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Original Article

Analysis of LH Receptor Expression in the Testes of Infertile Azoospermic Non-Obstructive (NOA) Men at High Serum Prolactin Concentrations

Ponco Birowo[1], Nurhuda Sahar[2], R. Muharam[3], Dwi Ari Pujianto[2], Rosalina Thuffi[4], Kusmardi Kusmardi[5-8,*], Conny Riana Tjempakasari[9]

Ponco Birowo[1], Nurhuda Sahar[2], R. Muharam[3], Dwi Ari Pujianto[2], Rosalina Thuffi[4], Kusmardi Kusmardi[5-8,*], Conny Riana Tjempakasari[9]

[1]*Department of Urology, Faculty of Medicine, Universitas Indonesia Jl. Salemba Raya No.6, Jakarta, 10430, Jakarta, Indonesia, 10430, INDONESIA.*

[2]*Department of Biology, Faculty of Medicine, University of Indonesia, Jl. Salemba Raya No.6, Jakarta, 10430, Jakarta, Indonesia, 10430, INDONESIA.*

[3]*Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia Jl. Salemba Raya No.6, Jakarta, 10430, Jakarta, Indonesia, 10430, INDONESIA.*

[4]*Magister Program Biomedical sciences, Faculty of Medicine, Universitas Indonesia Jl. Salemba Raya No.6, Jakarta, 10430, Jakarta, Indonesia, 10430, INDONESIA.*

[5]*Department of Anatomic Pathology, Faculty of Medicine, Universitas Indonesia, Jl. Salemba Raya No.6, Jakarta, 10430, Jakarta, Indonesia, 10430, INDONESIA.*

[6]*Drug Development Research Cluster, Indonesia Medical Educational and Research Institute, Jl. Salemba Raya No.6, Jakarta 10340, INDONESIA.*

[7]*Human Cancer Research Cluster, Indonesia Medical Educational and Research Institute, Jl. Salemba Raya No.6, Jakarta 10340, INDONESIA.*

[8]*Doctoral Programme Study of Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Jl. Salemba Raya No.6, Jakarta, 10430, INDONESIA.*

[9]*Departmen of Microbiology Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, INDONESIA.*

Correspondence

Kusmardi Kusmardi

Department of Anatomic Pathology, Doctoral Programme Study of Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Drug Development Research Cluster, Human Cancer Research Cluster, Indonesia Medical Educational and Research Institute, Jl. Salemba Raya No.6, Jakarta, 10430, Jakarta, Indonesia, 10430, INDONESIA.

E-mail: kusmardi.ms@ui.ac.id

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ABSTRACT

Background: Hyperprolactin is one of the endocrine disorders that causes male infertility (11%). The mechanism is not widely known; it is thought to occur through disruption of LH receptor activity on germ cells. **Objective:** The aim of study to compare the level of prolactin secretion with receptor expression in non-azoospermic infertile men (NOA). **Methods:** During the period from July 2019 to July 2021, 40 samples of testicular tissue and serum were obtained from infertile NOA men, aged 25-50 years who were recruited from Ciptomangunkusumo Hospital (RSCM) Jakarta, Faculty of Medicine, Universitas Indonesia and Bunda Hospital Jakarta. Subjects were divided into 4 groups based on prolactin levels (20 ng/ml, 20-50 ng/ml, 50-100 ng/ml and 100ng/ml). This group was tested for significance between groups and continued with a correlation test with the level of LH receptor expression. **Results:** ANOVA test showed a significant decrease in LH receptor expression between prolactin levels < 20 ng/mL with levels of 50-100 ng/ml and prolactin levels > 100 ng/ml ($P < 0.05$). Furthermore, the results of the correlation test showed a significant decrease between prolactin levels and LH receptor expression ($P < 0.05$). **Conclusion:** The higher the level of prolactin secretion in this sample, there is a decrease in LH receptor expression, so that testosterone production decreases and the spermatogenesis process will be disrupted.

Key words: Male infertility, Hyperprolactinemia, LH receptor expression, Non obstructive azoospermia (NOA).

