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RESEARCH ARTICLE

Male Infertility – An Analysis in a Low Resource Setting

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ABSTRACT
Purpose: The prevalence of male subfertility is increasing among couples seeking fecundity in recent years. A prospective study was carried out in a gynaecological outpatient, to study the benefit of a low cost algorithm for determining the etiology of infertility in adult males with suboptimal semen parameters. **Materials and Methods:** Thirty one males, who had a sperm concentration less than 15 million/ml were considered in the study. The cost of diagnosis was kept low; not exceeding 150 US dollars. A similar algorithm of investigation was followed for all patients and medical treatment provided as per treatment guidelines. **Results:** A confirmed etiology could be determined in 7 patients, while a probable diagnosis was suggested in 21 males. Endocrino-metabolic causes were the most important etiological factors in our Indian population. Lifestyle diseases like obesity, insulin resistance were prominently found in the suspected acquired hypogonadotropic hypogonadism group. Medical treatment was provided to 24 subfertile males, and 64% showed good improvement in seminal count, after 3 months of therapy. Only selected patients were referred to higher teritiary centres, for specific interventions like sperm retrieval techniques, intracytoplasmic sperm injection of the female partner. **Conclusion:** This study proves that male subfertility can be managed in a low resource centre, with the help of a simple algorithm, with ease and proficiency, thereby reducing economic burden on these couples. Also, this analysis has helped us to ascertain the relative propensity of etiological factors among adult males with infertility ,in North India in the present time.

KEYWORDS: Luteinising Hormone (LH), Ultrasonography (USG), Follicle stimulating hormone (FSH), Serum Total Testosterone (TT), Testicular Microlithiasis (TM)

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INTRODUCTION

Male infertility remains a scary riddle for the obgyn specialist. However in a developing country all patients do not have access to advanced infertility centres, because of the distance and expense involved . The true incidence of male infertility is difficult to determine, because of wide variation in reports from different countries. However, roughly a suboptimal semen result has been found in about 30% to 50% couples. (1) This study was performed to apply a simple , cost effective algorithm to subfertile males with oligospermia (WHO criteria 2010) to establish the etiology and determine the usefulness of the plan for diagnosis and improvement in sperm count. [2]

MATERIALS AND METHODS

Inclusion criteria included, men in the age group of 20-40 years of age, with seminal count less than 15 million /ml, who desired fertility and were willing to come for follow up, for at least 3 months.

Exclusion criteria were applied to men above 40 years of age, those who had ejaculatory problems, could not provide semen sample by masturbation, or had anatomical anomalies with the penis.

This study was performed in low resource, semi urban setting, keeping the expense for etiological diagnosis of infertility between 100-150 USD. Patients were drawn from the outpatient department of a single gynaecologist. Semen analysis was done during investigation of the infertile couple and men with a semen count less than 15 million, were enrolled for the study. Only seminal count, i.e. one parameter of semen analysis was considered for analysis and further improvement determination.

The algorithm followed for ascertaining the cause of oligo/azospermia consisted of the following steps :-

- History
- General examination

- Local scrotal examination
- Ultrasonography of scrotum
- Blood sugar testing
- Endocrinal assays
- Karyotype

A careful history was taken, which included the age of puberty onset, occurrence of infections like mumps and tuberculosis, hernioplasty, history of crypto-orchidism and orchidopexy, occupational heat exposure, tobacco consumption, alcohol or drug abuse and trauma to genitalia.

On examination the patient's height, weight, body mass index, blood pressure, features of virilization and other signs of medical illness were recorded.

A local scrotal examination was performed, but ultrasound of scrotum was considered as final, for uniformity.

Endocrinal assays included blood sugar, luteinising hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone(TSH), serum prolactin, and total testosterone level. Serum estradiol determination was performed only in men who were overweight or obese. Karyotype was offered to all the patients.; but agreed by some , because of the high cost involved. A total of 31 adult males were analysed and followed up for a minimum of 3 months . A careful diagnosis was attempted and medical treatment was provided to 24 men. Semen analysis was performed at 3 months and some patients were followed up for 9 months .

RESULTS

The results in the present study, were determined after analysis of certain parameters.

