Male subfertility and the role of micronutrient supplementation: clinical and economic issues

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Abstract

The concept of male subfertility has evolved rapidly since 2000. This term is discussed based upon evidence relating to its first entrance into the literature, along with contemporary references to its purported incidence and prevalence. Factors affecting sperm quality are described in detail, and available data pertaining to the effects of micronutrients on spermatic parameters and resulting pregnancies are described. The first cost-efficiency analysis of the use of micronutrients vs. assisted reproductive technologies is presented. This paper also describes a therapeutic approach to males, recognizing that many potential fathers have no recourse to medical facilities to evaluate their fertility. At a time when medical dollars are either nonexistent or precious, such an approach using micronutrient supplementation may be cost-effective in developing and possibly even in developed countries.

Introduction

Periconceptual vitamin supplementation for women (before and during pregnancy) has become a worldwide standard of care. Interestingly, the specific composition of these supplements has changed dramatically over time. In the early 1960s, such supplementation consisted of oral high-dose iron and vitamin pills with only a few components. Additional agents were added to multivitamins, particularly when the value of folic acid in prevention of neural tube defects was clinically recognized. More recently, the need to provide folic acid in the first 28d after conception has been documented, along with the requirement to maintain this for three months before conception. The value of folic acid supplementation has been demonstrated in population-wide reductions in the incidence of neural tube defects [1].

The current approach to male partners of women who are either unable to conceive or who are attempting to become pregnant is quite different. For men, there has been a tendency to focus upon problem solving for the individual. This contrasts sharply with broad-based care provided to women in terms of providing vitamin supplementation along with a structured program to provide optimal conditions for the gestation. In other words, there is no equivalent structure to offer a broad, public health approach for “future fathers” as for pre-natal counseling for women. Indeed, male factor fertility assessments have included little or no focus on providing vitamin supplementation to address potential nutrient deficiencies which might affect semen parameters. While providing optimal nutritional support to all patients seems logical, many clinicians may not be aware of how this may find application specifically to male reproductive potential [2]. For example, recent research suggests that folic acid administered to men unable to father children yields increased sperm counts, improves sperm motility, and reduces abnormal morphological forms [3].

UNICEF has estimated that a third of the world’s population is adversely affected by vitamin and mineral defi-
ciency [4], a problem associated with substantial economic burdens having special relevance to women and children. Although men were not specifically referenced in the UNICEF research, it is reasonable to generalize such findings to males sharing the same environments. The seriousness of vitamin and mineral deficiency among males appears valid even for populations where men are fed first, followed by children, with leftovers being given to women. In this context, our investigation explores a therapeutic approach to men who want to father children, recognizing that many potential fathers worldwide cannot access medical facilities to evaluate their own fertility potential.

Changes in understanding of male subfertility

Fertility describes the potential for actual production of offspring, while infertility is the inability to reproduce. According to the American Society for Reproductive Medicine (ASRM), “infertility is a disease defined as the inability to conceive following 12 or more months of unprotected sex before an investigation is undertaken unless the medical history and physical findings dictate earlier evaluation and treatment” [5]. As with other aspects of reproduction, exact figures regarding infertility etiologies vary, but the cause of infertility is commonly ascribed to the female in 40–50% of cases, to the male in 40%, to a combination in 20–30%, and remains unexplained in 15–20% of instances [6]. The related concept of subfertility, generally understood to mean a prolonged time of unwanted nonconception [7], is less familiar. In clinical settings and in the literature this term often is incorrectly used synonymously with infertility. Even whether the term subfertility should be used at all is controversial [7–8], although it can be useful with particular reference to males who may benefit from a simple intervention such as vitamin supplementation.

As in other aspects of medicine, the taxonomy of male reproductive potential has been shaped by the insurance industry; how the medical problem is classified can influence the reimbursement rate for consultation and therapy fees. If infertility, meaning the inability to become pregnant, is not considered a disease process per se, then such a medical model would fail to heed the contemporary approach of health as being “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” [9]. In this context, subfertility as an entity distinct from infertility is a useful demarcation, because such people (especially males) likely represent the majority of individuals with problems in achieving pregnancy worldwide.