BACKGROUND

Infertility is defined as the inability to get pregnant after a couple has been married for more than 1 year and has regular sexual intercourse without using contraceptives or drugs. Male factors contributed to the failure in half of infertility cases in these married couple.[1] Hyperprolactin is one of the endocrine disorders that can cause infertility in men, which is about 11% of men with oligospermia and azoospermia.[2-5] It is known that high prolactin levels inhibit pulsatile secretion of gonadotropin-releasing hormone, thereby leading to decreased pulsatile release of follicle-stimulating hormone, luteinizing hormone, and testosterone, which in turn interferes with spermatogenic cell development, sperm motility, and changes in sperm quality. directly affects spermatogenesis and steroidogenesis *via* prolactin receptors present in Sertoli cells and Leydig cells in the testes.[3]

Hyperprolactinemia also inhibits LH binding to LH receptors on Leydig cells which reduces testosterone synthesis and secretion.[6] Dabbous and Atkin recently reported that hyperprolactinemia induces abnormally high levels of adrenal steroid synthesis and secretion which further suppresses serum testosterone secretion.

The mechanism of action of prolactin on the hypothalamic-pituitary testicular axis occurs directly or indirectly through changes in the release of gonadotropins from the pituitary. Gubbay *et al* 2002, have identified prolactin receptors on Sertoli cells and Leydig cells.[7-9] Normal secretion of prolactin plays a role in testosterone synthesis through upregulation of LH receptors on Leydig cells. but its relationship to the physiology of reproductive physiology has not been elucidated. Research in rats shows that under normal conditions, endogenous prolactin plays a key role in maintaining the functional integrity of rat Leydig cells.[10] On the other hand, prolactin levels above normal cause testicular dysfunction, thereby interfering with the process of spermatogenesis. The mechanism of action of hyperprolactin in the process of spermatogenesis has not been fully elucidated. The results showed that injection of prolactin and administration of bromocriptine caused a decrease in the concentration of LH/hCG receptors on testicular cell membranes, without changing their binding affinity. On the other hand, Badal *et al.*[11] have reported an adverse effect of hyperprolactinemia on dopamine receptors that are downregulated and act independently of depressed levels of GnRH, FSH, LH, and TT to influence gonadal function in men with persistent erectile dysfunction. The inhibitory effect of high prolactin on the testes depends on the duration and intensity of the hyperprolactinemia. Although the role of prolactin is important for testicular function, however, observations suggest that high prolactin may have some inhibitory effects. The mechanism of azoospermia in infertile men with NOA cases with high prolactin levels may be due to impaired LH receptor expression in the testes. This study aims to analyze the relationship between high prolactin levels and the H-Score of LH receptor expression in testicular tissue.

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METHOD

Subject

The subjects in the study were NOA patients who were going to perform medical procedures at the FKUI Hospital and Bunda Jakarta Hospital. All patients enrolled in this study had signed an informed consent agreement, according to the protocol approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia. Testicular tissue was taken using the TESE method, and 1o mL of venous blood was taken. Subjects were divided into two groups, based on the results of the initial examination of FSH hormone levels, namely groups with normal FSH hormone levels and levels above 15 mIU/mL.

Collection of testicular tissue and blood

12 hours prior to the collection of testicular tissue and blood, the patient was fasted. Testicular tissue and blood were taken on the same day. Blood was taken with a volume of 10 CC from the cubital vein, centrifuged at 3000 rpm and stored at -20°C until all samples were measured. Testicular tissue was taken using the TESE procedure. After anesthesia, an incision is made in the epididymis, if no live sperm is found, the incision is continued in the middle of the scrotum, then tissue is taken in both testes, each of 1 gram. The TESE procedure is performed with the patient in the supine position under general or local anaesthesia. A vertical incision was made in the median scrotal area and the tunica vaginalis and an incision was made to the tunica vaginalis. opened to expose the tunica albuginea. Next, an incision is made to the tunica vaginalis. The left and right tunica albuginea were opened and then TESE was performed and the testicular tissue was taken, then the testes were sutured.

