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PROGNOSTIC ROLE OF SERUM FSH IN MANAGEMENT OF NON OBSTRUCTIVE AZOOSPERMIA: A PROSPECTIVE COHORT STUDY FROM SOUTHERN RAJASTHAN

Sharma K. R.	Assistant Prof. Medicine, Pacific Medical College And Hospital, Udaipur, Rajasthan, India.
Vishnoi Jagdish	Assistant Prof. Medicine, Pacific Medical College and Hospital, Udaipur, Rajasthan, India. *Corresponding Author
Sharma H.	Clinical Embryologist, IVF Centre, SMS Medical College, Jaipur, Rajasthan, India.
Verma S.	Medical Officer, Human Fertility Canter, Rnt Medical College, Udaipur, Rajasthan, India.
Bolya Y. K.	Medical Officer, Human Fertility Canter, Rnt Medical College, Udaipur, Rajasthan, India.

ABSTRACT

When newly married childless couples come to know that the male partner is without sperms (Azoospermia; 15% of infertile men), it is an unexpected terrible shock for them. The treating clinician and couples both remain in confused state and cannot decide the proper line of treatment. This unnecessary diagnostic delay further complicates the life of barren couples in many ways. The present study focuses on identifying and classifying the type of azoospermia and planning an appropriate course of management. A sample of 300 subjects was taken from Human Fertility Research Centre of RNT Medical College and Pacific Medical College & Hospital, Udaipur. This is the first study from the Southern Rajasthan in non obstructive azoospermic males. It was found that in the management of Category A, the Andrologist induces spermatogenesis with Gonadotrophins and in the cases of Category B, the Embryologist can perform either sperm retrieval from testicles or epididymis with advent of micromanipulation, and thus previously infertile men with azoospermia are given the chance to father their own children. It was also concluded that FSH plays a major role in identifying, classifying, early decision taking and management of azoospermia. Management procedures for pre-testicular and testicular azoospermia were stated. Implications and limitations of the study were drawn.

Introduction

Birth of a child is very much a spontaneous creation of nature, still more than 15% couples are childless and devoid of pleasure of parenthood. Among infertile couples male factor is solely responsible in about 20% of infertile couples and contributory in another 30-40%. Infertility is defined as the inability to become pregnant after 12 months of regular, unprotected intercourse [1]. Azoospermia [2] defined as complete absence of sperm in the ejaculate, is present in about 1% of all men [3] [4] and in approximately 15% of infertile men [5]. This group of patients represents a significant population in the field of male infertility[6].

Hypothalamic-pituitary-testicular (H-P-T) axis in adult male is responsible for spermatogenesis in seminiferous tubules of testes where FSH and Testosterone regulate germ cell production and survival, via intrinsic and extrinsic apoptotic mechanisms [7]. Out of them FSH is less pulsatile with longer half life and selective in imparting information, as it increases in damage to sperm producing units of testes which may result in total stoppage of sperms production (testicular azoospermia). While the low secretion from pituitary fails to stimulate spermatogonia to generate spermatocyte and ultimately causes no or very few precursors of spermatozoa which will be the cause of absence of sperms in the ejaculate, termed pre-testicular azoospermia [8].

If this H-P-T axis is working normally then FSH level is adequate and induction of spermatogenesis takes place normally but still there is absence of sperms on semen analysis then it will be termed post-testicular azoospermia. This is suggestive of exit block/outlet unit mal-developement [9].

The level of testosterone is not very much selective in imparting information in workup and management of azoospermia because of its pulsatile release and variability with the level of main initiator FSH[1] [10].

Hence on the basis of S. FSH level, azoospermia can be classified as:

A- Pre-testicular (FSH – less than normal)

B- Testicular (FSH – higher than normal)

C. Post-testicular (FSH – normal)

In category A and B as there is no obstruction in sperm outflow tract,so its management is usually less surgical and more medical. Hence a term non-obstructive azoospermia (NOA) is coined for them. Usually these conditions are associated with primary testicular failure (hypergonadotropic hypogonadism) or secondary testicular failure (hypogonadotropic hypogonadism) and this male population many times need replacement of testosterone with their infertility treatment. While in C category of azoospermia males are normogonadotropic normogonadic. Hence they do not require any supplementation of testosterone and management is by and large surgical procedure for making proper flow of sperm hence they are termed obstructive azoospermia (OA) [11].