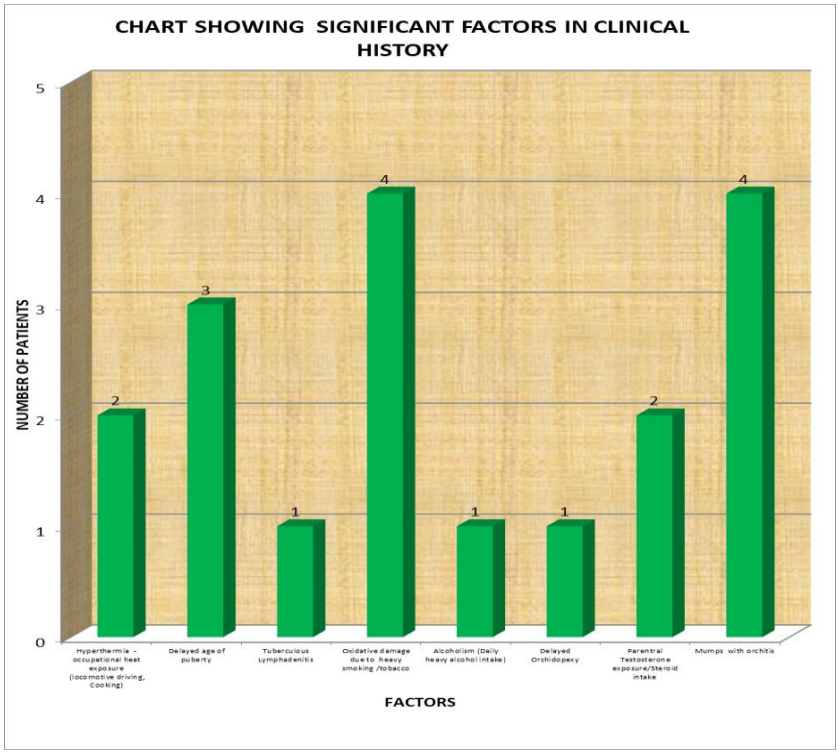
History

A careful history yielded fruitful results.

Table 1: Table showing number of patients with significant factors in history.

Hyperthermia - occupational heat exposure (locomotive driving, Cooking)	2
Delayed age of puberty	3
Tuberculous Lymphadenitis	1
Heavy smoking /tobacco	4
Alcoholism (Daily heavy alcohol intake)	1
Delayed Orchidopexy	1
Parentral Testosterone exposure/Steroid intake	2
Mumps with orchitis	4

Fig1.



Ultrasonography

Scrotal ultrasonography revealed abnormal findings in 26 patients. Suboptimal testicular size was seen in 24 of the 31 patients, enrolled in the study (normal testicular volume between 12 -19 cc). Varicocoele was evident in 11 patients on sonography, but only 1 patient had a palpable varicocoele on scrotal examination. Microlithiasis of testes was seen in one male patient. Hernia, hydrocoele, or epididymal abnormality were not reported in any of the males in the present study.

Table 2 : Table showing number of patients with abnormalities on ultrasound.

Scrotal abnormality	Number of patients
Suboptimal Testicular size	19
Varicocoele	11
Microlithiasis	1

Endocrinal Analysis

Endocrino-metabolic causes were found in 21 patients and 13 males were suspected to have hypogonadototropic hypoandrogenemia. One patient had congenital

hypogonadotropic hypogonadism, where magnetic resonance imaging was done and no intracranial space occupying lesion was found. Twelve patients had acquired suspected hypoandrogenemia due to metabolic conditions, like diabetes and elevated body mass index . Hypothyroidism was also present in two of these patients with acquired hypoandrogenemia. Magnetic resonance imaging was offered to all these patients, but patients ignored imaging, because of the expense involved, and were considered for trial of therapy after counselling.

Hypergonadotropic hypogonadism was found in 5 patients with low testosterone levels. These, 5 males had low total testosterone levels, with both raised LH and FSH, and hence treated as primary testicular infertility. One patient had low serum total testosterone levels, with raised LH, but normal FSH, and was thus considered as abnormal spermatogenesis.