Hormone level measurement

Hormone levels of Prolactin, LH, FSH and Testosterone were measured by the Chemiluminescent Competitive Immunoassay (Siemens Diagnostic) method. Polyclonal antibodies that had been bound to the bead were incubated together with the second antibody which had been coated with alkaline phosphatase enzyme and serum samples, for 60 minutes at 37° C. During the incubation period, there is competition between steroids in serum and enzyme-labeled steroids to bind to antibodies that have been bound to the bead. The second antibody bound to the enzyme which did not react during the incubation period was removed during washing. The chemiluminescent substrate was then added and incubated again for 10 minutes. The yellow color that arises due to the hydrolysis of the alkaline phosphatase enzyme to the substrate is measured with a luminometer. Prior to examination, all serum samples and reagents were stored at minus -20°C until all samples were measured

Histological examination of testicular tissue

Thin, 4 m thick sections of testicular tissue in paraffin blocks were stained by the Hematoxylene-Eosin (HE) method. The staining results were read under a light microscope with a magnification of 400x. Each testicular tissue sample was performed on 5 seminiferous tubules. The examination was carried out by observing the development of germ cells in the seminiferous tubules.

Immunohistochemistry for LH receptor expression

Testicular tissue embedded in paraffin blocks was cut to a thickness of 4 mm, pasted onto Aurona's premium polysine-coated slides. The tissue was paraffinized in xylene twice, for 3 minutes each, followed by rehydration in graded alcohol series (96%, 80%, and 70%) for 5 minutes each and washed in running water. The slides were put into methanol liquid containing 3% H2O2 (endogenous blocking) for 10 minutes, washed in running water. Tissue antigen retrieval was used using the One-Step method from the Neopoly Polymer Detection Kit. The slides were put in a container containing Tris EDTH with a pH of 9, then heated using Retrieval Generation One BioGear at 98 ^{0} C for 15 minutes.[12] The slides were cooled and washed in phosphate buffered saline (PBS) and re-incubated with FSH receptor monoclonal antibody (cat.no. GTX100008 GeneTex) Dilution.50x at 4^{0}C for 24 hours and washed again with PBS solution.

The second antibody, universal polymer HRP was added and incubated for 30 minutes and washed in PBS solution for 5 minutes, then added DAB and washed in running water. The slides were stained by the hematoxylin-eosin (HE) method and washed with running water. The last step, the slides were immersed in graded alcohol solution (70%, 80%, and 96%) for 5 minutes and in xylene for 3 minutes each and covered with entelan.

Data collection

Each sample of immunohistochemical slides was observed under a microscope with a magnification of 400 x, and 5 fields of view were photographed randomly using a special camera on a microscope that was connected to a computer. Photos were taken using an Olympus CX23 confocal camera with 40 x objective magnification and IndoMicroview software. The results of the photos were analyzed using a plugin from the imageJ software, according Kusmardi *et al.*[13]

Statistical analysis

All measurement data are tabulated and adjusted according to their distribution, mean and ranges. prolaktin hormone levels and LH receptor expression values were evaluated for normal distribution by the Kolmogorov-Smirnov test. Differences in prolactin levels with LH receptor expression were tested by ANOVA, then Spearman's correlation test was performed. The significance is if the p value < 0.5.

RESULT

Subject clarification

During the period July 2019 to July 2021, 50 testicular tissue and serum samples were obtained from infertile NOA men, aged 25-50 years who were recruited from Ciptomangunkusumo Hospital (RSCM) Jakarta, Faculty of Medicine, University of Indonesia and Bunda Hospital. Jakarta. A total of 50 patients with NOA cases had measurements of serum prolactin hormone levels and immunohistochemical assessment of LH receptor expression from testicular tissue. Hormone levels were grouped into 4 levels, namely (< 20 ng/ml, 20-50 ng/ml, 50-100 ng/ml and > 100 ng/ml. from 42 samples. The average level of prolactin hormone for each level was 12.12 ng/ml, respectively. ml, 40.56ng/ml, 60.88 ng/ml and 116.50 ng/ml.

