Lack of attention to immune abnormalities, the immunobiology of treatment regimens, and the inability of a small meta-analysis to achieve the required power can lead to unsupported beliefs. It is fortunate that Fig. 1 suggests a remedy with respect to secondary recurrent miscarriage. It should be noted that a recent observational study of IVIG in IVF failure patients has shown a similar result: only patients with immune test abnormalities showed a statistically significant treatment benefit with the sample size available (Clark et al., 2008). It would be more profitable in the case of so-called idiopathic recurrent miscarriage to work out mechanisms before expending large amounts of time, money and energy on conducting inconclusive RCTs in the hope that a convincing result can be obtained. With respect to the effects of paternal mononuclear cell treatment in unexplained primary recurrent miscarriage, about which Stephenson et al. suggest inefficacy, a more up-to-date appreciation of the literature on the biology and statistical considerations may alter antiquated notions (Clark, 2008). With respect to IVIG in secondary recurrent miscarriages, as with other syndromes of recurrent pregnancy loss, one may profitably begin by attempting to determine which test abnormalities and which treatment effects may correlate with a normal live birth in the control group and in the IVIG group (Yamada et al., 2003; van den Heuvel et al., 2007; Winger et al., 2011).

References


(Clark, 2008). Contrary to citation of Lachapelle et al. (1996), Clifford et al. (1999) and Quenby et al. (1999) as showing a role for CD56+ 16+ cells, Lachapelle et al. and Quenby et al. showed an excess of CD56+ 16+ cells in the preimplantation endometrium of women with recurrent miscarriage and Clifford et al. studied only CD56+ cells without reference to their CD16 phenotype. It has been reported by Yamada et al. (2003) that women aborting normal karyotype embryos had elevated blood CD56+ 16+ cells in contrast to women aborting abnormal embryos where blood NK cell levels were normal. Not all IVIG preparations are equally effective in suppressing elevated blood-type NK cells, and notably, Gamimmune which was used for some patient in the current Stephenson et al. study may be less potent than other types of IVIG (Clark et al., 2008). If a treatment is suboptimal, so would be the clinical outcome, and the only way to be sure a treatment is correcting a physiologic abnormality is to measure it!

We would like to address and clarify Dr Clark’s comments.

Sir,

This study was designed to show a treatment effect, based on prior publications which suggested evidence of benefit. Since this recent randomized controlled trial (RCT) (Stephenson et al., 2010), the largest to date, found that intravenous immunoglobulin (IVIG) was of no significant benefit, the next step would be an equivalency RCT, although obtaining adequate funding would be difficult due to the large sample size required.

Our RCT revealed that despite a history of 3–16 consecutive miscarriages, a clinical live birth rate of 94% can be achieved with preconception care and close first trimester monitoring in women with idiopathic secondary recurrent miscarriage, and without the addition of experimental drugs or blood derivatives. IVIG, a fractionated blood product, is expensive and not without risk, therefore,
its use should be based on the best evidence available. With our meta-analysis, no significant effect of treatment with IVIG was found, which was confirmed by a subsequent systematic review of IVIG for recurrent miscarriage (Ata et al., 2011). In addition to IVIG, a systematic review of randomized trials found no significant beneficial effect of paternal or third party mononuclear cell immunization, and trophoblast membranes over placebo in improving the live birth rate in idiopathic recurrent miscarriage (Porter et al., 2006). Presently, mononuclear cell immunization requires Food and Drug Administration approval under an investigational new drug application.

Although numerous immunologic tests have been proposed to identify an alloimmune etiology, there is a paucity of validated tests to assess the maternal immune response to pregnancy. Until miscarriages are routinely evaluated for numeric chromosome errors (trisomy, monosomy and polysomy), validating immunologic tests will be fought with difficulties because of the admixture of ‘explained’ aneuploid/polyploid miscarriages with ‘unexplained’ euploid miscarriages.

