more abortions in the randomized trials were treated as a whole, there was a 10% benefit after immunization, requiring 10 patients to be treated to achieve one extra live birth, i.e. similar to current success rates with in-vitro fertilization (IVF). A subsequent analysis (Daya and Gunby, 1994) was performed on primary aborters who did not possess antipaternal complement-dependent antibody. The live birth rate was 43% higher after immunization; six patients needed to be treated to achieve one extra live birth. The benefit increases in patients with five or more abortions and the number of patients requiring treatment to achieve an extra live birth decreases (Carp et al., 1993; Daya and Gunby, 1994). However, ETEP ignored this important information and stated that the success rates are questionable when set against the success rates without any therapy; an argument that can be used for any therapy for recurrent miscarriage. Which success rates are the authors referring to? Recurrent miscarriage is defined as three or more abortions. The subsequent live birth rate of 55–75%, which they quote, is only true for three abortions. The authors quote Knudsen et al. (1991) that the live birth rate is only 46% after four miscarriages. We (Carp et al., 1993), have published that it is 29% in the patient with five or more miscarriages. Is the patient with 10 miscarriages to be denied treatment that many believe effective, on the basis that the young patient with three miscarriages has a relatively good prognosis in her fourth pregnancy?

ETEP quotes Stirrat (1990) as stating that the benefits do not outweigh the risks. This was Stirrat's personal opinion and was valid in 1990 when the results of large-scale studies were not available. However, RTMIG (1994) assessed the side-effects reported in the 1753 patients in their register and concluded that the side-effects appear minimal.

Another controversial area is polycystic ovary syndrome (PCOS) and inappropriate LH secretion. The authors quote papers that believe these are causes of abortion but ignore the work of Kovaks et al. (1990) which claims that women with a raised LH had a better pregnancy outcome than those with a normal LH. The work of Johnson and Pearce (1990) was cited as justification for pituitary suppression and induction of ovulation with human menopausal gonadotrophin (HMG). However, a later publication by Pearce (1991) in which he contradicts his earlier paper and recommends awaiting a spontaneous decrease in LH levels is not quoted. Even though the conclusions of both these papers are suspect, we feel that if one is mentioned, a later opposing view by the same author should also be mentioned. This is particularly relevant as no comparative trials have been carried out.

The section on anatomical causes of miscarriages also leaves many questions unanswered. The authors state that hysteroscopic surgery is the treatment of choice in properly selected cases with a uterine septum. However, they do not state who should be 'properly selected'. Jones and Jones (1953) defined the presentation of the septate uterus as 'The delivery of a live or freshly dead fetus in the second trimester after mini labour'. Do they agree with Jones (1953) criteria? Should women with a septum and two blighted ova be operated upon? Should secondary aborters (with one or more live children) be operated upon? We find a clear benefit after hysteroscopic surgery in patients with second trimester abortions, but the picture is not clear in women with first trimester abortions. In first trimester abortions, it is necessary to show a subsequent live birth rate above 55–75% (the subsequent live birth rate according to ETEP) (1995), in a large series of patients.

There are two major pitfalls in any work on recurrent miscarriage: firstly, recurrent miscarriage is not a homogeneous condition. The authors recognize this and claim that a distinction should be made between different types of patient and miscarriage. Blighted ova resulting in first trimester abortion and abortions at 20 weeks, starting with contractions, are not identical and should not be considered together. Similarly, the patient of 40 with ten miscarriages does not have the same prognosis as a...
patient of 20 with three miscarriages. However, after having drawn this distinction, the authors then consider recurrent miscarriage as a homogeneous condition, and quote a live birth rate of 55–75% without further classifying the patients into subgroups. Secondly, the author’s claim that the abortus should be karyotyped. In our series, 40% of abortuses who could be karyotyped had an anomaly. Any trial of treatment will only treat maternal factors. If the outcome of the next pregnancy is complicated by a 40% chromosomal anomaly rate, no treatment will be shown to be effective unless corrected for the chromosomal defects.

References

H.J.A. Carp and V. Toder

Departments of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, and

Department of Embryology and Teratology, University of Tel Aviv, Israel

Dear Sir,

I wish to thank Carp and Toder (1995) for their comment and the opportunity to keep the discussion about recurrent abortion alive.

Thyrotoxicosis and Wilson’s disease are mentioned in our publication as rare and extremely rare respectively. With regard to diabetes we mentioned only that there is an increased risk of spontaneous abortion in cases of poor glycaemic control in insulin-dependent diabetic women. However, we do not know of any study on 1500 patients with recurrent abortion which systematically tested for hyperhomocysteinaemia.

The debate about the efficacy of immunopotentiation therapy will continue. The studies from Carp et al. (1993) and Daya and Gunby (1994) were available but we were not aware of the results of the ‘Recurrent miscarriage immunotherapy trialsist group’ and the benefits claimed from double-blind randomized and non-randomized trials. In the review and meta-analysis by Fraser et al. (1993) on data obtained from four randomized controlled trials and 19 case-series there was a simple final conclusion: unless its efficacy can be established through other randomized controlled trials, this treatment should be abandoned.

The facts about polycystic ovary syndrome (PCOS) and luteinizing hormone (LH) hypersecretion have been reviewed, as far as we feel, with considerable reserve. In a more recent study, 56% of 500 consecutive women presenting with a history of recurrent miscarriages (Clifford et al., 1994) had an ultrasound diagnosis of PCOS. Based on early-morning urinary LH analysis, 58% of these women demonstrated hypersecretion of LH. We agree about the fact that the Johnson and Pearce papers (Johnson and Pearce, 1990; Pearce, 1991) do not provide strong evidence about the efficacy of pituitary suppression but we also used other references.

The septate uterus is a difficult area in recurrent abortion. Theoretically, it has been suggested that early abortion in a septate uterus may be due to insufficient vascularization of the septum. Late abortion may be due to cervical incompetence. A combination of early and late abortions are often encountered in patients with a septate uterus. We do not know of studies indicating which cases should be operated on and which ones should be treated conservatively. By ‘properly selected cases’ we intended to make clear that an operation should not be obligatory.

In summary, we agree with the two major pitfalls. A third one could be: as abortion is time-related, treatment started during the next pregnancy is more effective when started late and 100% effective when started at the end of the abortion period.

References