In human body the male reproductive system regulates sex differentiation, virilisation and the hormonal changes that lead to puberty, spermatogenesis and fertility. For proper evaluation medical history, physical examination, semen analysis (primary **gold** standard test in male workup) and hormonal profile are essential [12]. Imaging studies, a genetic workup and a testicular biopsy (with cryopreservation) may augment the workup and management. Men with non-obstructive azoospermia should be offered genetic counselling before their spermatozoa are used because most common aneuploidy of male is Kleinfelter Syndrome (1 in 750 born male children)[1] [13].

Objectives

The major objectives of the present study are:

1. To identify diseased site in hypothalamic-pituitary-testicular (H-P-T) axis.
2. To categorize Azoospermia, e.g. non-obstructive azoospermia (NOA) and obstructive azoospermia (OA)
3. To plan out appropriate management options for infertile couples as early as possible.

Sample

The sample of 300 infertile males with azoospermia presenting to Human Fertility Research Centre of RNT Medical College and

Pacific Medical College & Hospital, Udaipur were included in the study, out of which N=12 (4%) were identified as Pre-testicular azoospermia and N= 204 (68%) as testicular azoospermia both clubbed as NOA while the rest of the sample, i.e. N=84 (24%) were the cases of Post-testicular azoospermia/exit block (OA).

All cases of vasectomy and other conditions where testes had been removed were excluded. Ethical clearance was taken from the ethical committees.

Methodology

300 azoospermic patients presented at the Human Fertility Research Centre of RNT Medical College and Pacific Medical College & Hospital, Udaipur, Rajasthan between January 2009 and June 2015 were included in the present study.This is the first study from the Southern Rajasthan in non obstructive azoospermic males. Their history, clinical examination, seminogram, endocrinal and additional investigations, e.g. testicular biopsy, karyotyping, etc. (according to the need and patients' acceptance) were performed.

A well designed questionnaire of infertile males attending the aforementioned OPDs was got filled including their history, clinical examination and semen analysis (twice, as per WHO criteria). The pellet received after 3000 revolutions per minute for 15 minutes was examined microscopically for the presence of sperms and their precursors. It was also found out if any systemic disorder was associated with azoospermia in background, like Kleinfelter Syndrome, (Figure- 1,) Kallman Syndrome (Figure-3), panhypopitutarism, hyperprolactenemia, hypothyroidism, etc. Patients' sexual maturity rating (SMR) was also calculated to know their hypogonadic status.

The final diagnosis of azoospermia was made when no spermatozoa could be detected on high powered microscopic examination of centrifugal seminal fluid on at least two occasions.

SMR of Normal and Hypogonadic Males

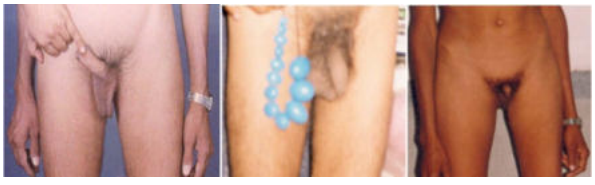


Figure- 1, Kleinfelter Syndrome Figure- 2, Normal male Figure-3, Kallman Syndrome

Interpretation / Results

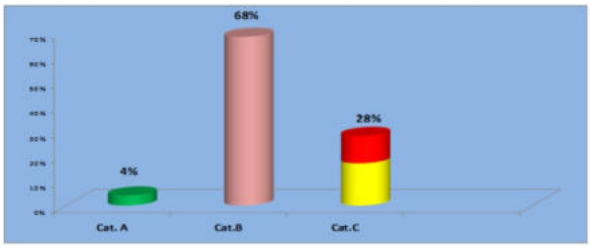
This study demonstrates that average age of presentation of Azoospermia was 33 years and Serum FSH level (normal – 1.4-18.1 miu/ml) was variable and related with testicular volume, where it was equal to or inversely proportional to spermatogenesis. Almost all cases in the category of NOA, testes were low in volume and usually atrophied. In our study :

(A) Pre-testicular Azoospermia (FSH < normal) – 4% with endocrinal abnormalities between hypothalamus, pituitary and testes, under-androgenised, hypogonadotropic-hypogonadic (HH). There was 1 Kallman Syndrome, 3 hypopituitirism and the rest 4 were idiopathic in aetiology.

(B) Testicular Azoospermia – 68% with intrinsic damage to testes and hypergonadotropic were again subdivided as : **(Graph1)**

(B1) – FSH < double of normal, small testes usually with haploid precursors, contributes 37% where common aetiology is viral orchititis, maturation arrest, testicular trauma, etc.