It is unclear when the term subfertility first appeared in the literature. It is mentioned in the title of a 1949 article [10], but since no references accompany the text it is impossible to determine if the author was the first to introduce this term. In 2005, three articles discussing subfertility appeared in Human Reproduction in a section characterized as “Debate” [7–8,11]. Of interest, this journal is directed toward specialists in reproductive medicine rather than the general obstetrician/gynecologist or even the general physician. Researchers have noted that the “terminology in reproductive medicine relating to reproductive success is ambiguous, confusing and misleading” [7]. Given this circumstance, subfertility as a term (especially when applied to males) will likely remain in use since it describes a large and specific portion of the male population—those who are unable to commission a pregnancy for varying durations of time but who may indeed be capable of fathering a child [12]. Further, the term is less psychologically disturbing to males than is infertility [13] and may not be as threatening to a man’s concept of virility as is infertility [14].

Incidence and role of clinical treatments

The exact frequency of male subfertility is not known. Among couples investigated for an inability to conceive, the rates attributable to males range from 25–50%, although many cases are classified as “unexplained” [11, 15–16]. Whether similar rates prevail in couples not attending for fertility evaluation is speculative. Interestingly, conceptions can still occasionally occur among couples who have been labeled infertile, but receive no treatment. One study found a cumulative livebirth rate of 52.5% at 36 months among such individuals [17]. A similar conclusion was reported in an observational study of >9,000 nontreatment months, where a cumulative pregnancy rate of 19.9% was noted in a population with “unwanted nonconception of at least one year’s duration” [17]. Finally, a slightly lower (14.3%) livebirth rate at 12 months was noted in a 1995 study [15]. These investigations show that clinical intervention is not absolutely necessary for pregnancy to ensue among patients thought to be infertile.

Concerns regarding declines in human semen quality and fertility rates have been expressed for many years [18–20]. Among the most commonly cited factors associated with these declines are environmental and occupational pollutants, changes in lifestyles, exposure to toxic agents, and changes in dietary habits [13,21]. Recent literature has also implicated oxidative stress and free radicals, which impair reproductive potential via gonadal toxicity and
associated altered spermatogenesis [16,22–23]. Causative mechanisms are investigated only in men who present to medical caregivers requesting an explanation for their inability to procreate.

In the healthy individual, reactive oxygen species (ROS) and antioxidants remain in balance. When this balance is disrupted in favor of ROS, oxidative stress (OS) occurs [22]. The production of ROS and reactive nitrogen species (RNS) is multifactorial [24]. Stated another way, when the balance of natural antioxidants is depleted, oxidative stress results in cellular damage [23]. A recent review of literature has confirmed the positive effect of antioxidants on reproductive capacity, with particularly strong evidence for carnitines, Vitamin C, and Vitamin E to be considered first-line therapy for male subfertility [25]. However, glutathione, selenium, and coenzyme Q-10 had been subject to fewer investigations and therefore could be considered only as second-line therapies [25].

**Male reproductive potential and lifestyle factors**

Smoking and alcohol often used socially at similar times, yet studies in the reproductive biology literature do not always consider their additive detrimental effects. This is in contrast to the epidemiological literature where their co-use represents classic synergy [26]. Cigarette smoke contains well-known somatic cell mutagens and potent carcinogens; the possibility that this has an adverse effect upon male reproductive health is not new [23,27]. The exact mechanism by which sperm damage occurs is not clear, but may be related to the increased vulnerability of spermatozoa to oxidative stress given these cells' high membrane fraction of polyunsaturated acids [28]. Excessive consumption of alcohol increases ROS levels [16] and many alcohol abusers consume insufficient dietary amounts of protective antioxidants [29]. Dietary deficiencies have been linked to oxidative damage in spermatozoa [16–17], but the literature on specific nutrients is often conflicting. Results of supplementation with folic acid and zinc are particularly relevant, because they appear to work synergistically and result in a >70% increase in sperm concentration when taken under study conditions [30]. Selenium supplementation has been shown to yield a significant dose-dependent increase in total sperm count after 26wks, although toxicity was reported at excessive doses [22].

