

Predicting human conception: the elusive 'fertility test'

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The ability to control human fertility has changed completely in the last half century, from the development of reliable contraceptive methods to assisted reproduction. The assessment of an individual's fertility, however, has progressed remarkably little in the last several decades. While the reproductive potential of both men and women is predicated on successful production of gametes, the likelihood of conception in women (or 'fecundability') is primarily determined by the release of a single egg each month. Conversely, in men it is based on the continuous production of large numbers of motile sperm with the ability to traverse the female reproductive tract and successfully fertilise that egg. Assessment of infertility therefore focuses on ovulation, spermatogenesis, and the patency of the fallopian tubes. The assessment of ovulation is now complemented by the ability to assess aspects of how many follicles the ovary contains (the ovarian reserve) through the measurement of circulating anti-Müllerian hormone (AMH), and the assessment of the ejaculate has progressed through several versions of the WHO Semen Analysis Manual, albeit with significant debate.¹

However, there are remarkably scarce data on how well these parameters of human gonadal function predict the likelihood of natural conception in the normal population. The concept of a 'fertility test' has huge appeal and potential commercial value, particularly with the current growth in direct to consumer marketing – but is there such a thing?

Developing a fertility test would first require analysis of prospective cohorts of couples discontinuing contraception, how many then successfully conceive, and the factors that predict this. Such a study has recently been performed by Lam *et al* in Hong Kong, who were able to recruit and follow-up a cohort of 100 couples.² A key part of the interpretation of such a study is an understanding of the demographic characteristics of the couples recruited:

this group were Chinese, highly educated (88% had tertiary-level education), of normal body mass index (BMI <25 kg/m² in 92%) and almost all non-smokers. The median age was 31.8 years, reflecting the current age of childbirth in many developed societies. Sexual activity was low, with only 24% reporting intercourse at least twice a week at recruitment. Couples with conditions likely to cause reduced fertility were excluded. Of 112 couples recruited, 100 completed the study and 61 conceived within 12 months.

The significant predictors of conception were age and AMH level in the female; female BMI, exercise and stress levels, and coital frequency were not predictors. In the male, the compound variables 'total motile sperm count' and 'total motile normal morphology sperm count' (TNMSC) were predictive, although simple sperm concentration and progressive motility were not. Intriguingly, lower high-density lipoprotein cholesterol was also a significant factor in both sexes. Following multivariate regression, only female age and TNMSC remained significant with odds ratios of 0.87 (95% CI 0.76 to 0.99) and 1.09 (95% CI 1.00 to 1.19), respectively, thus both only just reached statistical significance; no variable predicted time to pregnancy.

This is a valuable study, albeit relating to this specific and homogeneous population. Female age was unsurprisingly identified as the key variable in predicting conception but this acts as a positive control confirming the validity of this study to be able to detect relevant factors. AMH declines with age in the adult female, explaining why it was significant in the univariate but not multivariate analysis. AMH is produced by the population of small antral follicles and has a relationship with the total number of primordial follicles in the ovary.³ It is not an indicator of oocyte quality, which currently is only indicated by age, and the size of the ovarian reserve does not determine



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regular ovulation. Previous studies have assessed the predictive value of AMH in both younger and similar age groups to that studied here,^{4,5} confirming that it is not of value in predicting short-term fecundability. AMH has also been shown to have little predictive value in assisted reproduction⁶ so it is definitively not the elusive 'fertility test' that so many would wish it to be.

In the male, epidemiological studies have shown the predictive value of sperm concentration and to a lesser extent motility in the normal population;⁷ in an infertile population total motile sperm count may be more predictive,⁸ perhaps as it is the 'dose' of motile sperm delivered at ejaculation. While it may seem surprising that sperm concentration was not identified as a predictive variable in the Lam *et al* study,² this may reflect the overall high sperm concentration in this cohort (median 72.6 M/mL, lowest value 36.6 M/mL). There appears to be a rising chance of pregnancy up to a sperm concentration of about 40 M/mL, with little benefit from higher concentrations.⁷ As the lower limit of normality is currently regarded as 15 M/mL, there was an absence of men in the lower normal or subnormal ranges included in the Lam *et al* study. The proportion of morphologically normal sperm in the human ejaculate is notoriously low, with 4% being the current lower limit of normality. It is therefore surprising that any sperm variables were of value in this cohort, and the finding that the compound variable TNMSC was predictive requires confirmation in other populations. Other aspects of sperm function were not included in the Lam *et al* analysis; the field has a long history of often complex laboratory tests which have failed to become established.⁹ Conversely, home testing kits continue to be developed, some assessing motile sperm concentration with online image analysis.¹⁰

The Lam *et al*² study serves as a valuable reminder of our currently limited ability to predict human conception. Despite the efforts of the investigators to spread the net wide and include factors covering metabolism, exercise and stress, it seems that new approaches are needed to identify the factors that prevented (or delayed) conception in the remaining 40% of couples. If high-quality laboratory-based tests are of limited additional value, home testing of the basics of fertility, i.e. ovulation and the presence of good numbers of motile sperm, can offer important information to couples, albeit not providing that elusive 'fertility test'.

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