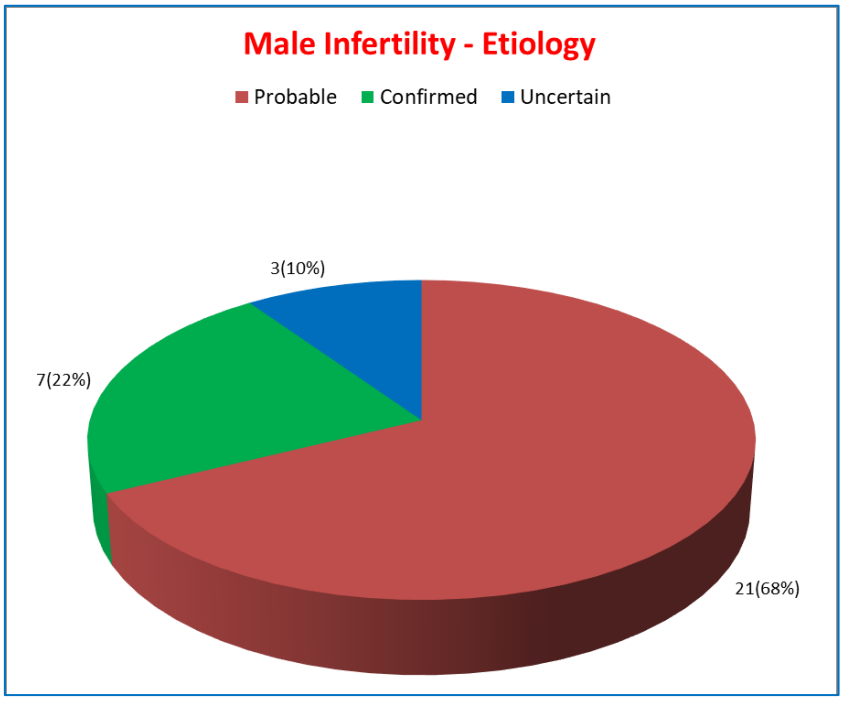
Mild hyperprolactinemia was found in two men, who refused imaging of pituitary gland, but insisted for medical therapy.

Cytogenetics

Karyotype study was offered to all patients , however only 18 patients got it done; while the rest declined because of the high cost involved . Sixteen patients with subfertility in this study were found to have normal karyotype (XY). Two patients with hypergonadotropic hypogonadism were found to have an abnormal karyotype i.e. Klinefelter syndrome (XXY). Both males with Klinefelter syndrome were azospermic, had very small testes, with testicular volume less than 2cc, and a total testosterone assay was less than 130 ng/ml.

Diagnosis

A diagnosis for cause of infertility was attempted after history, examination, ultrasonography, endocrinal assay determination and cytogenetics. The confirmed etiology for oligo-azospermia could be determined in 7 males, while a probable entity was suggested in 21 patients. In 3 subfertile males in this study, the cause remained uncertain. [Fig. 2]



- Confirmed etiology observed was seen as
  - Hypergonadotropic Hypogonadism - 5 patients
  - Abnormal spermatogenesis -1 patient
  - Congenital hypogonadotropic hypogonadism -1 patient.
  - Hyperprolactinemia – 2 patients
- Probable etiology
  - Suspected Hypogonadotropic hypogonadism was considered in 12 males with low testosterone and normal or suboptimal LH and FSH, where MRI was ignored by the patients.
  - Oxidative damage due to heavy smoking/alcoholism for more than 5 years was observed in 7 patients with subfertility.
  - Oxidative damage as a result of hyperthermia in 2 patients was considered as a probable cause of oligo-azospermia, owing to locomotive driving in 1 male,and delayed orchidopexy for crypto-orchidism in 1 patient .
- Uncertain etiology – The cause of subfertility could not be determined in 3 patients with this diagnostic algorithm.

Rare diseases observed in the study were :

