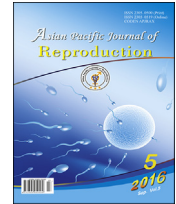


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## The important role of protamine in spermatogenesis and quality of sperm: A mini review

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## ABSTRACT

**Objective:** To prove that the decrease in the expression of protamine 2 affects the fertilization ability and the number of child production.**Methods:** During the development stage of elongating spermatids, human spermatozoa chromatin undergoes a complex transition where histone is extensively replaced by protamine. Histone substitution by protamine 1 and 2 plays a significant role in condensing chromatin required to induce the quality of potent spermatozoa. The substitution also has a key role in protecting spermatozoa from effects of free radicals which can degrade the spermatozoa quality.**Results:** The results revealed that protamine deficiency instigated a severe disruption of spermatogenesis affecting male infertility. In addition, the protamine expression disorder caused a decrease in number, motility, and morphology of spermatozoa.**Conclusion:** Our results of a study in mice confirmed that inhibin B injection caused a reduction in the expression of protamine 2 in cauda epididymis. It has implications in the decrease of motility, concentration, and spermatozoa viability so that it affects the fertilization ability and the number of child production.

## 1. Introduction

Spermatogenesis in mammals is a complicated process involving the division and differentiation of spermatogonial stem cells into mature spermatozoa. The spermatogenesis process consists of several phases, namely the mitosis proliferation of spermatogonial stem cells to produce spermatocytes, the division of spermatocyte meiosis to produce haploid round-spermatids, and the spermiogenesis or final stage involving the early stages of round spermatids to be mature elongated-spermatids [1].

During spermiogenesis, haploid spermatids undergo a series of changes in the composition and compactness of chromatin [2]. Meanwhile, in the round spermatid, the bond between deoxy nucleic acid (DNA)-histone will be replaced by transition proteins, whereas in elongated spermatids, the

transition protein will be replaced by protamine. Alterations from histone to protamine instigate spermatozoa chromatin condensation [3]. The process begins with changes of histone triggered by transition protein 1 and 2 and eventually replaced by protamine [4]. Alterations in transition proteins caused by protamine occur in the stage of elongating spermatid, and in humans, where 85% histone is replaced by protamine [2]. The content of protamine is indispensable for the final phase maturation of spermatozoa nucleus [5].

Facts reveal that a number of DNA in humans' mature spermatozoa binds to protamine [6]. In mammals, substituting histone by protamine is crucial in condensing and solidifying DNA into the spermatozoa head during spermatogenesis [7]. Somatic histone alterations by protamine result in a very compact DNA. It triggers the DNA in order to be protected from free radicals, such as free water and other compounds which are dissolved in water and causing the DNA damage [8]. Besides, alterations in a number of histones by protamine 1 (P1) and protamine 2 (P2) play a significant role in facilitating the compactness of chromatin package required for normal function of spermatozoa [9].

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The results showed that the increase in protamine expression leads to the deterioration in the spermatozoa quality and reduces the embryogenesis quality in couples which undergo in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) [10]; on the other hand, defects of protamine gene cause the disability of spermatozoa DNA and male infertility [7]. Torregrosa N *et al.* [11] found that the change of P1:P2 ratio within the spermatozoa leads to infertility. Moreover, [12] revealed the decrease in P2 expression in infertile male patients. It shows that P2 has a significant role in maintaining male's fertility.

## 2. Spermatozoa protamine

Protamine has a key role in spermatozoa chromatin condensation. Its deficiency causes negative effects on morphology and male fertility. It shows that protamine is required in the design and function of spermatozoa [13]. Protamine is a basic core protein contained in the head of spermatozoa [14] with a molecular weight about 5 kDa–8 kDa [15]. The content of protamine in the core of spermatozoa's head is vital to induce a compact spermatozoa chromatin condensation which is influential for male fertility [16].

In the core of spermatozoa's head, there are P1 and P2 [17]. P1 is synthesized as a mature protein, while P2 as a precursor [18], and they are located in the core of human's spermatozoa head [19]. P1 is found in spermatozoa of all mammals, while P2 spermatozoa is in mice, hamsters, stallions, some primates and humans [2]. Data presented that P1 and P2 are the abundant core proteins contained in the spermatozoa's head, and they function in packaging or protecting the male genome [20]. The results showed that the insufficiency of P1 or P2 causes infertility in mice, whereas P2 deficiency causes damage in spermatozoa's DNA and embryo mortality [21]. In general, these proteins are involved in various spermatogenesis mechanisms and sperm motility (Figure 1).