Immunohistochemical observation

The results of immunohistochemical staining of male testicular LH receptors are shown in Figure 1B. Positive expression values are indicated by the brown color that appears on the IHC slide preparation. The location of LH receptor expression was detected in germ cells and somatic cells contained in the seminiferous tubules with brown color intensity varying from weak to strong levels.

Qualitatively, LH receptor expression can be seen by comparing the intensity of the brown color in each field of view slide. LH receptor expression is detected through the brown color seen on the cell membrane. In Figure 1, you can see the difference in brown color that appears for each group. Figures 1A and 1B have a stronger brown color intensity, images 1C and 1D have moderate or weak brown intensity. All these color intensity results were grouped and statistically tested using ImageJ and SPSS, respectively.

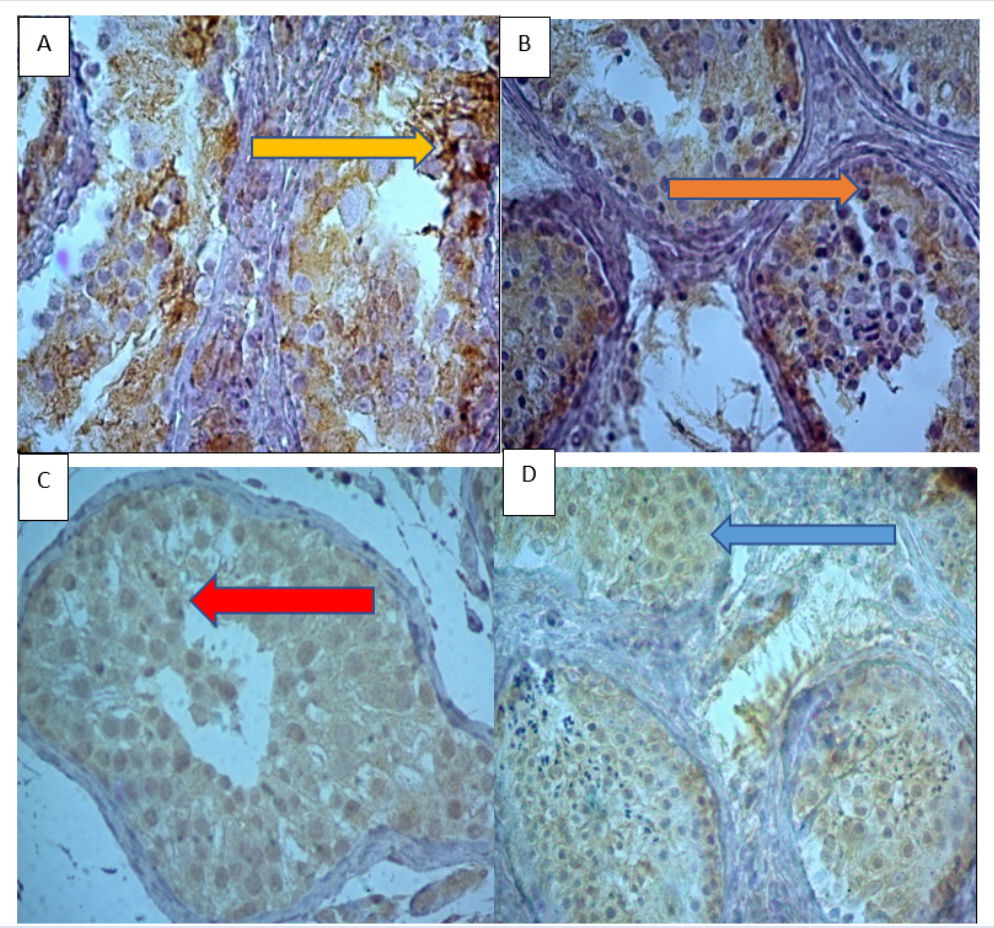

Figure 1: LH receptor expression in male testicular cells with NOA. A. group with prolactin levels <20 ng/ml. B, group with prolactin levels of 20-50 ng/ml. C, group with prolactin levels of 50-100 ng/ml and D, with prolactin levels > 100 ng/ml. Yellow arrow= Strong intensity. Brown arrow= strong and medium intensity. Red and blue arrow= medium and weak intensity.

