Kisspeptin: Role in reproduction and implications for infertility management

Sir,

Kisspeptins are a family of peptide hormones, which play a critical role in reproduction. They are found in the gonads, nervous system, anterior pituitary, and the placenta toward term. Kisspeptin receptor is a G-protein-coupled receptor found in the central nervous system, anterior pituitary, and the placenta. The kisspeptin acts through its receptor and brings about a release of predominantly Luteinizing Hormone (LH) from the anterior pituitary. The role of kisspeptin in bringing about the mid-cycle LH surge in response to increasing estradiol is being recognized based on rodent studies. Knockout Mice for kisspeptin receptor fail to mount an LH surge. Differential effect of estrogen on KISS 1 secreting neurons in the hypothalamic arcuate nucleus and in the hypothalamic anteroventral periventricular nuclear is responsible for the variable effect of estrogen on the pituitary secretion of gonadotrophins.

Kisspeptin is also involved in the link between nutritional status and fertility through its interaction with leptin, another peptide that is important in regulation of appetite and body weight. Kisspeptin may provide unique therapies for infertility. It provokes a rise in LH on subcutaneous infusion in normoovulatory women especially in the preovulatory phase. Women with hypothalamic amenorrhea show a rise in gonadotrophin level on biweekly injection of kisspeptin.

Gonadotrophins are the mainstay of treatment of subfertility at present. They are expensive and can lead to ovarian hyperstimulation syndrome and multiple gestations. The cost of gonadotrophins is prohibitive. Kisspeptin, because of its role in regulating the hypothalamo-pituitary-gonadal axis and causing gonadotrophin release, can be an important therapeutic option in subfertility. Cases of delayed puberty and hypogonadotropic hypogonadism are conditions where administration of kisspeptin shows promise. In addition, tropic action on LH release can be utilized in triggering ovulation in cases of intra-uterine Insemination and intra-uterine fertilization cycles. Further study of interaction of kisspeptin with other ligands like leptin and neurokinin B may reveal newer insights into regulation of reproduction and pave way for better therapeutic options for infertility.

Priya B Chittawar
Department of Obstetrics and Gynecology, Reproductive Medicine Unit, Sri Aurobindo Institute of Medical Sciences, Indore, Madhya Pradesh, India

Address for correspondence:
Dr. Priya Bhave Chittawar,
201, Adarsh, SAIMS Campus, Indore Ujjain State Highway, Indore-423111, Madhya Pradesh, India.
E-mail: priyabhave1@gmail.com

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Alcohol and fertility

Sir,

Alcohol is known to perturb the feedback mechanisms of hypothalamus–pituitary–gonadal (HPG) axis resulting in impairment of production and secretion of adequate quantity or potency of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to deterioration of Sertoli cells. The proteins required for spermatogenesis are damaged further resulting in Sertoli cell dysfunction. The Leydig cells are also affected and blood levels of testosterone are also reduced (due to decreased production and increased metabolic clearance). The consequence of reduced testosterone, LH, and FSH
translations to abnormal morphological development and maturation of spermatozoa, decreased rate of sperm production, gonadal atrophy, impotence, infertility, and reduced male secondary sexual characteristics. Moderate to heavy alcohol consumers can end up having “sertoli cell only” syndrome in advanced cases, indicating severe testicular damage.

Progressive deterioration in semen quality is linked to increasing alcohol intake. The influence of alcohol consumption on the quality of semen has a dose–effect and time–effect relationship. The sperm volume, vitality, and survival rate negatively correlate with the quantity of drinking. In a study on 100 alcoholics, only 12% showed normal semen parameters compared to 37% of the non-alcoholics. None of the heavy alcoholics showed normal semen parameters. Teratozoospermia, oligozoospermia, and their combined presence amongst alcoholics were double or more than that found in controls. Asthenozoospermia (sperm motility defects) is a very subtle, “early indicator” of reduction in the semen quality, which may get overlooked, and hence demands further exploration. Amount of alcohol intake per day positively correlates with all the three variables, asthenozoospermia, teratozoospermia, and oligozoospermia. A case report that followed up a male patient’s semen parameters for 6 years during heavy chronic alcohol intoxication showed a gradually progressive negative impact of alcohol. Isolated moderate teratozoospermia (initially) and oligoasthenoteratozoospermia (later) were noted, which worsened ultimately to cryptozoospermia and azoospermia. This reflected histologically as a maturation arrest of the germinal cells at the pachytene stage with no mature sperm cells. Upon alcohol withdrawal, a dramatic improvement of semen characteristics was noted within 3 months.

Prenatal exposure to alcohol may have a persisting adverse effect on Sertoli cells and sperm concentration. In a pregnancy cohort study (conducted in 1985–1987, followed up until 2005–2006) on 347 male offsprings, the sperm concentration decreased with increasing prenatal alcohol exposure. The adjusted mean sperm concentration among sons of mothers drinking ≥4.5 drinks per week during pregnancy was ~32% lower compared with those exposed to <1.0 drink per week. The semen volume and the total sperm count were also associated with prenatal alcohol exposure. It is postulated that prenatal alcohol exposure causes hypomethylation of the imprinted gene H19, which may contribute to the decreased spermatogenesis in the offspring.

High consumption of alcohol is known to increase the risk for infertility examinations and a significantly lower number of first and second partus. Alcohol consumption may also negatively impact time to pregnancy. Women consuming at least two alcoholic drinks a day are at a significantly increased risk of infertility and women consuming less than one alcoholic drink per day are at decreased risk compared with moderate consumers of alcohol (>1 to <2 drinks per day). A study pointed that alcohol dependence results in overall delayed reproduction in women, the effect being particularly strong for older women (73% decreased likelihood of first childbirth after age 29 compared to 40% decreased likelihood of first childbirth after age 24). Women trying to conceive sport a degree of oxidative stress secondary to a combination of lipid peroxidation, protein oxidation, and DNA damage. Moderate alcohol consumption is associated with decreased concentration of plasma antioxidants and increased concentration of isoprostanes.

Apart from alcohol, body mass index (BMI) and smoking negatively influence sperm concentration and motility. In a study, it was seen that while alcohol had a negative influence on the fertilization rate, and positive influence was seen with cereal consumption, the number of meals per day, and consumption of fruits and cereals.

To conclude, alcohol has a detrimental effect on both male and female fertility, and infertile couples especially warrant adequate counseling for strict alcohol abstinence.

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