## 3. Role of protamine in spermatozoa's DNA abnormalities and disability

Fertilization involves a direct interaction amongst spermatozoa and oocytes, a merger of the cell membrane, and a union of

male and female gamete genome [22]. The process can thoroughly take place when supported by the compact spermatozoa DNA integrity [23]. Spermatozoa's DNA integrity plays a significant role in delivering accurate genetic information [24].

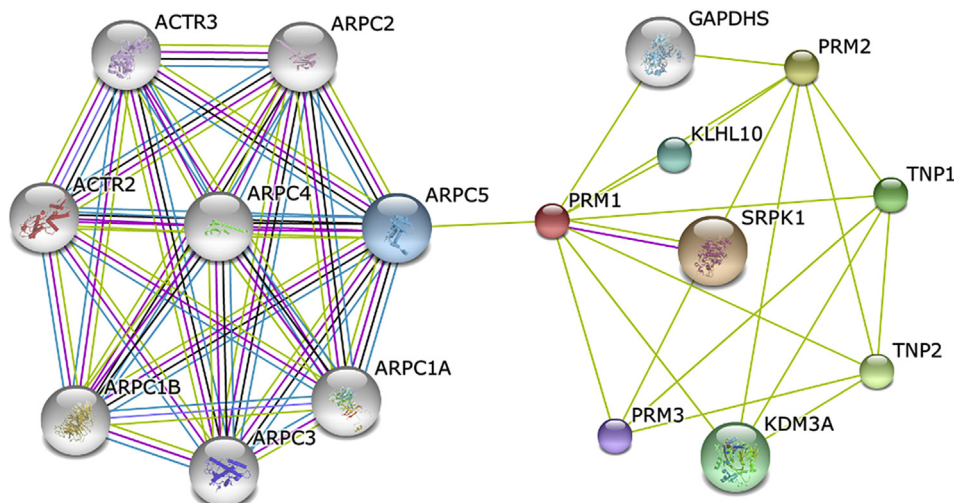
Spermatozoa's DNA must be well protected, such as by somatic cell's chromatin in order to be resistant toward nucleases [25]. Normally, spermatozoa's chromatin is well structured, the structure is compact with DNA content, and the nucleoprotein is heterogeneous [26]. The compactness of spermatozoa chromatin is due to the bonding between DNA and proteins of core spermatozoa, particularly the protamine [27]. Various abnormal forms of spermatozoa's chromatin or DNA damage result in male infertility [24]. Damages in spermatozoa's DNA are supposed to play a role as an infertility biomarker [28]. A number of causes why spermatozoa DNA damages are the protamine deficiency, DNA fragmentation, and abnormal chromatin composition [29].

Protamine plays an important role in male's normal fertility. The deficiency in P1 and P2 causes subfertile or severe infertile condition [10]. The results indicated that DNA damage in human spermatozoa produces the disruption of reproductive outcomes [30]. Damages in germ cells' DNA can increase mutations which ultimately lead to birth defects, genetic diseases, and cancer [31]. Damages in spermatozoa's DNA are considered to be closely related to the occurrence of male infertility and abnormal spermatogenesis [29]. An abnormal expression of protamine results in pathology connected with the spermatogenesis disruption [9].

## 4. Correlation between inhibin B and protamine

Inhibin is a glycoprotein hormone secreted by testis' Sertoli cells [32]. Inhibin B is significantly secreted by the Sertoli cells of testes [33], and the most important form of inhibin in male [34]. Inhibin B secretion by Sertoli cells is stimulated by follicle stimulating hormone (FSH) [35], whereas inhibin B regulates the FSH secretion through negative feedback regulatory [36]. A feedback control system of FSH is significantly regulated by inhibin B [37].

The bond between FSH and its receptor (FSH-R) in Sertoli cells will induce the activation of five molecular pathways,



**Figure 1.** Protein network protamine (PRM1).

PRM1 protein has linkage to several proteins accumulated in two biological mechanisms: regulation of actin filament polymerization (left cluster) and spermatogenesis (right cluster). Data was retrieved from String-DB.

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