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Antioxidants In Male Infertility: What Evidence Is Saying ?

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Introduction

Inability to have children affects 10% to 15% of couples worldwide. Male factor is estimated to account for up to half of the infertility cases with majority of male subfertility is considered to be due to the effect of oxidative stress. Oral supplementation with antioxidant is thought to improve sperm quality by reducing oxidative damage. However there are varying evidence on usage of antioxidants in male infertility. Additionally it needs to be noted that evidence of antioxidants in patients entering IVF with male factor infertility is different from those who are trying naturally or with IUI.

Summary

Systematic review and meta analysis published in 2018 analysed sperm DNA damage and association with an increased risk of pregnancy loss after IVF and ICSI [1]. They analysed 11 studies and suggested a combined OR of 2.48(95% CI 1.52,4.04,p=<0.0001) indicating that spem DNA damage is predictive of pregnancy loss after IVF and ICSI.

Cochrane in 2019[2] tried answering the question of role of antioxidants in male subfertility. 61 RCT comparing 18 different antioxidants with placebo, no treatment or another antioxidant in a population of 6264 subfertile men. They concluded that antioxidant taken by subfertile males may increase the chance of a pregnancy and live birth, though the overall quality of evience was low. Thus overall conclusion was inconclusive due to poor reporting methods, failure to report clinical outcomes live births and clinical pregnancy and small study sizes. Thus Cochrane concluded that large RCT are required to address general use of antioxidnats (AoS) in male subfertile population.

The study by Steiner [3] et al. sought to address the basic question related to the effects of AoS in an adequately powered, randomized double-blind placebo-controlled trial. Steiner et al. examined the efficacy of a commercially available antioxidant combination pill as their intervention as a treatment for infertile men with abnormal semen parameters and DNA fragmentation at 3 months and pregnancy resulting in live birth after up to 6 months of treatment, among couples with male factor infertility. The trial was called Males, Antioxidants, and Infertility (MOXI) trial. The results were sobering-there was no beneficial change in bulk semen parameters (concentration, motility, or morphology) nor any significant change in sperm DNA fragmentation indices. They also did not find any difference in pregnancy (both by natural means or intrauterine insemination with ovulation induction) or live birth rates. Among the 66 oligospermic men at randomization, sperm concentration did not differ at 3 months between the antioxidant and control groups: 8.5 (4.8, 15.0) million/mL versus 15.0 (6.0, 24.0) million/mL. Of the 75 asthenospermic men, motility did not differ at 3 months: 34% ± 16.3% versus 36.4% ± 15.8%. Among the 44 men with high DNA fragmentation, DNA fragmentation did not differ at 3 months: 29.5% (21.6%, 36.5%) versus 28.0% (20.6%, 36.4%). In the entire cohort, cumulative live birth did not differ at 6 months between the antioxidant and placebo groups: 15% versus 24%. Limitations of this trial were Coenzyme Q10 which has a promising Level 1 evidence supporting its ability to improve sperm concentration and motility was not administered in this trial. The formulation chosen may not have been appropriate. There were more men with secondary infertility in the placebo group. The study excluded men with severe oligozoospermia and lastly men with oxidative stress should have been chosen.

Conclusion

Antioxidants should not be offered to address abnormal DNA fragmentation. while study is a very compelling argument to save our patients the cost and burden of empiric therapy with over-the-counter antioxidant nutraceuticals. Sperm DNA damage can be conisered in patients who experience unexplained early miscarriage after an IVF/ICSI cycle

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Sperm Genomic Integrity In Recurrent Pregnancy Loss: A Promising Diagnostic Or Stilla Dilemma ?

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Recurrent pregnancy loss (RPL), one of the most complex and challenging condition in reproductive medicine is mostly heralded by a host of accepted etiologies with a few evidence-based diagnostics and treatment strategies on platter. This highly heterogeneous condition is defined as spontaneous loss of two or more clinical pregnancy losses before 20 weeks of gestation.[1] Despite the number of accepted etiologies of RPL, idiopathic RPL (iRPL) gets to be more frustrating and adds to more physical and emotional morbidity in approximately 50% patients.[1]

The contribution of male factor in the evaluation of RPL has been largely ignored. The current paradigm is shifting towards evaluating the paternal contributions as a causal factor. The evaluation of the male partner is still restricted to karyotype and semen analysis, while the sperm function testing is undertaken less.[2] But by large, semen analysis is generally not a part of the initial assessment of RPL due in part to its limitations as a functional test. Whether the quality of sperm DNA or its packing should be considered as a determinant of idiopathic/unexplained RPL still remains an enigma. Various studies have highlighted the association between sperm DNA damage and RPL.[2-7]

The integrity of the sperm nuclear DNA is a vital determinant of semen quality as it not only correlates with successful fertilization but also normal embryonic development and subsequent health of the progeny.[7-10] Various techniques are available to measure the extent of DNA damage and are categorized into those that i) measure DNA damage after denaturation- sperm chromatin dispersion (SCD), sperm chromatin structure assay (SCSA), comet assay, acridine orange assay; ii) directly measure single and double stranded breaks- TUNEL and comet assay; iii) assess sperm chromatin structure/integrity-toluidine blue staining, aniline blue staining, and chromomycin A3 staining.[11,12] Along with the disrupted genome integrity in the spermatozoa, the dysregulation in sperm gene expression profile in male partners of females with RPL as a potential contributory factor as per the studies conducted in our department.[7]

The evaluation of sperm genomic integrity comes with its own pool of limitations as per the already published studies owing to the variations in the different methodologies adopted. The sensitivity of most of these assays is also limited. The comet assay, which is considered to be the most sensitive method among the others, has an estimated lower limit of 100 double stranded breaks per cell. The lack of consensus among the assays (except SCSA) and standardization of different protocols, inter-observer variability, intra-assay variability, and the huge discrepancies in establishing the cut-off values for the assays contribute to the poor accuracy and reproducibility of the assessment.

Various previous studies conducted to assess the effect SDF in RPL patients had shown mixed results. Robinson et al[13], conducted a systemic review and meta-analysis and first confirmed a link between sperm DNA damage and RPL. This meta-analysis spawning across 16 studies involving 2969 patients, showed that there was a significant increase in miscarriage in patients with high DNA damage (risk ratio = 2.16 [1.54, 3.03], $P < 0.00001$) compared with those with low DNA damage. A number of subsequent studies also further supported the findings of the 2012 systematic review.[2,6,7]

Another characteristic of SDF testing in iRPL is that usually the male partners in RPL are normozoospermic, so, in contrast to infertility patients no other male seminal parameter exists to be analysed.[6,7] Similarly, seminal oxidative stress (OS) and Y chromosome microdeletions are also assessed as causes of RPL.[3,7,14,15]

Although the ASRM doesn't recommend the use of analysis of sperm genomic integrity in male partners of women with RPL, the current evidence from the studies conducted since the ASRM guidelines were published suggests that testing of SDF may contribute as a potential mechanism of paternal contribution in iRPL.

Conclusion

Assessment of the sperm chromosomal abnormalities and DNA fragmentation may serve as a reasonable diagnostic for male partners of RPL patients, along with referral to a genetic counselor if needed. Disruption in genomic integrity is a likely outcome from multiple pathways and involves an overlap between genetics, epigenetics and environmental factors. Understanding the mechanisms contributing to these disruptions is thus pertinent in order to even develop therapeutic approaches. However, further understanding of this complicated clinical condition will allow couples to make more educated, albeit difficult reproductive decisions.

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