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Dear Sir,

We do indeed believe that the demonstration of a Th1 bias in a proportion of unexplained recurrent aborters by several researchers (Hill et al., 1995; Piccinni et al., 1995; Marzi et al., 1996; Makhseed et al., 1999; Raghupathy et al., 1999, 2000) will lead to the application of strategies that mitigate a Th1 bias and redirect maternal reactivity away from the potentially harmful Th1 dominance to a more conducive Th2 bias.

While we did not speculate on possible strategies in our paper (Makhseed et al., 2001), what we did have in mind included some of the methods suggested by Check, such as i.v. immunoglobulins, drugs that down-regulate Th1 cytokines, anti-cytokine antibodies, etc. However, one of the approaches that we believe is most amenable to immediate testing is progesterone supplementation based on three lines of evidence, which we have cited in other communications from our laboratory (Raghupathy, 1997; Raghupathy et al., 2001).

First is the impressive data that have emerged from the laboratory of Szekeres-Bartho. An extensive series of studies from this laboratory has shown that in the presence of progesterone, lymphocytes from pregnant females produce an immuno-modulatory protein, progesterone-induced blocking factor (PIBF), which inhibits several Th1-type responses in vitro and prevents resorptions in mice induced by transfer of spleen cells with high natural killer activity (Szekeres-Bartho and Chauvat, 1990). In the presence of PIBF, murine splenocytes activated with mitogen produce significantly higher levels of IL-10 and IL-4, bringing about a Th1 to Th2 shift (Szekeres-Bartho and Wegmann, 1996).

Secondly, Piccinni et al. have reported that progesterone favours Th2 cytokine production (Piccinni et al., 1995). At concentrations that are similar to those seen at the feto-maternal interface, progesterone favours the development of Th2 cell lines and interestingly is even capable of transiently inducing the production of Th2 cytokines in established Th1 cell lines. Therefore, they propose that progesterone may be responsible, at least in part, for a Th1 to Th2 switch at the maternal–fetal interface (Piccinni and Romagnani, 1996, 1998; Piccinni et al., 1998).

Thirdly, Hill and colleagues recently presented data demonstrating that the production of type 1 cytokines by trophoblast antigen-activated peripheral blood mononuclear cell cultures was significantly inhibited by co-culture with progesterone (Choi et al., 2000).

Thus, progesterone may act via PIBF and by direct effects on lymphocytes. Moreover, progesterone supplementation may actually work via immune manipulation by bringing about a shift in the overall cytokine profile from a Th1 bias to a more pregnancy-supportive Th2 bias or at least an inhibition of Th1 dominance. Women with inadequate levels of PIBF may have Th1-dominance and may thus be abortion-prone; such women may benefit from progesterone supplementation. In other words, we do agree with Check’s suggestion that progesterone supplementation is well worth studying as an approach for ‘restoring the proper immunological milieu’ in unexplained recurrent aborters who have a strong Th1 bias. We consider it worthwhile to examine the effects of progesterone and its derivatives on Th1–Th2 cytokine balance and to investigate the connections between the hormonal milieu and Th1 versus Th2 bias.

However, we cannot exclude the possibility that some women may not produce sufficient levels of PIBF despite adequate levels of progesterone. We also feel that it may be a bit too simplistic to expect that the majority of recurrent aborters will respond to aggressive supplementation of progesterone. Check’s speculation that the group who respond to immune manipulation would be a small group is only a conjecture at this time and not supported by data. The size of the subgroup that would benefit from such treatment can be ascertained only after proper trials are conducted. There is as yet no information on the proportion of women who suffer recurrent abortion due to immunologic effectors, and furthermore there might well be a subgroup of aborters who are refractory to treatment with progesterone.

References


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