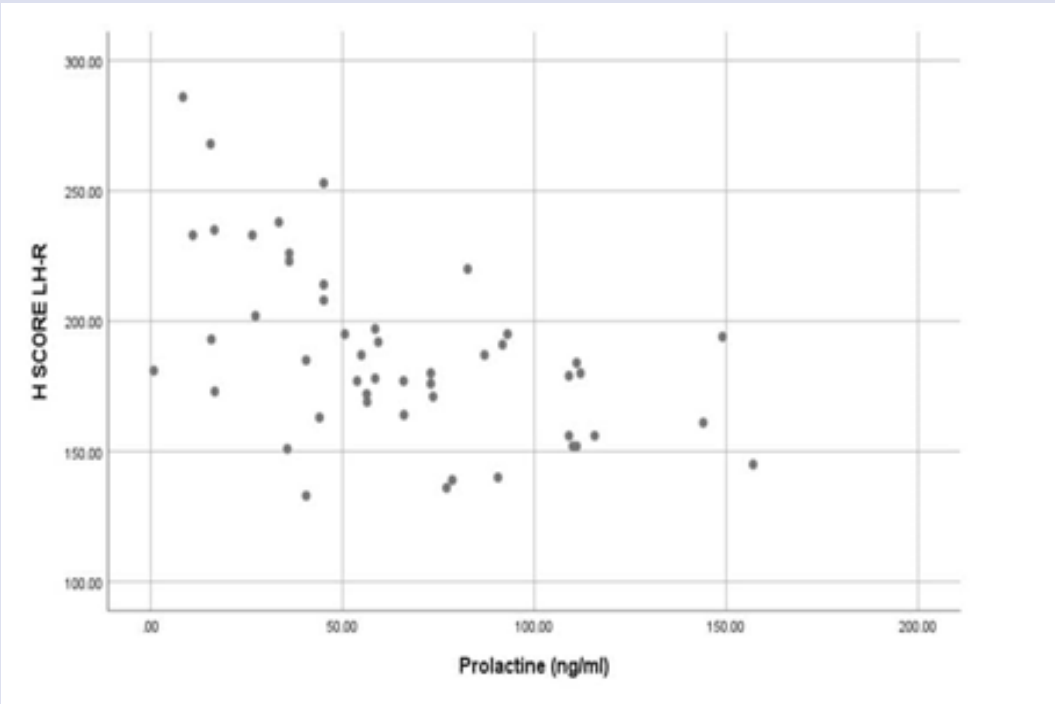

Figure 2: Spearman correlation test between prolactin level and H-Score LH receptor expression.

Table 1: Mean levels of prolactin and H-Score of LH receptor expression in human testicular tissue.

Level prolactin	n	H-Score LH	Prolactin level	P value
< 20 ng/ml	7	224.12	12.12	
20-50 ng/ml	12	198.16	40.56	0.39
50-100 ng/ml	20	170.00	60.88	0.03
>100 ng/ml	10	169.50	116.50	0.01

The quantification of all LH receptor expressions in the figure above was assessed by calculating the average H-Score for all groups. The results are shown in table 1. The Tukey HSD test showed that the H-Score value of LH receptor expression in the procatin group < 20 ng/ml with a prolactin level of 20-50 ng/ml was not significantly different (P = 0.39) with a prolactin level of 50-100 ng/ml. ml brrbrds (P = 0.03 and with prolactin > 100 ng//ml (P = 0.01). Furthermore, there was a significant difference between prolactin levels of 20-50 ng/ml and prolactin levels > 100 ng/ml (P = 0.025). prolactin levels of 50-100 ng/ml with prolactin levels > 100 ng/ml were significantly different (P = 0.03).

Correlation between prolactin levels and the H-Score value of LH receptor expression

Spearman correlation test was conducted to determine the relationship between the concentration of the hormone prolactin and the level of LH receptor expression in testicular tissue using the H-Score value. The results of the correlation test between prolactin levels and LH receptor expression showed a significant relationship (P = 0.01) with a negative correlation between the increase in prolactin levels and a decrease in LH receptor expression (p = 0.01, r = - 0.516). Thus, the higher serum prolactin levels in men with NOA, there was a decrease in LH receptor expression.

