Is antioxidant therapy a promising strategy to improve human reproduction?

Antioxidants may protect against infertility

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It has been known for long time that supplementation of culture media with reactive oxygen species (ROS) scavengers, disulphide-reducing agents or divalent cation chelators: (i) prevents the mouse 2-cell block in vitro (for reviews, see Noda, 1992; Johnson and Nasr-Esfahani, 1994); (ii) promotes male pronuclear formation and conceptus development to the blastocyst stage in pigs (Yoshida et al., 1993; Grupen et al., 1995; Sawai et al., 1997) and bovine cattle (Takahashi et al., 1993; Caamaño et al., 1996; De Matos et al., 1996); (iii) increases cleavage rates and tolerance of mouse concepti to the stress of freezing–thawing by slow cooling techniques (Tarín and Trounson, 1993); (iv) prolongs the motility of reactivated bull spermatozoa after freezing–thawing (Lindemann et al., 1988); (v) prevents, at least in part, the negative effect of oocyte ageing in vitro on fertilization, cellular fragmentation and development of concepti until the blastocyst stage (Tarín et al., 1998); and (vi) counteracts the disturbing effects of the thiol-oxidizing agent diamide on chromosomal distribution on the metaphase II (MII) spindle of mouse oocytes matured in vitro (Tarín et al., 1998).

Antioxidant therapy appears to be efficient not only in vitro but also in vivo. In fact, a growing body of evidence points out supplemental intake of vitamin A (the retinoids and carotenoids), vitamin E (α-tocopherol) and/or ascorbic acid (vitamin C) as an efficient strategy to improve reproductive function in laboratory and farm animals (for reviews, see Hurley and Doane, 1987; Chew, 1993; Luck et al., 1995). Recently, we have also demonstrated in the mouse model that dietary supplementation with a mixture of vitamins C and E: (i) prevents the age-associated decrease in ovulation rate after exogenous ovarian stimulation (J.J. Tarín, J. Ten, F.J. Vendrell and A. Cano, unpublished data); and (ii) neutralizes the disturbing effects of maternal ageing on both chromosomal distribution on the MII spindle and segregation of chromosomes during the first meiotic division of oocytes (Tarín et al., 1998).

Despite this overwhelming evidence from laboratory and farm animals supporting a protective role of antioxidants on reproductive function, only a few studies have been devoted to analyse the effect of antioxidant therapy in vitro or in vivo on human gamete/concepti physiology. In-vitro studies on spermatozoa have demonstrated that supplementation of culture media with antioxidants neutralizes the loss of motility caused by ROS generated by polymorphonuclear leukocytes and defective spermatozoa and improves sperm–oocyte fusion after treatment of spermatozoa with ferrous ions (Irvine, 1996; Parinaud et al., 1997). In-vitro studies on oocytes/concepti have shown no effect of ascorbate-supplemented media on conceptus development (Tarín et al., 1994). As discussed previously (Tarín et al., 1994, 1995), the lack of effect of ascorbic acid on conceptus development may be due, among other factors, to the short-term culture employed. In particular, concepti were kept in culture until day 3 (64–66 h post-insemination). At this point, it was not possible to assess any effect of ascorbate on spontaneous cleavage arrest in vitro, an event typically occurring in humans between the 4- and 8-cell stages (Braude et al., 1988).

In-vivo trials on human beings have shown that administration of antioxidants improves sperm quality in heavy smokers (Dawson et al., 1992) and in patients with ‘male factor’ infertility (Lenzi et al., 1993) as well as increasing the fertilizing potential in healthy men with high levels of ROS in semen (Kessopoulou et al., 1995) and fertile normospermic men with low fertilization rates in previous in-vitro fertilization (IVF) cycles (Geva et al., 1996). It has been reported also that oral administration of 400 mg of ascorbic acid daily enhances the ovulation-inducing effect of clomiphene in anovulatory women (Igarashi, 1977).

Antioxidant therapy, however, may be a double-edged sword with negative and undesirable effects if a safety threshold dosage of antioxidants is surpassed. In fact, high doses of vitamin A (retinoids) may have embryotoxic and teratogenic effects, including neural crest or tube, musculoskeletal and urogenital anomalies (for reviews, see Meyers et al., 1996; Hathcock, 1997). Heavy consumption of carotene-containing vegetables may cause amenorrhoea by increasing faecal excretion of oestrogens and thus decreasing blood levels of oestradiol (Martin-Du Pan et al., 1990). Large doses of ascorbic acid may be associated with inhibition of ovarian steroidogenesis (for review, see Levine and Morita, 1985), reduced fertility (for references, see Igarashi, 1977) and increased probability of abortion (for references, see Pintauro and Bergan, 1982). It has been reported also that high maternal ascorbic acid intakes increases the ascorbic acid metabolism of offspring in humans and guinea pigs (for references, see Blom and Dabrowski, 1996). This maternal effect on the progeny may cause scurvy in infants with an apparently adequate ascorbic acid intake. Moreover, plasma saturation of ascorbic acid occurs in humans
at daily doses of 1000 mg (Levine et al., 1996), and higher doses may induce the formation of renal calculi because of the excretion of high concentrations of oxalate. We should, however, emphasize that conditioned scurry and oxalate kidney stones induced by high ascorbic acid intakes have been widely discussed and speculated, but not substantiated (for review, see Hathcock, 1997).

Taking into account the pros and the cons of antioxidant therapy on reproductive function and health, we cannot keep any longer our eyes closed to the potential advantages that it offers. With the design of an appropriate diet, benefits certainly may exceed potential undesirable effects on fertility and health. Antioxidant therapy has been for long time and is still in the forefront of preventive medicine and we need to impart it to our world, i.e. of human reproductive medicine.

References

Antioxidant treatment for male subfertility: a promise that remains unfulfilled

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It is more than 50 years since Macleod (1943) demonstrated that incubation under oxygen was toxic to human spermatozoa and the deleterious effects of reactive oxygen species (ROS) in vitro are now incontrovertible. ROS generated by xanthine/xanthine oxidase or by contaminating leukocytes can impair the ability of spermatozoa to fuse with zona-free hamster eggs or to acrosome react and can decrease sperm motility. The effects of ROS can be prevented or decreased by the addition of antioxidants such as vitamin E (α-tocopherol) or hydroxylated butyl toluene and there is no doubt that antioxidants are effective against ROS damage to spermatozoa in vitro (Aitken et al., 1985).