EDITORIAL COMMENT

Exercise and fertility: an update

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Introduction

The last several decades have resulted in a tremendous upsurge in physical activity among both men and women. This enhancement can be seen in the level of participation in both casual and competitive sports endeavors. For example, the marathon was once considered the pinnacle of endurance athletic achievement, capable of being completed only by a select few. In 2007, however, there were 340 marathons run in the United States, with 403 000 finishers (40% women). This represents an increase of roughly 35% in only 7 years! Additionally, sports league participation for softball, basketball, and even bowling are at all-time highs.

With more active participants in casual athletic activity, and increased participation in serious training and competition, it is critical to understand the impact this trend may have upon reproduction. In particular, an increasing number of couples heavily involved in physical activity are actively attempting conception. When difficulties arise for this subpopulation, it is imperative that the treating physician be well versed in the potential role of sports and exercise and be competent to advise them appropriately.

This article will review our understanding of the link between exercise and reproduction, with an emphasis on recent publications that enhance our knowledge and understanding of the relationship between the two.

Exercise, fertility, and women

Women, more so than men, have become increasingly physically active over the past several decades. Societal changes, legislation, physician endorsement, and popular culture have all contributed to create new opportunities for women in athletics. It is clear that exercise offers substantial health benefits; however, there is an undercurrent of concern that excessive activity can result in adverse effects on fertility. It is critical to sort myth from fact in order to allow appropriate appraisal by the budding athlete of the risks and benefits inherent to the activity being pursued.

Clinical abnormalities

Investigation of the relationship between exercise and reproduction has centered on several clinical disorders.

Infertility

Reproductive dysfunction has been reported to have a higher prevalence in athletes than in nonathletes [1,2]. However, few studies have focused on infertility as an outcome of physical activity. In a large cohort study more hours of vigorous exercise were associated with a reduced risk of ovulatory activity [3,4]. Additionally, data from a large in-vitro fertilization (IVF) program reported an adverse effect of exercise on pregnancy rates (see below) [5].

A population-based health survey was conducted in Norway during 1984–1986 with follow-up a decade later [6••]. The study included 3887 women and focused on infertility. Results indicated that increasing the frequency, duration, or intensity of physical activity was associated with an increase in difficulty conceiving. Women who exercised most days had a 3.2-fold greater chance of being infertile, and exercising to exhaustion increased the risk of infertility 2.3 times. These findings were independent of age, smoking, and BMI.

Menstrual dysfunction

Menstrual disturbances have been reported in female athletes of all degrees of physical activity, from the purely recreational women to the woman undergoing intensive, strenuous training for competition. The most severe form of menstrual abnormality is amenorrhea, which has a prevalence of from 1 to 44% of all athletic women, depending on the sport of interest [7,8]. The highest prevalence is among those elite athletes in sports that emphasize thin physiques with low BMI.

More subtle is an abnormality termed luteal phase defect, which may affect as many as 79% of athletes intermittently [9]. This disorder of corpus luteum function results in subnormal estrogen and progesterone production following ovulation, with an accompanying short luteal phase (less than 10 days). The end results may be abnormal uterine bleeding, infertility, and early pregnancy loss [10]. Although studies of this entity suffer from poor criteria of definition and inadequate diagnostic tools, the use of strict, prospective protocols with frequent hormonal sampling has shed considerable light on this subject. It is now clear that many female recreational

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runners suffer from this disorder despite the presence of regular menstruation [10].

The linkage between absence of menses and infertility is obvious and has been clearly established. The association between fertility and luteal phase defect, however, is more tenuous. Nevertheless, the realization that women frequently exhibit these abnormalities, often reverting back and forth between normal and pathologic states, suggests that careful attention to ovulatory function must be given to the female athlete presenting with subfertility.

Other effects

IVF should theoretically remove any adverse effects of exercise on the rate of pregnancy. The process involves ovulation induction with exogenous gonadotropins, artificial triggering of final oocyte maturation, retrieval of oocytes without reliance on follicle rupture, and exogenous hormonal support of the luteal phase (and early pregnancy). Thus, it would seem that exercise should confer no disadvantage to the IVF participant. However, in a recent study of 2232 women undergoing a first cycle of IVF [5], those who reported exercising 4 h or more per week for 1–9 years, were 40% less likely to have a live birth, three times more likely to experience cycle cancellation, and twice as likely to have implantation failure. These findings suggest that, beyond simple alterations of endogenous hormone responses that affect menstrual function and cyclicity, exercise may also contribute to subtle detriment of the developing follicle (oocyte and/or surrounding cellular support system). Caution is needed to not overinterpret these findings, and replication would be desirable. Nonetheless, the data from this large, prospective investigation are intriguing and serve as a cautionary note against taking an overly simplistic view of the effects of exercise on female fertility.

Mechanisms of exercise effects

Numerous potential mechanisms for the pathophysiology of exercise-related reproductive disorders have been proposed.