DISCUSSION

When secretion is normal in serum, prolactin acts synergistically with LH on Leydig cells to maintain the number of LH receptors on the cell surface, so that testosterone secretion and spermatogenesis are normal.[14-16] The results of other studies have shown that PRL has been shown to be responsible for the induction of Leydig cell proliferation and differentiation in hypophysectomized mice, maintenance of Leydig cell morphology, and upregulation of LH hormone receptor expression.[17,18] It is likely that prolactin plays a more prominent role in maintaining LH receptor and testosterone production, as with FSH, it may increase inhibin secretion from Sertoli cells, and thereby influence the negative feedback regulation of FSH secretion at the pituitary gland level. The role of prolactin to promote LH receptors on Leydig cells has been reported as in some rodents.[19] The effect of endogenous prolactin in modulating LH receptors has been evaluated only when the testes are well developed.[20,21] However, in cases of high serum prolactin (hyperprolactin) it is always associated with ologozoospermia or azoospermia and decreased testosterone levels (decreased libido), but the mechanism has not been elucidated. In this study, we would like to explain the mechanism of action of high prolactin in infertile men with cases of non-obstructive azoosprmia (NOA). Hyperprolactinemia in adult animals has a negative effect on testosterone production, a result hitherto thought to be largely a consequence of decreased LH secretion.[22,23] The pathological aspect of hyperprolactinemia is primarily a negative effect on testicular function. If high prolactin levels persist for a prolonged period of time it will affect testicular function, even if the response has a long latency. Loss of ligand-binding activity is closely related to loss of steady-state level of LHR 22 mRNA. The mechanism of testicular failure to produce sperm due to high prolactin cases in infertile men with NOA cases, we suspect that occurs through downregulation of LH receptors on germ cells. During ligand-induced down-regulation, LRBP expression is increased *via* the cAMP/PKA and ERK signaling pathways, is translocated to the translation ribosome, binds to LH receptor mRNA and forms an untranslatable ribonucleoprotein complex. This complex is then directed to the mRNA degradation machinery resulting in decreased LHR mRNA levels and cell surface expression of LH receptors.[24] Whether the mechanism of LH receptor downregulation due to high serum prolactin concentrations, needs further study.

In this study, the impact of high prolactin concentration on testicular tissue LH receptor expression by immunohistochemical technique in infertile men has been designed in the case of NOA. We show the results through the distribution and location of LH receptor expression in germ cells in immunohistochemical preparations (Figure 1). The brown color that appears in IHC preparations in the high prolactin level group indicates a low color intensity. This indicates that there has been a decrease in LH receptor expression in the high prolactin level group. Induction of hyperprolactin in rams has also been shown to reduce testosterone secretion by the developing testes.[25,26] Based on the H-Score value, a significant decrease in LH receptor expression began to occur in the prolactin level group > 50 ng/ml. The prolactin concentration of all samples in this study, 86% was above normal (> 20 ng/ml). The decrease in LH receptor expression was indicated by a weak brown color intensity in the preparation. Thus, high serum prolactin levels in infertile men with NOA decrease LH receptor expression. Reduced LH receptor expression can reduce the sensitivity of Leydig cells to LH, thereby affecting testosterone secretion and germ cell development in the testicular tubules.[27] Therefore, the negative effect of hyperprolactinemia on testosterone production in adult animals is partly direct and not solely due to a decrease in LH secretion. ng/ml. This suggests that in a dependent manner, hyperprolactin can affect testosterone biosynthesis *via* the LH receptor. The decrease in these receptors is also followed by a decrease in tissue responsiveness to the same stimulus.