(B2) – FSH > double of normal, primary testicular failure with low testosterone were 31% where testes were grossly damaged Histologically diploid precursors of spermatogenesis or only sertoli cells were present. The majority of cases were Kleinfelter Syndrome (which is most common male sex



Graph1- Indicating the percentage of three types of Azoospermia out of the total N =300

Discussion

In non obstructive Azoospermia (NOA) both primary and secondary testicular failure may lead to bilateral testicular hypotrophy. Again serum FSH level will be able to distinguish between them. The FSH and Testosterone below normal with small soft testicles in hypogonadic males, who were 4% (12) in our study, are all medically treatable.

This pre-testicular azoospermia group (hypogonadotrophic hypogonadism) in our study we observed that its best to initiate the treatment with virilisation of males with the supplementation of long acting Testosterone, Testostrone Undecanoate 1 gram (4ml) on Day 1, Day 45, Day 90 and again after 3 months. Total maintenance dose will be such 4 injections in a year for life-long. It will develop and maintain secondary sexual characters in infertile hypogonadic males. Then induction of spermatogenesis done with the use of appropriate doses of Gonadotrophins (FSH, LH) or GnRH analogues. Various studies show that in more than 90% cases, spermatogenesis is initiated and the men have ejaculated sperms. However, therapy may take more than 6 months to be effective.

Testicular biopsy should not be performed in all the cases of azoospermia[13]. It is needed only when there is no distinct difference between testicular volume and endocrine profile to differentiate NOA from obstructive Azoospermia (OA).

In testicular azoospermia usually the testes are rudimentary where FSH is more than normal and testosterone is low (hypergonadotrophic hypogonadism)[14]. Then these patients are first virilized as mentioned above and then their infertility part is treated by assisted reproductive technique where testicular sperm extraction may be used to identify sperm (reported success up to 75%, mean 52%) which can then be processed for use in an ICSI programme. At present, the optimum way to identify these pockets of sperms is to perform an extensive, surgical dissection of the seminiferous tubules (testicular sperm extractions). Large sections of the seminiferous tubules of the testes are examined with an operating microscope. Those tubules which are larger in size are more likely to have spermatogenesis than smaller diameter tubules. The advantage of this technique over the regular random biopsy method is the ability to identify those areas of the seminiferous tubules, which are more likely to contain sperms before the tissue is removed from the testicle. Using this technique the chances of finding sperms is higher than the older technique of taking random testicular biopsies alone (in one series 63% compared to 45%), and where the procedure is laborious (surgical time may exceed 3 hours) the damage to the testicle is minimum due to the minimal amount of testis tissue eventually taken. ICSI pregnancy rates using sperm from a testicular sperm extraction programme are reported to be between 19% and 50% [15].

Patients with FSH more than double the normal are untreatable as their testes are atrophic (figure 4 a,b,c.) and hence they need counselling for gamete/ embryo donation or adoption.

Therefore, the present research is related to identifying, classifying and planning the management of pre-testicular and testicular

Azoospermia (NOA).

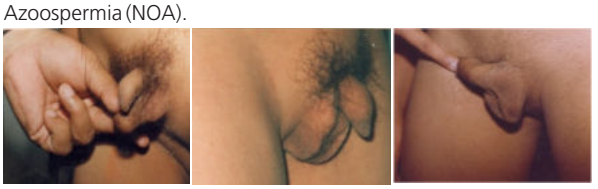


Figure-4(a&b), Atrophic testes of NOA; 4(c), Empty scrotal sacs of the patient

Conclusion

According to WHO nearly 85% couples conceive spontaneously within a year. Hence it is important to identify causes and search treatment options in the remaining more than 15% barren couples. In these cases we see, serum level of FSH to be very useful in their management and counselling [16].

In our study, out of 300 azoospermic males, in 216 (72%) serum FSH level were abnormal that are categorized as NOA while in remaining 84 (28%) serum FSH were normal, labelled as OA. Both the categories have totally different ways of management, as in NOA all hypogonadic males need virilization with testosterone replacement therapy (TRT). In all hypogonadotrophic hypogonadic cases successful induction of spermatogenesis can be done by the use of Gonadotrophins, where borderline high FSH cases are referred to IVF centres for assisted reproductive procedures like PESA, TESE.

Patients with FSH level more than double the normal, are untreatable and need counselling.

Implications/Suggestions

The high prevalence of NOA (72%) in South Rajasthan is much more as compared to the studies of other regions, which is likely to be the result of infections leading to viral orchititis in early childhood, which needs further evaluation. Larger prospective studies are required to improve sperm parameters and fertility rates in azoospermic males among infertile couples.

Limitations

Because of the financial constraints and insufficient available facilities, the genetic evaluation of Y-chromosome micro deletion analysis and FISH testing which provide more prognostic information in these men, was not possible.

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