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Atorvastatin and Male Infertility: Is There a Link? *Androlog* Summary

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Pharmacologic agents in use in the United States undergo extensive study prior to release, regulated by the federal government. However, medications in common use often harbor effects on the reproductive system, and these may extend beyond those identified prior to approval. Since the system for the investigation of drugs is most intensive in the preapproval phase, less attention is paid to agents already in use, prompting physicians to wonder whether anecdotal experience may be indicative of a global effect or of a sporadic occurrence.

Jim Daitch writes of the highly commonly prescribed dyslipidemia agent atorvastatin (Lipitor):

> Over the last several years I've noticed many men on Lipitor who have low motility in their sperm parameters. I don't see anything in the PDR (Physician's Desk Reference) concerning this, but theoretically its effect on cholesterol metabolism could affect motility. Has anyone else noticed this?

Ahmed Mahmoud replies with a putative mechanism should such an effect be real:

> This may be a consequence of coenzyme Q(10) (CoQ10) deficiency because inhibition of cholesterol biosynthesis also inhibits the synthesis of CoQ10. Even brief exposure to atorvastatin causes a marked decrease in blood CoQ10 concentration (Rundek et al, *Arch Neurol.* 2004;61:889–892).
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> CoQ10, the predominant form of ubiquinone in man, functions as an electron carrier in the mitochondrial respiratory chain as well as serving as an important intracellular antioxidant (Hargreaves, *Ann Clin Biochem.* 2003;40:207–218). Both properties are vital for sperm motility.
>
> CoQ10 is present in high concentrations in seminal plasma and its level in this biological fluid correlates positively with sperm motility and was found to be reduced in idiopathic and varicocele-associated asthenozoospermia. Recently, an open pilot study reported CoQ10 supplementation in infertile men with idiopathic asthenozoospermia resulted in a significant increase in sperm motility (Balercia et al, *Fertil Steril.* 2004;81:93–98).

Peter Schlegel sensibly cautions that the described putative effect is not biologically established in controlled studies:

> The comments of Dr Mahmoud were most interesting and enlightening regarding the potential effects of Lipitor on sperm motility. Dr Mahmoud quoted the Balercia trial of CoQ10 supplementation on sperm motility. It is important to recognize that the Balercia study was an uncontrolled open pilot study. The results of this study, as with many other uncontrolled trials, should not be interpreted to demonstrate efficacy of this agent. Properly controlled trials need to be done to adequately evaluate the relationship between CoQ10 and motility. It is well known that patients who are evaluated for a variable laboratory parameter (eg, sperm motility), where the patient population is selected for low numbers (eg, asthenozoospermia), will have a tendency to increase that parameter (increased sperm motility) with any intervention (or no intervention). This is commonly referred to as ''regression to the mean.'' In addition, any substance normally found in sperm or within the testis will correlate with sperm concentration, motility, and (sometimes) normal morphology. However, this correlation should not be interpreted as reflecting an independent, causative role in affecting sperm motility.

Finally, Ahmed Mahmoud calls for future studies:

> I agree with Dr Schlegel. Certainly, more studies are needed. Further search on the subject indicates that exposure of rats to doses of atorvastatin many times higher than those used in humans had adverse effects in some of the animals including, and I quote, ''aplasia and aspermia in the epididymis'' and abnormalities in testis volume and sperm parameters including motility. However, a 2 year study in dogs revealed no such effects. For further details see this PDF file from the Food and Drug Administration (FDA) through the link below. http://www.fda.gov/cder/foi/label/2001/20702s25lbl.pdf

The pertinent excerpt from the Atorvastatin label that refers to fertility effects appears as follows:

> Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC (area under the curve) at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg, and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 2 years.

The discrepancy between male reproductive effects in rats and dogs with atorvastatin is sufficient to give one pause: on which side of the spectrum would humans fall? Even subtle effects would be of concern if the male in question had an underlying reproductive defect to which small alterations in reproductive potential may be confounding. With medications that are in common use, given throughout the life span of the individual and often initiated at a young age, studies on their reproductive effects are certainly needed.