Hormonal alterations

The hormonal abnormalities in women engaged in sports are generally due to disruption of the hypothalamic-pituitary-ovarian axis. The primary target site is suppression of hypothalamic pulsatile release of gonadotropin-releasing hormone (GnRH), which decreases pituitary release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [11]. The resulting lack of ovarian stimulation produces an anovulatory, hypoestrogenic state. When the effect is less extreme, intermittent absence of the LH surge will produce occasional anovulation, with luteal phase inadequacy when the surges occur but are attenuated.

In some cases, such as in sports in which power is a major determinant of performance, the hypothalamic-pituitary-adrenal (HPA) axis may become activated. The resulting increased level of serum androgens impairs follicular development, producing ovulatory dysfunction [12–14].

Stress

Exercise represents a stress condition because it diverts many systems toward adaptation to a new condition [15]. Both of the primary stress activated systems – the sympathetic nervous system and the HPA axis – are activated during exercise. The latter results in elevated corticotropin-releasing hormone (CRH) in the portal system and measurable increases in adrenocorticotropic hormone and cortisol result [16,17]. Interestingly, such elevations are diminished in highly trained athletes: the HPA axis is 'trained' to undergo a milder response over time [17].

It is CRH that is likely responsible for suppression of GnRH neurons, producing malfunction of the reproductive system. CRH is also a potent inhibitor of LH effects in Leydig cells. The resulting decrease in reproductive function helps to preserve the individuals state of 'alert' demanded by the stress response.

Energy balance

Although stress is clearly linked to suppression of normal menstrual function in physically active women, the type of stress is in need of defining. The term 'stress' encompasses any sympathoadrenal activation producing a catabolic state wherein metabolic compounds are broken down to produce energy [18]. Thus, it has been theorized that menstrual disruption is a result of stress not from the exercise activity itself, but rather from a low level of energy availability. A randomized experiment investigating this issue found that exercise stress that was not due to energy availability had no effect on LH pulse frequency; by contrast, low energy availability due to either dietary energy restriction or exercise energy expenditure suppressed LH pulsatility [19]. Further studies in men confirm that reproductive hormones can be normalized despite continued exercise-induced stress via adequate caloric intake to compensate for the exercise-induced energy deficit [20].

The effect of different sports

The incidence of menstrual irregularities and adverse effects on fertility are highly variable, and depend on intensity, volume, and type of activity. The latter point is illustrated by the widely varying rates of menstrual dysfunction when examined by sport. Weight-bearing sports, with their premium on leanness, clearly have the highest prevalence. Nonweight-bearing endeavors such as cycling and swimming are considerably less likely to produce menstrual dysfunction, but nonetheless double that seen in the general population [21].

Conclusion: exercise and female infertility

Exercise is a highly beneficial activity for most women, producing an improved quality of life. However, adverse effects on reproduction can and do occur. The mechanism for this appears to be via production of a metabolic fuel deficit, forcing the body into a catabolic framework, which optimizes health by shutting down the reproductive system. Clinical sequelae include menstrual abnormalities as well as ovulatory dysregulation and possibly adverse effects on the oocyte. The resulting infertility can likely be reversed by attention to fuel replacement in a timely and sufficient manner. This is a trial waiting to be performed.

Exercise, fertility, and men

As with women, alteration in reproductive function has also been noted anecdotally in men. However, investigations have been much more limited, and the use of insensitive surrogate outcomes has resulted in little definitive information. Nevertheless, studies do exist that give us important clues as to which directions future investigation might head.

Clinical abnormalities

In men, too, clinical abnormalities have been catalogued and investigated. These outcome parameters demonstrate areas of specific concern.

Semen analysis

Semen quality has been investigated in numerous studies of endurance athletes. Several have failed to show any alteration in semen parameters among athletes [22–24], but the majority do indeed demonstrate a significant effect. In runners, all parameters have been shown to be adversely affected [25–27], and the volume of training seems to be directly proportional to the degree of effect [28,29]. Endurance training among cyclists has proven detrimental to sperm morphology [30]. Furthermore, in men whose semen parameters are already somewhat compromised by varicocele, the adverse effect seems to be additive [31]. However, with rare exceptions the numbers seen in these studies are generally within the normal range. In fact, most comparisons of endurance-trained athletes versus sedentary control individuals produced a statistically significant but clinically dubious difference.

It must be noted, however, that semen analysis is a particularly poor method to assess diminished reproductive capacity. The test is known to have tremendous interindividual and intraindividual variability. There is seasonal variation, and abstention interval affects results. Finally, the various properties of a semen analysis are undoubtedly of unequal importance, but the relative contribution to fertility potential has not been well quantified.

Other tests of reproductive potential, such as the DNA fragmentation assay and motion-capture sperm forward velocity are available, but have not been applied to this issue. Furthermore, it is unclear what alterations in these tests might mean in terms of fertility capacity.

Impotence

Cycling has been the most highly investigated sport when studying the relationship between exercise and impotence, with data suggesting that damage or entrapment of the pudendal nerves and/or arteries can occur following lengthy bicycle rides or extensive training [32]. Nevertheless, the incidence appears to be fairly low and generally transient, unless the insult produces demyelinization. However, should this rare phenomenon occur, 6 months or more might be required for recovery [33]. The bicycle industry has become aware of this issue, with structural changes in the bicycle seat now implemented, which are expected to reduce the incidence of such problems.