Numerous environmental pollutants have been linked with testicular oxidative stress [16]. Among these are air pollutants such as diesel particulate matter [31], a factor of special importance in countries that use unleaded automotive fuels. Cadmium and lead have been specifically linked with sperm oxidative damage [32]; mercury and arsenic are also toxic to sperm [33]. The male reproductive system is also adversely affected by agricultural pesticides and industrial chemicals [33], and illustrates the importance of recording potential occupational exposures in the clinical history. Hyperthermia, whether from tight clothing or from working in a continuous sedentary position (e.g., truck driving, computer work), has also been implicated in the production of elevated levels of ROS and RNS, since seminal cells respond to increased temperature by production of heat-shock proteins [33]. Another major concern, only beginning now to emerge, is the potentially negative effect of the continued use of cell phones. Because this technology is ubiquitous, if it has a negative effect on spermatic function, it would represent an important area of future investigation. While not every cell phone user is unable to father a child, but as cell phone usage varies enormously among individuals, this potential risk factor must be quantified. This matter was explored in a recent Cleveland Clinic study, which reported that among 361 males attending a clinic for infertility, the use of cell phones adversely affected semen parameters in an exposure-dependent manner [34]. Participants were grouped by sperm count (greater or less than 20 million/mL) and by daily active cell phone use (talking time), from no use (n=40), <2 hours/day (n=107), 2–4 hours/day (n=100), and >4 hours/day (n=114). The difference between cell phone user groups for each parameter was significant, with differences in motility, viability, and normal morphology among the two sperm count groups (p<.0001).

Sperm DNA damage increases with advancing age in both fertile and infertile men, possibly because of normal increases in ROS levels over time [16]. Bacterial and viral infections can also impair semen parameters [33]. Both produce leukocytes and granulocytes that are believed to release various pro-inflammatory cytokines, ROS, and other bioactive molecules causing oxidative stress, thus adversely affecting spermatozoa [35]. Psychological stress reduces semen quality with a central underlying mechanism being impairment of gonadotropin drive [33]. Stress also reduces sperm quality by increasing plasma ROS generation and decreasing antioxidant protection [36].

Extremes of exercise have also been linked with oxidative stress [16]. Muscle-aerobic metabolism is the cause of ROS in those who exercise regularly [37]. ROS therefore may be heightened in those employed in strenuous occupations where physical exertion is routine (i.e., agricultural workers, day laborers, construction, etc). It is noteworthy that these job classifications often are low-paying...
(especially in developing countries) and the diets of such individuals may be more likely to be protein and vitamin/mineral deficient. Among the obese, adipose tissue releases pro-inflammatory cytokines that increase leukocyte production of ROS [35]. Several recent population-based studies have shown an increased likelihood of abnormal semen parameters among obese men [16]. The increasing worldwide prevalence of obesity is of concern to all medical professionals, especially as it is a risk factor for Type II diabetes mellitus. Hyperglycemia increases ROS and adversely affects spermatic parameters.

Several medications, chemotherapeutic agents, antimicrobials, and radiation may affect gonadal function and can possibly result in azoospermia [35]. Cannabis, heroin, and cocaine adversely affect spermatic parameters, but the extent to which they do so is dependent upon the quantity and frequency of use [38]. The interplay of known factors resulting in altered semen parameters is summarized in Figure 1.

