Do Herbal Supplements Impair Male Fertility?-An Expert Responds to the Loma Linda Studies

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Summary: The authors analyzed the effects of four herbs (St. John's wort, saw palmetto, Echinacea purpurea, and Ginkgo biloba) on sperm DNA and the fertilization process. They determined the percentage of sperm penetration of hamster oocytes using zona-free egg penetration test and analyzed the denaturation of sperm DNA by the herbal supplements and their association with the mutation of BRCA1 exon 11 gene linked to the development of breast and ovarian cancer. The authors reported that high concentrations of St. John's wort, echinacea, and ginkgo had adverse affects on oocyte penetration rates suggesting that, at high concentration, they damage reproductive cells. St. John's wort was found to have mutagenic effects on sperm cells.


Summary: The authors analyzed the effects of four herbal supplements (saw palmetto, Echinacea purpurea, Ginkgo biloba, and St. John's wort) on sperm motion parameters using a computer-assisted semen analyzer following up to 1, 4, 24, and 48 hours of incubation at 37°C. St. John's wort at high concentration (0.6mg/ml) inhibited sperm motility and decreased curvilinear velocity and beat-cross frequency. High concentrations of saw palmetto, echinacea, or ginkgo inhibited motility after 24 or 48 hours of incubation. The mechanism involved in the reduction of sperm motility by St. John's wort was suggested to be spermicidal in nature as it resulted in a reduction in the percentage of viable sperm after 48 hours of incubation.

Comments/Opinions: These two recent articles by Richard R. Ondrizek and colleagues on the effects of herbal supplements on penetration of zona-free hamster oocytes and the integrity of sperm DNA, and on the inhibition of human sperm motility, have generated an incredible amount of press, including an article by Jane Brody in the New York Times entitled "Herbal remedies tied to pregnancy risks" (March 9, 1999).

The article appearing in Fertility and Sterility provided the primary fuel for the press, and on the surface provides interesting information on the effects of four herbal supplements on sperm DNA and on the fertilization process. This study, in my opinion, overstates its findings and draws incorrect conclusions that do not allow the extrapolation of these findings to the normal population that may be consuming ginkgo, St. John's wort, saw palmetto, or echinacea supplements.

First, the criteria for selection of dose for each herbal supplement are unclear. One thousandth or one millionth of the recommended daily dose dissolved in 1 ml of the medium is confusing. The in vivo and in vitro effects of a given amount of the compound are different, and the level of each compound in the serum and the amount reaching the specific organ site are different. It is important to know if the authors conducted studies to determine the levels of the active ingredients in each of these herbal supplements present in the serum and seminal plasma of the individuals taking these supplements. Perhaps an initial screening by high-performance liquid chromatography could clarify the question of the dose used in the study. Animal studies could also determine the LD50 dose of these herbal supplements. Studies using an animal model with these supplements for a period of 2-3 months could be conducted to study the various biochemical metabolisms to illustrate whether the effects are reversible or not, and to determine whether these supplements were mutagenic.

Second, the authors did not describe the solubility of each herbal supplement in the selected medium and the reason for their use of a 0.8 mm filter instead of the conventional 0.2 mm filter.

Third, the authors fail to explain the reasons for exposing sperm to the herbal supplements for seven days, as sperm in vivo do not encounter such a delay before coming in contact with the egg. The authors do not mention the conditions under which the sperm suspensions were incubated for seven days and if these suspensions contained antibiotics, and at what concentration. Antibiotics themselves can affect sperm motion characteristics, especially over a period of seven days. Did the authors examine the suspension for bacterial contamination? Also, why was albumin excluded from the medium, and to rule out what confounding effects?

Fourth, the authors exposed both the oocytes and the sperm to the herbal supplements. However, it is not clear
why the oocytes were exposed. While the sperm penetration assay provides clinically useful results, it is new, and its outcomes are highly controversial and difficult to reproduce.\textsuperscript{1,2} The results of a negative sperm penetration assay cannot be used to eliminate men from consideration for in vitro fertilization. The authors should look at the second generation sperm function protocols, which are reported to provide more accurate information.\textsuperscript{3}

Fifth, although the authors demonstrated that DNA denaturation and damaged DNA were detected as a point mutation with St. John's wort, these results need to be reproduced and validated by other standard assays, such as COMET, TUNEL, or FISH.\textsuperscript{4-7} In short, no conclusions can be reached from their reported results.

Finally, the main problem with the statistical analyses is the calculation of power. One source of confusion is the researchers' statement that the study has a type (error of 0.95 and a type II error rate of 0.8, which are probably meant to represent 0.05 and 0.2, respectively. Even if this is the case, their sample sizes of 8-9 per group provide a power of, at most, 14% rather than 80% to detect a 20% difference. A sample of at least 35 per group would be required to provide 80% power. In addition, tests like chi-square would not be appropriate for their small sample sizes.

In the second paper, which appeared in the Journal of Assisted Reproduction and Genetics, the use of a single fertile donor does not rule out the possibility that there may be variable responses in both the donors and different patient populations. Secondly, the authors measured various sperm motion kinetics using a computer-assisted semen analyzer (CASA) at a concentration of 10 x 10\textsuperscript{6} sperm/ml. However, it is well-known that the accuracy of CASA is limited at both higher and lower sperm concentrations.\textsuperscript{8} Did the authors examine the motility manually to validate the CASA results? Counting of only 100 sperm cells is not only inadequate, but also a potential source of erroneous results.

Some of the variations reported by the authors in motion characteristics are difficult to explain. In Table 1 of the study, curvilinear velocity in the control, was lower at 24 hours compared to 48 hours and it increased after four hours before dropping following subsequent incubation with echinacea. Similarly, the increase in percent of hyperactivation with echinacea and ginkgo after four hours and then decreasing to zero and still being insignificant from controls is not clear. Again, the beat-cross frequency pattern was not consistent, with ginkgo showing an increase at four hours, a decrease at 24 hours, and again increasing at 48 hours. An opposite trend was noted with St. John's wort. These findings are questionable, and it is difficult to draw a meaningful conclusion. Similarly, in Table 2, the results of beat-cross frequency are unclear, with inconsistent results with both saw palmetto and echinacea, as well as St. John's wort at higher concentrations. In the absence of studies elucidating the mechanism of action and the influence of these herbal supplements on sperm metabolism, the observations, although provocative, warrant serious in-depth study before they can be extrapolated to humans.

Although the sample sizes in this study appear sufficient, a statement of power and the degree of differences that they could detect would be helpful in interpreting the results.

In summary, the authors' findings of the effects of four herbal supplements on sperm function and motion characteristics have serious deficiencies and must be interpreted with caution. These results cannot be extrapolated and generalized to human beings who may be using these herbal supplements.

About the Reviewer: Dr. Agarwal is the Director of Research at the Center for Advanced Research in Human Reproduction and Infertility at The Cleveland Clinic Foundation in Cleveland, Ohio. He is board certified as a Clinical Laboratory Director in Andrology, and is recognized as a leading expert in the area of oxidative stress in male and female infertility, sperm cryopreservation in patients with cancer, and epididymal physiology. Dr. Agarwal received his postdoctoral training at Harvard Medical School from 1984 to 1986 and was an Instructor and Assistant Professor of Urology from 1988 to 1993 before joining The Cleveland Clinic Foundation.

References