fact be addressing the same question as our study. Furthermore, such longitudinal studies would also be complicated by the effect of the ‘dependent variables’ they discuss.

Two small studies have presented such longitudinal data. Crittenden et al. (1992) demonstrated no difference in semen parameters in five men followed after AZT administration, and Robbins et al. (2001) demonstrated an increase in sperm motility in men with early disease (CD4 > 200), and an increase in normal morphology in men with late disease with antiretroviral treatment (n = 26). These benefits are likely to be as a consequence of improved health status with treatment (supported by the increase in CD4 and decrease in viral load seen), but Robbins et al. (2001) also demonstrated no change in lymphocyte genetic endpoints or sperm aneuploidy rates with treatment, which supports the findings of most studies of no detrimental effect on semen of antiretroviral treatment (Politch et al., 1994; Lasheeb et al., 1997; Nicopoullos et al., 2004).

Although some reports do indeed use an average of available semen analysis, there is no clear consensus with other reports assessing the impact of HIV on semen parameters also using a single analysis. However, reanalysis of our data using the method suggested by van Leeuwen et al. does not alter our conclusions, with significant impairments in semen volume (P = 0.02), concentration (P = 0.003), total count, total motility, progressive motility and morphology (all \( P < 0.0001 \)) still demonstrated in the HIV positive group.

The first aim of our paper was to present data from the largest group of HIV positive men seeking fertility treatment in the UK to add to the limited data on the effect of HIV on semen. In our opinion, there is a clear consensus amongst the published data of a detrimental effect of HIV on semen parameters in a number of studies that have used a number of different control groups as we have described (Nicopoullos et al., 2004).

The second aim was to present the first data on the outcome and predictors of outcome of sperm washing/intratubular insemination (IUI). This also enabled us to use IUI groups for comparison. Although the difference in total count was diluted by the minimum criteria acceptable for IUI, differences in motility and morphology persist.

Our choice of thresholds for CD4 count and HIV-RNA viral load for analysis of outcome were made clinically, e.g. CD4 count dichotomization was based on CDC (Centres for Disease Control) classification of HIV/AIDS. As the numbers of HIV positive men seeking fertility treatment continues to expand, we will go on to report the outcome from a significantly larger number of cycles, and as suggested aim to confirm our current findings on the predictive capacity of these individual variables on the outcome of IVF and ICSI, as well as IUI using a multivariable approach.

In conclusion, we remain of the opinion that our data confirms the deleterious effect of HIV on semen parameters whilst accepting that there remain difficulties in study design as we have discussed. Similarly, we believe that the outcome of fertility treatment of HIV positive men may be significantly improved when undertaken whilst HIV RNA viral load is undetectable.

References

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Recurrent miscarriage and embryonic loss

Sir,

I read with interest the publication by Morikawa et al. (2004) concluding that women with a history of recurrent miscarriages are more likely to have an embryonic loss rather than a fetal loss when compared to control patients without such a history who subsequently abort. In their discussion they imply that since this difference in loss pattern occurs especially in the recurrent miscarriage group where chromosomome analysis of the fetal products of the last miscarriage was normal, there may be some condition that may be reme
dial so that early institution of some treatment may prevent a subsequent miscarriage. As an example they refer to a previous publication from their group showing the benefits of high-dose immunoglobulin therapy (Morikawa et al., 2001).

There are data suggesting that the production of an immunomodulatory protein expressed by \( \gamma/\delta \) T cells can inhibit natural killer cell cytolytic activity and cause a shift from TH1 to TH2 cytokines (Szekeres-Bartho et al. 1989a, 1996). The production of this immunomodulatory protein requires the \( de novo \) induction of progesterone receptors in the gamma/delta T cells by an allogenic stimulus and requires
the interaction of a high concentration of progesterone with these receptors (Szekeres-Bartho et al., 1989b). The protein has been termed the progesterone induced blocking factor (PIBF) (Szekeres-Bartho et al., 1985).

Low levels of PIBF expression have been found in pathological pregnancies compared to healthy normal pregnancies (Szekeres-Bartho et al., 1995). We found, however, that in progesterone-treated women there was no difference in PIBF expression in those who abort versus non-aborters (Check et al., 1997a). The possibility exists therefore that women with recurrent miscarriage may have a need for a greater amount of progesterone to stimulate sufficient PIBF to suppress immune rejection. Progesterone therapy has been demonstrated to reduce the frequency of miscarriage (Check et al., 1987). Possibly progesterone therapy may be one method to allow pregnancies to progress from the embryo to fetal stage in women with recurrent miscarriages. To test this hypothesis, we evaluated the percentage of embryonic losses compared to fetal losses in women undergoing IVF who had an isolated sporadic miscarriage compared to women with recurrent losses. Both groups were supplemented with progesterone. The percentage of embryonic losses in 104 women with recurrent miscarriages was 30.8 versus 31.0% in women with sporadic miscarriages.

Morikawa et al. (2004) suggested that possibly high-dose immunoglobulin therapy may be one treatment that could inhibit early embryonic losses. However, progesterone therapy seems to completely reverse the embryo loss pattern in women with recurrent miscarriages. I am curious to know what was the percentage of embryonic loss in the small number of patients that the authors treated with immunoglobulin therapy? Even if this therapy was effective, progesterone therapy is a lot less expensive.

Theoretically, in some instances the fetal semi-allograft may prove insufficient to induce progesterone receptors in γ/δ T cells (if one uses the proposed model) and a more potent immune stimulus may be needed in addition to progesterone treatment (Check et al., 1995, 1997b). However, it may be that the majority of patients with recurrent miscarriage just need extra progesterone at least to progress from the embryo to the fetus stage.

References

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Reply to ‘Recurrent miscarriage and embryonic loss’

Sir,
Thank you for the opportunity to reply to Dr Check’s letter in which he recommends progesterone therapy rather than high-dose intravenous immunoglobulin (HIVIg) therapy in order to reduce risks of early pregnancy loss, i.e. embryo loss, because the former is less expensive.

It has been widely acknowledged that HIVIg therapy, but not low or medium dose of immunoglobulin, as immunomodifier is beneficially effective in several diseases such as idiopathic thrombocytopenia, Kawasaki disease, and Guillain-Barré syndrome. From 1993, we have applied the HIVIg treatment (20 g/day, 5 days) in severe cases of women with recurrent miscarriage (RM) of unexplained aetiology: down-regulation of NK cell activity and subsets. Am J Reprod Immunol 37,330–334.


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