**Impact of micronutrient supplementation on semen parameters**

Medical teaching generally espouses that, among healthy individuals, nutritional needs can be met by diet alone. However, this dictum must be reexamined in light of the evidence that folate supplementation in the absence of known deficiencies has reduced the incidence of neural tube defects by 50–60%, both in populations where these defects were prevalent (e.g., China and India) and in parts of the world where they were less common [1]. The folate example highlights the fact that clinicians routinely treat entire female populations without regard to a known folate deficiency (the absence of any useful clinical test for folate deficiency must also be recognized). Such a preventive treatment strategy works because of the presumption that some members of a given population are deficient; extending the possibility of potential folate deficiency to men [4] therefore seems reasonable. It is also plausible that folate deficiencies do not exist alone, but rather coexist with other vitamin, mineral, and/or micronutrient deficiencies.

There is considerable public interest in vitamin supplementation, as 30% of the American public regularly use such products [11,39]. Ideally, vitamin supplements should be evaluated in randomized controlled trials with measurable clinical endpoints, as with pharmaceutical medications. Because the individual components are food-based, however, the vitamin industry is outside the regulatory remit of the FDA. Should such trials be undertaken, they invariably would be complicated and the results potentially difficult to interpret given the varied ingredients and formulations. Of greater importance, supplement manufacturers have no incentive to sponsor such clinical trials because potential profits do not warrant it. Given the low cost of standard multivitamins, and recognizing a greater likelihood of benefit over harm with their use, a daily multivitamin that does not exceed recommended allowances for all components seems reasonable [40]. This is particularly true because serum measurements for many micronutrients are not widely available except in specialized research laboratories. Even in these locations, such tests are expensive, in contrast to the relatively low cost of supplementation on an annual basis [40].

Dietary intake of vitamins C, E, and beta-carotene, as well as folate and zinc, are important for normal semen quality and reproductive function [25,41–42]. Some investigators have noted the paucity of published studies on folate and

**Figure 1.** Overview of known factors resulting in impaired male reproductive potential.
male reproduction [43,44]. One study described zinc (60mg/d) and folic acid (5mg/d) administered over 26 weeks to 47 fertile and 40 subfertile males, which resulting in a significant increase in sperm concentration among subfertile males (no other semen factors were affected) [45].

Vitamin and mineral deficiencies can occur in settings of obesity as well as malnourishment. Increasing levels of obesity in women are seen worldwide, paralleling higher rates of PCOS with its underlying hormonal imbalance and gonadal dysfunction. Of interest, the micronutrients that presently are recognized to function in the etiology of PCOS are similar to those that affect spermatic parameters and include calcium, magnesium, chromium, zinc, vitamin B12, folic acid, inositol (B8), vitamin B6, selenium, and manganese [46]. Interestingly, clinical testing for any of these substances is not routinely offered. Although not widely appreciated, iron absorption is reduced in the presence of spices or phytates [47–49]. This dietary interplay is important especially where low levels of nutritious food intake and high spice consumption is common. When an individual migrates from an adequate to an inadequate-but-subclinical mineral status, any resulting impairments are usually gradual and incremental (see Figure 2). This decline may be influenced by any number of confounding factors, including alcohol use, smoking, drugs, and quantity and types of spices in the diet.

Following papers by Wallock et al. [42] and Ebisch et al. [44], the use of a supplement containing vitamins, minerals, and antioxidants was further investigated in two recent Indian studies. In one national non-randomized observational study, 81 physicians provided data obtained from 103 subfertile males [50]. Forty-two of these individuals received a product (Oligocare) containing 18 components including folic acid, iron, manganese, and zinc (Wellman Conception, Vitabiotics UK). The remaining 61 patients received the same product plus one or more additional supplements (such as lycopene, co-enzyme Q-10, vitamin E, and B Complex). In both study groups, sperm counts more than doubled (18.02 to 46.66 M/ml and 21.66 to 45.88 M/ml, respectively). Patients had complained of an inability to conceive very shortly after marriage, but investigations of the male partner were minimal, being limited to a basic semen analysis. Outcomes were judged by spontaneous conception. After a median 3 months of supplementation, pregnancy ensued in 25% of Oligocare monotherapy couples and in 46% of those who received Oligocare combination therapy [50]. A subsequent non-randomized study of azoospermic men (with maturation arrest verified by testis biopsy) evaluated treatment either with multivitamins, micronutrients, and co-enzyme Q10 (n=24) or not (n=11) [51]. After three months, the treated group achieved significant increases in motility and morphology (p<.05) and two pregnancies [51]. With limited yet growing literature to support the association between micronutrient deficiency and male subfertility, the subject appears to be complex and worthy of detailed investigation. It is difficult to advance many conclusions from the available research because no standards exist for comparison, either in terms of semen parameters or types of supplementation. For example, whether supplementation

