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# Stress relief to augment fertility: the pressure mounts

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Current studies have not conclusively demonstrated an objective and consistent marker of an aberrant stress response; an effect of such a stress response on reproductive outcome; or a benefit of counseling on reproductive outcome in such patients. (*Fertil Steril*® 2011;95:2462–3. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** Infertility, stress response, alpha-amylase, psychological testing, psychological counseling

Dr. Buck Louis and colleagues provide intriguing data supporting the use of salivary  $\alpha$ -amylase as a marker for stress. This marker correlated with day-specific probability of conception, although not with fecundability (1). Although the function of salivary  $\alpha$ -amylase is to digest dietary starch, there is evidence that  $\alpha$ -amylase rapidly increases in the setting of stressful stimuli (2–4). To place the present article in context, several critical questions must be addressed.

## WHAT IS STRESS?

Stress is a physical, mental, or emotional response to events that causes bodily or mental tension. Extreme stress (e.g., anorexia nervosa) certainly can disrupt reproductive function, but the impact of less dramatic stress in humans is unclear. In addition, determining what is stressful is complex, in that individual responses to stressful stimuli can differ dramatically. The relevant issue is stress response, rather than the stress itself. Were all stressful stimuli deleterious to fertility, it is likely our species (as well as all other species) would have ceased to exist long ago. Assuming that an excessive or aberrant stress response is indeed deleterious and a method existed to remove this deleterious response, then a technique to accurately identify patients with such an aberrant response would be extremely helpful.

## HOW IS AN ABERRANT STRESS RESPONSE CURRENTLY MEASURED?

Personality tests are the most common method to identify traits that correlate to aberrant stress response with poor reproductive outcome (5–21). However, despite the wide array of testing, no consistent personality characteristic has been identified. Physiologic responses are thought to be less subjective than personality tests and have also been studied as stress response markers, with similar mixed results (6, 11, 16). Finally, various biochemical markers of acute (1, 11, 15, 17) and chronic (1, 22, 23) stress have been studied. Unfortunately, the correlation between these markers and poor reproductive outcome have been subtle or nonexistent. Either the current methods do not adequately measure aberrant stress response, or the impact of aberrant stress response on fertility is truly subtle or nonexistent.

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In addition to identifying the ideal objective measure of the stress response, the timing of such a measure can confound findings. Clinicians exert significant effort to predict the outcome of a future infertility intervention, providing prognostic information that can correlate with both stress and outcome. The finding of elevated stress at the beginning of an infertility intervention may represent recognized expectation of poor outcome, and elevated stress toward the end of an IVF cycle may reflect a recognized poor progress, whereas elevated stress after the cycle may reflect disappointment of a failed cycle. To avoid these biases, stress analysis must be done before the collection of any prognostic data, and data must be age-matched.

## DOES STRESS NEGATIVELY IMPACT FERTILITY?

The studies on the association between an aberrant stress response and poor fertility outcomes are mixed, with studies supporting an association (1, 6, 8, 11, 12, 15, 17, 22, 24–26), studies refuting an association (13, 18, 27–29), and even a study suggesting a positive impact of stress on reproduction (14). In addition, there are studies demonstrating a negative impact of stress on male reproduction (19, 30, 31). It remains unclear whether the mixed literature represents difficulty in measurement, difficulty in determining the appropriate fertility endpoint, statistical aberrations resulting in one outcome or the other, or a subtle impact requiring larger sample sizes.

There is also ample anecdotal and documented evidence demonstrating that the diagnosis of infertility and the process of IVF are stressful events (10, 11, 20, 21, 32, 33). Few life experiences rival infertility assessment in its level of personal invasiveness, which certainly increases stress. Removing these confounders is difficult, which can make assessment of the independent influence of an aberrant stress response on fertility outcomes challenging. This is particularly valid given the wide variation in individual responses to the stress of infertility or IVF.

## DOES INTERVENTION REDUCE STRESS?

Assuming that an aberrant stress response is considered a negative influence on fertility intervention, is there a way to intervene such that the stress response itself can be mitigated? Fortunately, this issue does not seem to be controversial. There is evidence that counseling does decrease the stress response in an infertility population (16). Regardless of the impact on fertility, decreasing the stressful experience is of value. The existence of counseling services, regardless of whether the couple participates, is reassuring to patients (34, 35).

## DOES REDUCED STRESS IMPROVE OUTCOME?

Assuming that an aberrant stress response has a negative impact on fertility, and assuming that this aberrancy can be corrected with counseling, does counseling improve fertility rates? Unfortunately the data are limited and not encouraging; counseling does not seem to improve fertility outcomes (36), except perhaps in the extreme case involving induced hypogonadotropic hypogonadism (37). There is certainly opportunity to improve on the counseling intervention and study design to document benefit, but until there is clear and documented benefit, the emotional cost of assuming a negative impact of stress on reproductive outcomes is troublesome.

## IMPLICATIONS OF A "STRESS" DIAGNOSIS

Response to stressful stimuli is highly individualized, and assigning such a response as a causal factor for poor reproductive performance is controversial. Theoretically, an aberrant response can be "unlearned," providing a patient-controlled method for improving fertility. However, should fertility intervention fail, it is possible for both patient and clinical staff to infer that the blame for such failure was an inability of the patient to control their stress response. Such an interpretation adds additional guilt and frustration. Until it

is possible to convincingly demonstrate a negative impact of an aberrant stress response on fertility, until we can adequately measure this stress response, and until we can provide an effective intervention that improves reproductive outcome, it is prudent to avoid adding to the challenges our patients already undergo.

## CONCLUSIONS

Buck Louis and colleagues address one of the challenges in studying the question of aberrant stress response on fertility, that of an easily measurable marker. However, the lack of correlation with fecundability remains a concern. Given the controversy that exists in the literature, it is unlikely that any single study will address the optimal stress response marker, confirmation of an aberrant stress response on poor fertility outcomes, and confirmation that a specific intervention corrects the problem. Proponents who believe that a deleterious stress response does harm reproduction can argue that negative studies used the incorrect tool to identify the aberrant stress response or that the studies were underpowered, whereas opponents can argue that the positive findings to date are spurious and inconsistent. Ultimately, relevance will be based on confirmation of a causal relationship and successful intervention.

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