Offering women with idiopathic recurrent miscarriage an evidence-based evaluation and management plan, to optimize their likelihood of having a subsequent successful pregnancy outcome, requires leaving entrenched personal biases behind and using results of well-designed RCTs. This will move the field forward.

References


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Women’s age at menarche and offspring sex ratio

Sir,

Fukuda et al. (2011) recently suggested that women’s age at menarche may be related to their offspring sex ratio. In their sample of 10 847 premenopausal Japanese women producing 21 208 live singleton births, women having the highest offspring sex ratio reached menarche at the age of 14 years. Women reaching menarche at younger or older age had lower offspring sex ratio (Fukuda et al., 2011).

This is an interesting preliminary finding. Unfortunately, there are some methodological shortcomings that may have affected the results. First, as acknowledged by the authors themselves, offspring sex ratio in humans may potentially depend on various physiological, life-style and demographic factors (Lazarus, 2002). Therefore, it is rather surprising that the authors made no attempt to control for any of such confounding factors in their analyses, but relied on univariate association between menarcheal age and offspring sex ratio only. Second, the statistical procedure used in the study may not have been fully appropriate. This is because the analysis likely failed to account for the fact that since 10 847 women gave birth to 21 208 offspring, not all offspring could be regarded as independent data points. Independence of observations is a basic assumption of many statistical models and failure to account for it when needed likely produces underestimated variances and thus too narrow confidence intervals, making statistical inference unreliable (Littell et al., 2006). Moreover, it may be argued that since the authors found no statistical support for their heterogeneity chi-square test, i.e. no overall association between women’s age at menarche and offspring sex ratio, it was unwarranted to proceed to pairwise comparisons (Harrell, 2001).

Nonetheless, the findings of Fukuda et al. (2011), if real, are exciting and require replication. I examined the association between recalled age at menarche and lifetime offspring sex ratio using data on 241 post-menopausal Finnish women having a total of 494 singleton offspring (Helle and Lilley, 2008). In these women, mean age at menarche was 13.02 years (SD = 1.38, min = 10, max = 17) and mean offspring sex ratio, calculated as the proportion of males and not as the ratio of males to females (Wilson and Hardy, 2002), 0.531 (SD = 0.50). Due to small number of observations, the youngest and the oldest groups of age at menarche were added to the nearest age group. We applied logistic regression model with binomial errors and logit link function to model the likelihood of an offspring being a male in relation to her mothers’ age at menarche (six categories). Because many mothers produced several offspring (i.e. pseudoreplication within a mother), we used generalized estimating equations (GEE) with exchangeable working correlation structure to accommodate such clustering (Lipsitz and Fitzmaurice, 2009). Statistical inference in this GEE model was based on Score test (Lipsitz and Fitzmaurice, 2009). Our model also controlled for several factors that have previously been suggested to relate to offspring sex: maternal age at birth (Lazarus, 2002), educational attainment (e.g. Almond and Edlund, 2007) and smoking (e.g. Fukuda et al., 2002).

In these data, women’s age at menarche was not associated with offspring sex ($\chi^2 = 6.84, P = 0.23$). Those women who reached menarche at the age of 12 years produced the highest proportion of sons [mean, 95% confidence intervals (CIs) = 0.55, 0.43–0.67]. Instead, the lowest proportion of sons (mean, 95% CIs = 0.38, 0.30–0.46) was produced by those women who experienced menarche at the age of 14 years. This conclusion remained unchanged when all the other predictors were omitted from the model ($\chi^2 = 6.88, P = 0.23$).

Although based on a smaller sample size, these results provide no evidence to suggest that women’s age at menarche is associated with their lifetime offspring sex ratio. This result thus contrasts the findings of Fukuda et al. (2011). It would be interesting to see whether their results hold after correcting for those methodological shortcomings argued above. If the results remain and other studies provide similar observations, we may begin to evaluate what physiological, and perhaps even evolutionary, factors are responsible for the phenomenon.