Figure 2. Summary of physiological effects associated with trace element decline (adapted from [48]).
should be provided as monotherapy (i.e., folic acid only) or a combination of vitamins, minerals, micronutrients, and antioxidants remains controversial. Combined therapies potentially are more beneficial in managing subfertility because antioxidants act by different mechanisms: either scavenging oxygenated radicals or improving the status of enzymatic antioxidants (superoxide dismutase, catalase, and glutathione peroxidase). If a complex formulation is selected, however, there is no accepted means to disentangle specific effects of the individual components upon semen parameters, a challenge that even randomized-controlled trials could not fully resolve. Despite such difficulties, the question posed regarding the value of micronutrient supplementation is not beyond scientific investigation and is testable. For example, Figure 3 describes a model for future spermatic testing that has been developed considering the inadequacies of the existing literature, presenting a potential four-arm study of supplementation. Large population sampling is essential for such a research model, washout periods are necessary, and appropriate follow-up (for both males and females) is mandatory. Standardization of abstinence before obtaining semen samples would also be necessary.

The economics of male subfertility

Cost analyses of ICSI generally focus on cost per cycle initiated, cost to achieve a pregnancy, or the additional cost to achieve a live birth relative to other therapeutic interventions. Table 1 summarizes three potential costing analyses for estimating healthcare expenditures related to alternative approaches to treating involuntary childlessness.

The ingredients perspective incorporates a bottom-up vantage point to estimate unit costs of consumables, procedures, and hospital costs. The results from such an analysis would offer a reasonable estimate of the direct costs relating to procedures delivered in hospital settings. On the other hand, the society-as-payer perspective would include expanded costs, such as speciality care required for neonates and social services for the involuntarily subfertile. The human capital perspective focuses on the patient with an emphasis on her/his status as a wage-earner and contributor to the family. Costing analyses may adopt any or all of these perspectives, as well as others. The human capital approach is likely to invoke the highest costing estimates, because the financial consequences of not working or falling victim to work absenteeism can be enormous and compound with time. However, when progeny are considered as consumers of social and other services, the societal approach may capture expanded resources arising from progeny requiring special needs. If this latter circumstance were the case, it would be balanced by the fact that these children ultimately will give back to their families and to society in many ways, thus reducing ultimate time lost from work when the generations overlap.

