

## The Impact of Nicotine on the Hypothalamic-Pituitary-Gonadal Axis and its Repercussion on the Gametes and Future Generation

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The endocrine system is a group of glands that maintain body homeostasis via the secretion of different hormones. Many of these hormones are regulated via various regulatory axes including the hypothalamic-pituitary-adrenal axis (HPA), the hypothalamic-pituitary-thyroid axis (HPT) and the hypothalamic-pituitary-gonadal axis (HPG). The HPG axis is activated by gonadotropin-releasing hormone (GnRH), which is released from the hypothalamus and then stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. FSH and LH stimulate the testes and ovaries to release sex hormones, estradiol in females and testosterone in males [1].

It is known that cigarette smoking is associated with a lot of diseases, including cancer, and also with decreased fertility in both males and females, however, little is known about the endocrine effects of nicotine and smoking [1]. Some studies have been showing that cigarette smoking stimulate the HPA axis and proceed via a central mechanism to stimulate CRH and/or arginine-vasopressin (AVP) which then leads to the release of ACTH from the anterior pituitary, resulting in hormonal alterations in men and women [2-4]. Nicotine is the major component of tobacco responsible for the stimulation of the HPA axis [1] and it is considered an endocrine disruptor [5,6].

Several studies have already shown that exposure to drugs, such as nicotine, during gestation can cause changes in the development of gonads, thus affecting offspring fertility [7,8].

The HPG axis is active in the midgestational foetus but silenced towards term because of the suppressive effects of placental hormones on the foetal hypothalamus and pituitary. This restraint is removed at birth, leading to reactivation of the axis and an increase in gonadotropin levels. Gonadotropin levels are high during the first 3 months of life but decrease towards the age of 6 months except for FSH levels in girls that remain elevated until 3 - 4 years of age. After this, the HPG axis remains quiescent until puberty. The postnatal gonadotropin surge results in gonadal activation in both sexes. However, the exact role of this transient activity for further reproductive development still remains uncertain, this period might be important for further reproductive health and disease [9]. As placental hormones (such as estriol, human placental lactogen and  $\beta$ -human chorionic gonadotropin) are negatively correlated with the number of cigarettes smoked per day and whereas placental hormones may affect fetal brain development [1], this may explain why some effects of nicotine on the HPG axis during pregnancy and lactation are just noticed in adult offspring.

Researches conducted by our working group verified that the exposure of rats to nicotine during the intrauterine and lactation phases causes morphological and functional changes in Leydig, Sertoli and germline cells [10,11], besides the reduction of the spermatozoa quality in the adult phase [12]. We have concluded that the harmful effect of nicotine on the levels of pituitary gonadotropins (mainly FSH) seems to be the triggering factor responsible for the structural and functional impairment of Sertoli cells, and consequently, and of germ cells and Leydig cells [11].

In women, nicotine may affect the meiotic division and maturation of oocytes. In addition, it has been shown that inhibition of ovarian growth in nicotine treated rats may be due to the lack of availability of pituitary gonadotrophins [13]. As in mammals the oocyte reserve is established at birth, the effect of exposure to cigarette and/or nicotine during gestation may, irreversibly, impair the offspring fertility. It has already been demonstrated that exposure to nicotine in the intrauterine and lactation stages compromises the development of the ovaries of the offspring by altering the proliferation of their somatic cells, reducing the number of follicles and, consequently, oocytes [8].

Although the effects of cigarette smoking are already well known within the scientific community and widespread by the media, 22.5% of the world's population smokes (around 1 billion people) [14] and a high rate of women maintains smoking during gestation and breast-feeding [15]. We cannot forget that nicotine can cross the placental membrane, concentrating on fetal tissues in amounts still larger than those observed in the mother, and it can be transferred through breast milk [16]. Therefore, considering that all the events that occur in the embryo development stage will determine the future fertility of the offspring, we must continue to improve our knowledge and create ways to protect the future generation of cigarette smoking damage.

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