Previous studies have reported testicular histopathology in infertile men with hyperprolactinemia reporting varying degrees of impaired spermatogenesis ranging from hypospermatogenesis to absence of germ cells.[28,29] The degree of damage that occurs appears to be related to the concentration of the hormone prolactin and may also be the result of prolonged exposure to high protein levels. When it comes to our data, there is a negative correlation between the level of prolactin secretion and decreased LH receptor expression. (r = - 0.516). In conclusion, the higher levels of prolactin secretion in this sample, the lower the expression of LH receptors, so that testosterone production decreases and the spermatogenesis process will be disrupted.

Our research does have limitations. Clinical data from the sample used in this study is known thoroughly, when they were exposed to high prolactin hormone levels and also there were no normal patient controls.

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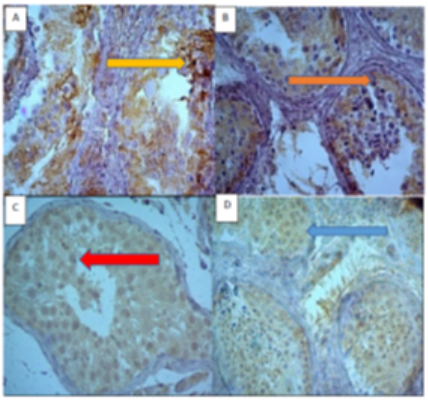
GRAPHICAL ABSTRACT

Infertile azoospermia non-obstructive (NOA) men

Testicular tissue

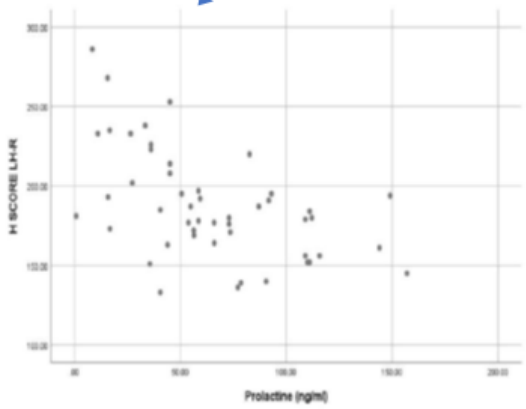


Blood

Table 1. Mean levels of prolactin and H-Score of LH receptor expression in human testicular tissue

Level prolactin	n	H-Score LH	Prolactine level	P value
< 20 ng/ml	7	224.12	12.12	
20-50 ng/ml	12	198.16	40.56	0.39
50-100 ng/ml	20	170.00	60.88	0.03
>100 ng/ml	10	169.50	116.50	0.01

H-Score of LH receptor expression



Correlation between prolactin levels and LH receptor

ABOUT AUTHORS

Ponco Birowo is a professor Urology at Department of Surgery, Division of Urology, Faculty of Medicine, Universitas Indonesia/ Cipto Mangukusumo Hospital. Research interest in ICSI, endocrinology.

Nurhuda Sahar is a lecturer and Researcher at Biology Reproductive, Faculty of Medicine, University Indonesia. Research Interest in Reproductive Endocrinology, Assisted Reproductive and Animal model for human Reproductive research.

R. Muharam is a Assoc. Prof at Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia.

Dwi Ari Pujianto is a Assoc. Prof. at Department of Medical Biology, Faculty of Medicine, Universitas Indonesia. Research interest in Molecular Human Reproduction, Human Genetics, Molecular Andrology.

Rosalina Thuffi is Post graduated from Masters Program in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia. Research interest: reproductive medicine, embryo cryopreservation, reproductive endocrinology.

Kusmardi Kusmardi is a Assoc. Prof. at Department of Anatomic Pathology, Drug Development Research Center Indonesian Medical Education and Research Institute, Human Cancer Research Center Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia. Research interest in Immunology, Pathology, Cancer Biology, Herbal Medicine, Biomedical Sciences, Oncology, Animal Model for Cancer Research, Biostatistics and Research Methodology.

Conny Riana Tjampakasari is a lecturer and Researcher at Department of Microbiology, Faculty of Medicine, Universitas Indonesia. Head of Bacteriology and Environment & Industrial Microbiology Division at Department of Microbiology, Faculty of Medicine, Universitas Indonesia. Research interest in Bacteriology, Mycology and Environment & Industrial Microbiology

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