Intracytoplasmic sperm injection (ICSI) is an assisted reproduction technique that involves micro-injecting a single sperm into an oocyte. Including consumables, personnel, and facility costs, the incremental cost per live birth (for patients unsuited for conventional IVF) has been estimated in an Australian study to be between US$8,594 (A$8,500) and US$13,548 (A$13,400) (where: A$1 = US $1.01104, xe.com), or approximately three times the cost of standard IVF in Australia [52]. Taking the mean of these estimates would yield $11,071 per additional ICSI-live birth. In Australia and elsewhere, ICSI is classified as an “expanded procedure” associated with additional out-of-pocket expense for patients. This could limit access to IVF by rendering the entire procedure unaffordable for some individuals, with procedural point costs far exceeding these weighted costs (per live birth). In contrast, if the procedure is purchased the expenditure would likely exhaust any discretionary money that might otherwise be available for emergency health or family needs.
More than 2 billion people worldwide may be affected by mineral and/or vitamin deficiencies [51]. A USAID study of outreach programs in Ghana, Nepal, and Zambia estimated that the average cost per child dosed twice per year with Vitamin A would be about forty cents (US$1.15 when costs included personnel and capital items such as vehicles, office provisions, and long-term training) [53]. Assuming a 20-year cost of multi-vitamin supplementation at 10 times the higher annual amount cited above (US$11.50 per year), and a 30yr interval to have offspring with their partner, $345 would still be far less than one ICSI intervention or conventional IVF. Under these rather conservative assumptions of a 30-year fertile period for the male, averting the cost of one ICSI procedure could easily pay for the 30-year multi-vitamin supplementation of 32 individuals. Adopting the society-as-payer or human capital perspectives would certainly expand this cost-offset attributable to early and effective intervention. In other settings, the cost differential between nutritional supplementation vs. IVF+ICSI is even more pronounced. Whereas a 1-month supply of nutritional supplements ranges in currency-adjusted costs from US$13.15 to $186.00, IVF costs range from US$1,096 to $3,289. Under such circumstances, IVF costs range 6 to 250 times the cost of supplementation with no additional benefits. Health economists call this type of cost-minimization comparison a dominant decision because, when outcomes are equal, the choice of comparator is the less expensive option, which in this case is timely supplementation. With absolute costs of IVF and ICSI amounting to $9,500 and an additional $1,200, respectively [54], the cost analysis presented above is likely to underestimate the putative value of supplementation in comparison to downstream care for male subfertility.

**Assisted fertility options in the Developing World**

The use of assisted conception in the developing world traditionally has drawn controversy [55]. Nevertheless, there are social and economic consequences to childlessness in the developing world [56]. Whereas in tropical regions, health-related priorities focus on treating infectious diseases rather than subfertility and family size tend to be larger than in other parts of the world, subfertility still represents a substantial, cultural, economic, and medical problem. According to the WHO, involuntary childlessness is a problem that affects all populations at more or less the same incidence of 1 in 6 couples [57]. In the developing world, access to advanced reproductive technology is limited and only the wealthy have the ability to pay for it; this makes vitamin supplementation not just a cost-effective option, but the only option available for the majority in poor populations. Prioritizing vitamin supplementation in such settings would meet Millennium Development Goals in addition to mitigating male subfertility. This type of double-benefit is known as a positive externality, because it extends beyond the initial targeted unit of beneficence.

**Conclusion**

The concept of subfertility is evolving, especially as it relates to males. Whereas in the past men may have been classified as infertile when they were unable to father a child, it currently is recognized that many such individuals indeed are capable of becoming fathers. Among the factors that may temporarily prevent a given man from impregnating his partner is some form of micronutrient/mineral insufficiency. Several micronutrients have been shown to improve reproductive outcome when administered to subfertile men, but it is not clear whether such deficiencies act alone or in synergy with other factors. To date, questions on best therapeutic practice regarding vitamin supplementation have been addressed insufficiently. Considering the extent of subfertility on a worldwide basis and the stress it places on couples desiring a child, it seems prudent to at least consider multivitamin supplementation as an early and essential broad-based therapeutic intervention for both males and females. Such a benign inter-

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**Table 1.**

Basic cost analysis models to estimate multi-generational expenditure related to alternative approaches to treating involuntary childlessness

| Perspective         | Costing Inputs                          | Definition                                      | Projected cost (generation n) | Projected cost (generation n+1) |
|---------------------|----------------------------------------|------------------------------------------------|-------------------------------|--------------------------------|
| Ingredients         | Consumables, personnel time, cost or price of procedures | Inputs identified and assigned unit costs       | $                             | $                              |
| Society-as-Payer    | Expanded resources such as cost of specialty care and social services | Inputs include wider social and educational expenditures | $\$                         | $$$                            |
| Human Capital       | Wages lost because of days missed from work, school, caregiving | Inputs focused on individual as wage-earner and contributor to society | $\$                         | $\$                           |
vention is less expensive and more accessible in many areas of the world where specialist medical care for infertility is out of reach for the vast majority of the population.

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