The quality of ovulation is strained in normal women

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Submitted on February 12, 2013; accepted on February 18, 2013

“Ovulatory dysfunction” bears the imprimatur of a succinct medical diagnosis, but what does it really mean and above all, how do you diagnose it, especially in women with a normal menstrual history? Although we have multiple measures in our modern toolbox: ultrasound for daily follicular monitoring, hormonal assays of serum, urine and saliva (some for instance LH available over the counter to our patients), and even, heaven forbid, an endometrial biopsy; these are expensive, invasive and labor intensive for both physician and patient to document, and often lacking in evidence-based cutoffs. The bottom line is that the most common clinical practice to screen for ovulatory dysfunction is a menstrual history. Much of our knowledge of the normal length of the menstrual cycle and the effects of age on the menstrual cycle comes from the classic studies of Treloar et al. (1967) which were based on menstrual diaries collected on the back of a postcard, beginning in young women recruited during their college years and then collected over their lifetimes. We are likely to assume that a woman is ovulating regularly if her menstrual cycle length is 21–35 days (thanks to Treloar).

Therefore, the BioCycle study by Hambridge et al. (2013) reported in this issue of the journal offers important and novel data about ovulatory function in normal women, including the frequency of anovulation (12%), and the influence of anovulation upon ovulatory cycles (adversely in terms of integrated serum estrogen and progesterin measures). The BioCycle study investigators prospectively enrolled a cohort of 259 healthy, menstruating women, 18–44 years of age (excluding confounders such as hormonal use, history of ovulatory disorders, etc.). Women were asked to provide eight timed serum specimens during each of two menstrual cycles, and these were timed in relation to self-monitoring for ovulation using urinary LH and estrogen kits, to allow for comparison at similar phases of the cycle. The current study includes 250 women who provided (at least some) data from two menstrual cycles. A significant strength of the study is the retention and compliance in the protocol for such a large number of women. Over 94% of the women completed seven or more of the planned visits per cycle (far exceeding the average dropout in randomized clinical trials) and all women had at least five visits per cycle. An additional strength is that the investigators studied more than one menstrual cycle in each subject, and carefully collected confounders of the menstrual cycle in the cohort.

The investigators used a serum progesterone cut-off point (>5 ng/ml) to categorically determine whether ovulation took place in the cycle, analogous to our own clinical practice of documenting ovulation with a mid-luteal serum progesterone level. Overall 12% of the women with a normal menstrual history had at least one anovulatory cycle and of these 3% had two anovulatory cycles. Women with two ovulatory cycles were older (mean age of this group was 28 years) and women with anovulatory cycles were significantly younger (the mean age of women with one anovulatory cycle was 5 years younger and with two anovulatory cycles 8 years younger). Women with anovulatory cycles were also more likely, not surprisingly, to be unmarried and nulliparous, and anovulation was not associated with smoking, former OCP use or physical activity.

However, the most important and novel observation of this study is the effect of anovulation on subsequent ovulation, and hence the title of this editorial. The investigators utilized complex modeling to construct the menstrual cycle (and also created some elegant figures) based on their repeated serum hormonal measures, and divided the subjects categorically on the basis of their ovulatory status. They found diminished integrated levels of serum sex steroids in the ovulatory cycles of women who also had one anovulatory cycle (and this was independent of the temporal relation of the ovulatory cycle to the anovulatory cycle), compared with those women who had two ovulatory cycles. In regard to integrated progesterone levels there was a dose–response stepdown in integrated progesterone levels with highest in the women with two ovulatory cycles, followed by those with one ovulatory/one anovulatory cycle followed by those with two anovulatory cycles. This may be (in the periodic ovulators) the clearest depiction of the long hypothesized luteal phase defect (Jones, 2008) that I have seen. While these hormone levels represent only a surrogate of oocyte quality or endometrial function, and ultimately fecundity, they offer evidence, that documentation of an anovulatory cycle in a woman suggests altered and likely diminished ovulatory quality (with potential downstream endometrial effects) in these women when they do ovulate. In other words, the anovulatory
cycle is not an isolated aberration, but a suggestion of some more global problem in ovulatory function.

Clinically, this suggests we should suspect that even a single failure to document ovulation with our current tools (despite the inherent limitations of such timed tests) may be a harbinger of strained ovulation even if ovulation is subsequently detected in another cycle. Additionally, ~12% of the time, a normal menstrual history will fail to identify women with ovulatory dysfunction.

The mechanism of this strained ovulatory function in normal women is beyond the scope of this study, because although there is a trend towards increased FSH levels in anovulatory women (implying a compensatory hypothalamic–pituitary response), there are, unlike the sex steroids, no significant differences in integrated levels between groups. This may result from an inadequate sample size (since only a fraction were anovulatory and single measures of gonadotrophin are poor predictors of even short-term fluctuations), or that the ovary in women with anovulation is just resistant to normal gonadotrophin levels without compensatory hypothalamic/pituitary response. I thought, from an editorial standpoint, that I would never see the day where I would wish for AMH levels in a study, but this measure, or ovarian ultrasound with antral follicle counts and/or sequential follicular development, might have provided some additional insight. For example, it may have weeded out the women with ovulatory forms of polycystic ovary syndrome by the Rotterdam criteria and benefitted the search for potential mechanisms.

Although the menses as popularly stated may be a vital sign (ACOG Committee on Adolescent Health, 2006), a menstrual history alone is not enough to diagnose ovulatory function. There are, as the Hambridge et al. (2013) demonstrates, a substantial number of women with a normal menstrual history who experience anovulatory cycles. Our recent study noted that morbidly obese women with prolonged menstrual cycles were actually ovulatory (over 90%), with the main effect of massive weight loss after bariatric surgery being the shortening of the follicular phase (women ovulated at the same rate, before and after surgery) (Legro et al., 2012). So if we cannot rely on either a normal or abnormal menstrual history to accurately diagnose ovulatory dysfunction, what should we do?

The expert panel from the recent NIH sponsored Evidence-Based Methodology Workshop on PCOS recommended in their final report to ‘Improve the methods and criteria used to assess ovulatory dysfunction’ (http://prevention.nih.gov/workshops/2012/pcos/docs/PCOS_Final_Statement.pdf). I concur, though like them I am lacking in a specific test or method. Based on the current study, my wish list includes a one-time circulating glycohemoglobin-like measure of integrated progesterin exposure over time in lieu of multiple measures obtained over multiple visits. But to avoid a surfeit of hope on one illusory marker, or to rely too much on the evidence from one ovarian cycle let the advice of Antonio, the Merchant of Venice, guide our investigative efforts: ‘My ventures are not in one bottom trusted, nor to one place’.

References


