(Gibson and Mace, 2003), showing that the sex ratio is higher in women with a larger fat store.

The studies that Dr Jongbloet claims contradict our interpretation indeed seem to support it. The secular trend of sex ratio increase in Southern non-metropolitan areas in Italy (Astolfi and Zonta, 1999) and among the Black population in the USA (Marcus et al., 1998) probably indicates, and certainly does not contradict, that the sex ratio increases with amelioration of caloric availability and reduction of undernutrition. All other evidence cited by Dr Jongbloet to support his hypothesis also fit with the concept that male offspring are antagonized by the non-optimal conditions such as those induced by an earthquake (Fukuda et al., 1998), the East German socio-economic collapse (Catalano, 2003) or a bombing attack in Croatia (Zorn et al., 2002). In support of his hypothesis, Dr Jongbloet maintains that, although males are conceived in less than optimal conditions, reversal of the sex ratio may occur in most extreme conditions. Although the decline of the sex ratio was not linear and was evident only in the first quartile of body weight, this cannot be defined as an extreme condition, since it applies to 25% of women living in one of the wealthier areas of Italy. Similarly, the seasonal modulation of the sex ratio supports a fine modulation of the sex ratio exerted by environmental factors rather than an effect exerted only by extreme conditions. Dr Jongbloet maintains that our interpretation is incorrect because it seems not to fit with his theory based on the over-ripeness ovopathy concept (Jongbloet, 2004). Although, the present data may or may not fit his interpretation, the seasonal modulation of the sex ratio does not seem to support his hypothesis, as already discussed (Cagnacci, 2003). Available evidence on sex ratio modulation, as well as our present (Cagnacci et al., 2004) and past data (Cagnacci et al., 2003) may be explained by theories formulated by other authors (Trivers and Willard, 1973; James, 2001, 2004).

References


Submitted on April 27, 2004; accepted on May 20, 2004

Angelo Cagnacci
Dipartimento Integrato Materno Infantile, Ginecologia e Ostetricia, Policlinico di Modena, Via del Pozzo 71, 41100 Modena, Italy

E-mail: cganci@unimore.it

DOI: 10.1093/humrep/deh364

Value of basal FSH concentrations: prognostic implications for pregnancy outcome

Sir,

We have read with interest the recent paper by van Montfrans et al. (2004). In this study, the authors prospectively evaluated 129 women with no history of subfertility who were planning to attempt conception in the near future, and measured their basal FSH levels during three menstrual cycles. Following evaluation of the data, the authors concluded that basal FSH concentrations as a marker of ovarian ageing were not related to the incidence of early pregnancy loss (EPL).

We do not question the premise of the study since there are data in the literature associating diminished ovarian reserve with aneuploidy and the subsequent risk for pregnancy loss (Levi et al., 2001). However, there are some very significant issues with the methodology used in this study which have a dramatic impact on the interpretation of these data. It would be most concerning if a practicing clinician were to read this manuscript and conclude that ovarian ageing as evidenced by basal FSH levels does not impart a higher pregnancy loss risk.

Most critical to the interpretation of these types of data is how an abnormal result is defined. The accuracy of the diagnosis of ovarian ageing (commonly termed diminished ovarian reserve) is principally dependent on what FSH level is selected to distinguish normal from abnormal. The authors use a value of 12.5 IU/l and refer to a prior publication from their group (van Montfrans et al., 2000). A review of that publication demonstrates that much of the analysis was done using a level of 10 IU/l and that the pregnancy and delivery rate above that level were substantial. No threshold analysis was done. Foregoing the inconsistency in definitions by the authors, it is evident the threshold between normal and abnormal—typically selected at a level where the residual...
Letters to the Editor

Allison Styne-Gross1,2,3, Karen Elkind-Hirsch2 and Richard T. Scott2

1Division of Reproductive Endocrinology and Infertility, Emory University School of Medicine, Atlanta, GA, USA 30322 and 2Reproductive Medicine Associates of New Jersey, Morristown, NJ, USA 07962

Reply to ‘Value of basal FSH concentrations: prognostic implications for pregnancy outcome’

Sir,

Dr Styne-Gross and colleagues correctly note an inconsistency in one of our previous papers (van Montfrans et al., 2004). In this study, we accidentally reported having used the Amerlite ILMA for FSH, whereas in fact the immunometric assay from Delfia, Wallac Turku, Finland was used. Test characteristics were described correctly, however. The cut-off value for elevated FSH in the Amerlite assay (10.0 IU/l) that was used previously in our institution (van Montfrans et al., 2000) corresponded to 12.5 IU/l in the Delfia assay, and described the threshold for decreased success in our IVF programme.

