



Figure 2 Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of embryo transfer on the live birth rate in women undergoing IVF when sham acupuncture technique was used in the control groups.

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Influence of activating and inhibitory killer immunoglobulin-like receptors on predisposition to recurrent miscarriages

Sir,

We read with interest the paper from Faridi *et al.* (2009) 'Influence of activating and inhibitory killer immunoglobulin-like receptors on predisposition to recurrent miscarriages' published recently in *Human Reproduction*.

This is one of many recent papers on this topic which have presented frustratingly conflicting results and conclusions. There have been reports of a lack of association of recurrent miscarriage with maternal KIR repertoire (Witt *et al.*, 2004), a lack of inhibitory receptors (Varla-Leftheriota, 2005), a lack of activating receptors (Hiby *et al.*, 2008; Hong *et al.*, 2008) or related to an increase in the frequency of activating KIR (Wang *et al.*, 2007).

Of concern is the disparity in the findings in these studies with no consensus and increasing confusion. The reasons for this are likely to be as follows.

- (i) The studies all have small numbers of patients that have used different selection criteria. To determine any influence of the highly polymorphic KIR genes in a heterogenous condition

such as recurrent miscarriage, it is essential to strictly define the affected group. Only women with three or more first trimester miscarriages and no live births should be included. Investigations ruling out other possible causes should be undertaken (e.g. anti-phospholipid antibodies, thyroid disease, uterine anomalies etc.).

- (ii) The controls should be matched with regard to age and ethnicity and should all have had a normal first pregnancy with no history of preeclampsia or fetal growth restriction.
- (iii) There are large numbers of KIR haplotypes that differ in both gene content and allelic polymorphism at individual KIR loci. These have been categorized as KIR A or KIR B haplotypes based on the presence/absence of particular KIR genes, and it is essential that they are defined in the same way. A current working definition provided by the IPD KIR database being as follows; Group B haplotypes are characterized by one or more of the following genes: KIR2DL2, KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5 and KIR3DS1. Conversely, Group A haplotypes are characterized by the absence of all these genes. The distinction between Group A and B haplotypes is a useful one, having potential biological and medical significance.
- (iv) Studies of populations worldwide have established that KIR gene frequencies and KIR genotype occurrence vary markedly among different ethnic groups (Middleton *et al.*, 2008; Single *et al.*, 2008).

In view of the above considerations, there are several possible explanations for why this paper on recurrent miscarriage has conflicting findings. The patients and controls were carefully selected on the basis of their clinical characteristics but consisted of four different caste groups divided into 12 different populations. It is known that the KIR gene frequencies differ quite considerably in some of these groups, and this may have skewed their findings (Rajalingam *et al.*, 2002; Kulkarni *et al.*, 2008). Even though the authors have tried to match numerically the controls and affected women as closely as possible with such small numbers, bias is still likely to be introduced.

There is also some concern because the KIR gene frequencies in the controls are very different from those previously published in a North Indian population (Rajalingam *et al.*, 2002). This latter study was performed by an experienced KIR reference lab giving additional confidence in their findings.

Genotyping for the very similar KIR genes, often employing a PCR–SSP method (as used in the Faridi *et al.* study), is not trivial. We suggest that in future each group should check their KIR typing in reference to controls provided by designated KIR reference laboratories. The UCLA International KIR Exchange Program (ClientServiceUIC@mednet.ucla.edu) now used by some 60 typing laboratories worldwide provides such a source of DNA to help confirm the accuracy and reliability of the KIR typing method employed. Otherwise, experienced typing groups can be approached individually to check typing schemes through the exchange of DNA samples.

We suggest that in future vigorous verification of such anonymized samples is performed on studies such as these, so clarification and not confusion about the role of KIR in recurrent miscarriage is possible.

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