Mechanisms of exercise effects

A number of mechanisms by which clinical abnormalities may be linked to exercise have been proposed and investigated.

Hormonal alterations

Serum hormone levels are easily measured and have been shown to correlate reasonably well with semen parameters [34]. Numerous reports suggest that testicular steroid production and secretion are compromised by regular participation in intense physical exercise, particularly endurance training. Other studies, however, have failed to corroborate these findings. This discrepancy is seen in both cross-sectional and prospective studies, and may be attributable to subject selection, sampling techniques, and the type of exercise program. These studies have been reviewed previously [35]. Interestingly, the vast majority of these reports involve runners, particularly marathon runners. Few data exist on endurance swimmers or cyclists, although the little data that do exist suggest similar findings [35–37].

In addition to altering testosterone levels, it is entirely plausible that exercise might directly affect the hypothalamus and/or pituitary. Cross-sectional studies have suggested that endurance training produces changes in LH pulsatility and pituitary sensitivity to GnRH [36,38,39]. Initially, prospective data failed to corroborate this [40]. However, recent data by Safarinejad *et al.* [27]demonstrated a decrease in both LH and FSH as well as a blunted response to GnRH in runners training 10 h weekly for 24 weeks.

Prolactin, a central nervous system stress hormone, will when elevated have a detrimental effect on testosterone production (as well as spermatogenesis and fertility). No evidence exists to show that endurance athletes have a higher than normal rate of hyperprolactinemia. However, prolactin responses to stress are augmented in male athletes [41,42]. The clinical significance of this finding is unknown.

In summary, hormonal alterations in the endurance athlete are frequently seen in investigations. However, the significance of these findings remains unclear. Further investigation will be needed to help clarify the picture painted by these often discrepant studies.

Oxidative stress

Exercise increases the production of reactive oxygen species, which may damage multiple cellular functions. A concern with endurance activities is the possibility of altering semen parameters or hormonal values via generation of oxygen radicals and depression of antioxidant levels. Research has confirmed that extreme endurance events do indeed increase oxidative stress: this has now been demonstrated in long-distance runners [43] and Ironman triathletes [44]. Interestingly, exercise causes oxidative stress only when exhaustive; moderate amounts of exercise actually upregulate powerful antioxidant enzymes [45].

Scrotal temperature

Heat-induced alterations on male reproductive function have been extensively reported [46]. For testicular tissue to function appropriately, its temperature must be approximately 2.5°C below rectal temperature. External heat that raises the scrotal temperature for 30 min has been noted to affect spermatogenesis [47], altering all parameters of the semen analysis [46,48]. Recently, Jung *et al.* [49] investigated the effect of cycling on scrotal temperature. With individuals cycling for 60 min at 25 W of power, there was no correlation between cycling duration and scrotal temperature.

Trauma

Testicular cancer has been linked to microtrauma to the testes; cycling and horseback riding have been claimed as risk factors [50]. However, the effect of microtrauma on testicular function in the reproductive process has not yet been adequately investigated.

The effect of different sports

Both exercise volume and intensity have been shown in some studies to affect male fertility surrogate markers such as hormone levels and semen analysis results. Given the variations in required conditioning as well as types of body stress produced by different sports, it might be expected that the type of activity might well prove to be another important variable. Few data exist regarding sport-specific comparative effects on fertility, with most studies utilizing a single type of athlete for analysis. Attempts in reviews to determine the relative impact of each type of athletic endeavor generally utilize extrapolation across published studies, a not particularly valid method to compare activities.

Recently, Vaamonde *et al.* [51] sought to investigate semen parameters in three groups of men: physically active individuals who participated in nonprofessional endeavors approximately three times per week, water polo players who practiced 7.5 h weekly, and elite Ironman triathletes who exercised on average 20 h/week. Results indicated that a higher training load produced a greater alteration in semen samples, with strict morphology (Kruger) criteria being the most noticeably affected. These results suggest that those who choose to participate in highly time-intensive sports may well have altered reproductive capability. However, as this hypothesis was not directly tested, it remains a theory in search of substantiation.

Conclusion: exercise and male infertility

A cause–effect relationship between intense exercise and altered male reproductive function will be needed to promote the clinical admonition that less physical activity will be beneficial to the male member of an infertile couple. Such a cause–effect relationship can only be established by well designed studies (randomized or cohort) that are properly controlled and that utilize relevant, appropriate endpoints. To date, no such studies exist. Although a large amount of athletic activity might be disadvantageous to the fertility of some athletes, it is at present unclear what that subpopulation might be and to what degree they might be affected. The story at present is merely cautionary: if a couple is having fertility difficulties and a male factor is shown or suspected, decreasing exercise in the extremely physically active might be one avenue to explore. However, the individual should be assured that such a recommendation in 2010 has little scientific validity and may well prove to have adverse effects on other aspects of his quality of life.

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