Several publications in the recent literature describe the concept of diminished ovarian reserve and its relationship to aneuploidy (e.g. Nasseri et al., 1999; van Montfrans et al., 1999; Freeman et al., 2000). Two factors complicate studying this relationship. First, no direct markers for ovarian reserve are available. Secondly, there is no uniform definition of diminished ovarian reserve. It may lead to early menopause and subfertility while pursuing spontaneous pregnancy or during assisted reproduction technology (ART), which are all separate clinical entities. Cut-off values for normal and abnormal cannot be interchanged automatically between these entities.

Our study described basal FSH values in relation to an indirect marker of ovarian function, i.e. the rate of (early) pregnancy loss (van Montfrans et al., 2004). As no data on basal FSH and (very) early pregnancy loss (i.e. measurable HCG during a presumed menstrual period without a noted increase in cycle length) have been published previously, no cut-off value for abnormal FSH was available either. This implies studying the putative relationship by measuring the effect of basal FSH on pregnancy outcome, preferably in a prospective study design. Analysing the data in such a study implies regression analysis, or a comparable test, to evaluate the existence of such an effect. A $\chi^2$ test can be performed as well, with the 5% of participants with the highest FSH levels classified as being abnormal. Classifying the highest 5% of values as abnormal is in common use in medical statistics when no prior data on cut-off levels are available.

We used the cut-off level of 12.5 IU/l for FSH, correlating with decreased fertility in IVF in our clinic, corresponding to the highest 6% of values in the current study. Strictly

References


pregnancy rate is between 1 and 2%—should in fact be much higher. Based on their prior study, a threshold for an elevated basal FSH level would certainly be >20 IU/l in their laboratory. It is entirely possible and perhaps even likely that not a single patient in this study had an FSH level consistent with advanced ovarian age.

Even if the arbitrary definition of 12.5 IU/l were accepted, there were only five patients in the study whose levels exceeded that threshold. That number is certainly inadequate to accurately characterize the pregnancy and loss rates for this population of women. If as the title states the authors are evaluating the impact of ovarian ageing on early pregnancy loss, the power analyses should have been based on the study population (those with a study diagnosis of ovarian ageing), which means a sample size of five women at most. That being the case, the sample size is woefully inadequate.

If the authors were to argue that the entire population should be studied, then the focus of the study would shift from evaluating the impact of ovarian ageing on EPL, and would become an evaluation of whether or not variability in basal FSH levels within the normal range has predictive value for pregnancy outcome. The data as presented here clearly demonstrate that it does not. Having said that, one might question why anyone would suspect that it would. Variability within the normal range for endocrine hormones rarely, if ever, predicts changes in clinical performance or outcome. A suitable analogy might be found when evaluating the clinical symptoms associated with hyperthyroidism. For example, applying the methodology used in this study to evaluate the relationship between hyperthyroidism (as evidenced by low TSH levels) and tachycardia, the authors would bring in 129 women and measure their serum TSH levels and heart rates. Almost all of them would have TSH levels in the normal range. It is extremely probable that no relationship with tachycardia and TSH levels would be identified. Would it then be legitimate to conclude that hyperthyroidism as diagnosed by TSH levels has no relationship with tachycardia? While seeming silly, it is an exactly analogous situation. Variability in basal FSH levels within the normal range has never been demonstrated to be predictive of outcome.

Perhaps this paper might more correctly be entitled ‘Variations in basal FSH within the normal range does not predict early pregnancy loss.’