

O-064

Antioxidants in the treatment of male factor infertility: Results from the double blind, multi-center, randomized controlled Males, Antioxidants, and Infertility (MOXI) trial

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Study question:

Among couples with male factor infertility, do antioxidants improve male fertility, as measured by semen parameters and sperm DNA integrity at 3 months, and pregnancy by 6 months of treatment?

Summary answer:

Antioxidant treatment of the male partner does not improve semen parameters, sperm DNA integrity, or in vivo pregnancy rates in couples with male factor infertility.

What is known already:

Clinical trials suggest that antioxidants have a positive effect on sperm motility, DNA integrity, and pregnancy rates in couples undergoing assisted reproductive technologies; however, there are significant gaps in our knowledge of their impact on male fertility. To date research studies have used: 1) small sample sizes, usually less than 50 subjects, 2) heterogeneous populations and a variety of single antioxidants, 3) changes in semen parameters or DNA integrity as the endpoint, rather than clinical outcomes, and 4) antioxidants in conjunction with in vitro fertilization with intracytoplasmic sperm injection (ICSI) when assessing effectiveness.

Study design, size, duration:

174 couples were enrolled in a multi-center, double blind, randomized, placebo-controlled trial of a daily antioxidant formulation, containing 500mg vitamin C, 2000IU vitamin D3, 400IU vitamin E, 1mg folic acid, 20mg zinc, 200mcg selenium, and 1000mg L-carnitine. Males were treated for a minimum of 3 months and a maximum of 6 months. Couples attempted to conceive naturally during the first 3 months and with clomiphene citrate with intrauterine insemination in months 4 through 6.

Participants/materials, setting, methods:

Males with sperm concentration ≤ 15 M/ml, motility $\leq 40\%$, normal morphology $\leq 4\%$, or DNA fragmentation $> 25\%$ were eligible. Female partners were ≤ 40 years old, with documented tubal patency and ovulation. Semen parameters and DNA fragmentation were assessed at randomization and following 3 months of treatment. Data are presented as median (interquartile range) or mean \pm standard deviation.

Main results and the role of chance:

After 3 months of treatment, change in sperm concentration differed slightly between the antioxidant [-4.0 (-12.0, 6.0) M/ml] and placebo groups [+3.2 (-9.0, 15.5) M/ml] ($p=0.03$). However, there were no significant differences between the two groups in the change in morphology, motility, or DNA fragmentation. Among the 66 oligospermic men at randomization, concentration did not differ at 3 months [8.5 (4.8,15.0) M/ml versus 15.0 (6.0,24.0) M/ml; $p=0.30$] between antioxidant and placebo groups. Among the 76 asthenospermic men, motility did not differ at 3 months ($34\pm 16.3\%$ versus $36.3\pm 15.6\%$; $p=0.93$). Among the 40 men with teratospermia, normal morphology did not differ at 3 months [2.0 (0.6,4.5)% versus 3.0 (2.0,4.0)%; $p=0.28$]. Among the 34 men with high DNA fragmentation, DNA fragmentation did not differ at 3 months [28.9 (21.6,36.5)% versus 28.8 (21.6,37.4)%; $p=0.68$]. In the entire cohort, cumulative pregnancy rates did not differ at 3 months (10.5% versus 9.1%; $p=0.76$) or at 6 months (22.1% versus 29.6%; $p=0.26$) between the antioxidant and placebo groups, respectively.

Limitations, reasons for caution:

While the trial was adequately powered to examine changes in semen parameters, the trial is underpowered to assess differences in pregnancy rates between antioxidants and controls. However, the DSMB recommended not proceeding with the larger trial, given the results of the internal pilot.

Wider implications of the findings:

Antioxidants do not appear to improve semen parameters or DNA fragmentation among men with male factor infertility. While previous data suggest that antioxidants improve pregnancy rates in in vitro fertilization, these data suggest they do not improve in vivo conception.

Trial registration number:

NCT02421887

Yes

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