Congenital Hypogonadotropic Hypogonadism--1 patient

Microlithiasis of testes -- 1 patient

Klinefelter syndrome – 2 patients

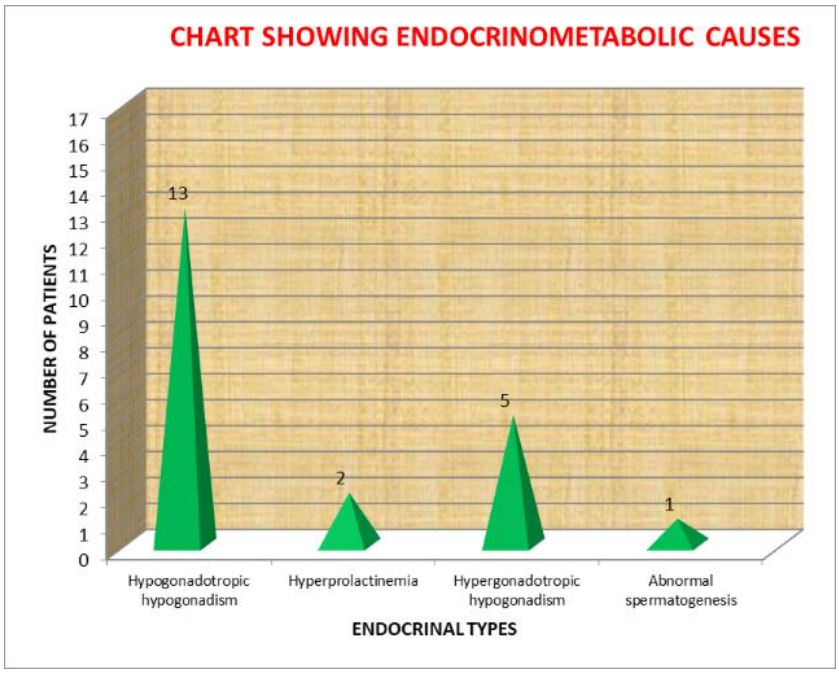
Treatment

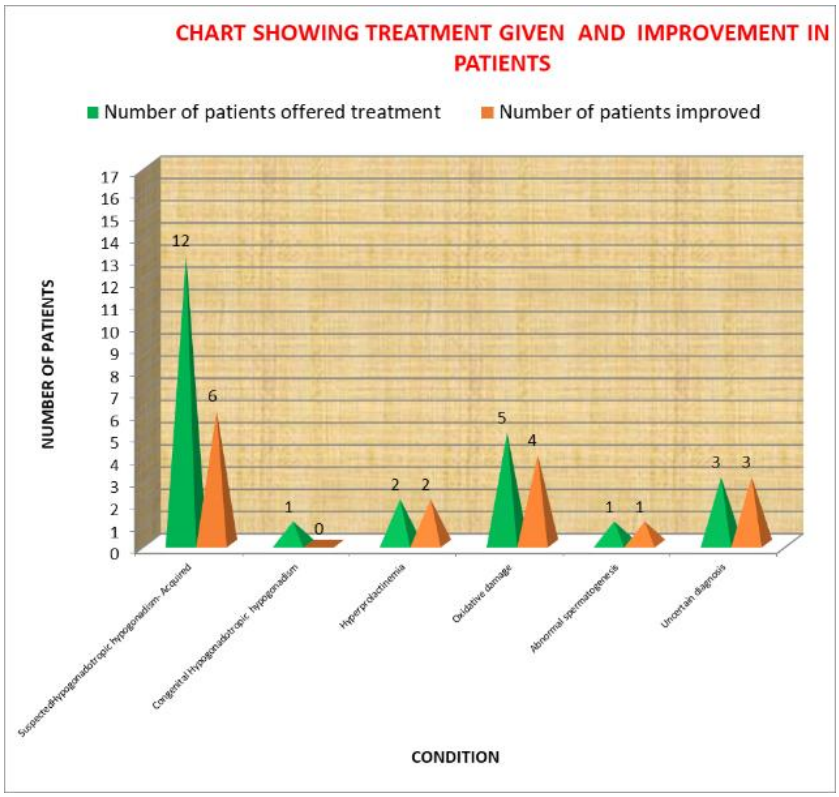
Patients with hypergonadotropic hypogonadism were not put on medical therapy and were considered for sperm donation. Medical treatment was offered to 24 patients and good improvement was observed in 16 patients (64%).

Table 3 : Table showing types of medical therapy given and improvement in patients

Condition	Number of patients offered treatment	Medical Treatment	Number of patients improved
Suspected Hypogonadotropic hypogonadism- acquired	12	Weight reduction, Anastrazole. Thyroxine, Metformin where required.	6
Congenital Hypogonadotropic hypogonadism	1	Gonadotrophins	0
Hyperprolactinemia	2	Cabergoline	2
Oxidative damage-probable	5	Antioxidant	4
Abnormal spermatogenesis	1	Antioxidant	1
Uncertain diagnosis	3	Antioxidant	3

Figure 4.





DISCUSSION

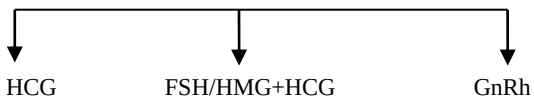
Acquired hypogonadotropic hypoandrogenemia constituted the largest category in the subfertile males analysed in this study, and was found in 12 of 31 i.e. 38.70% subjects. Elevated body mass index (overweight/obesity) was found in 9 men in this group. Diabetes mellitus, hypothyroidism, dyslipidemia were found in several men which were treated accordingly. Eight patients out of 9 with acquired hypoandrogenemia with raised body mass index, also had disturbed testosterone / estradiol ratio , which was found to be less than 10 . An aromatase inhibitor, anastrazole in a dose of 1 mg daily was also administered to them for 3 months. A monthly total testosterone and estradiol analysis was done. At the end of 3 months the testosterone/estradiol ratio was reversed in 6 of the 8 patients. There was an increase in the seminal count in all these 6 patients, hence anastrazole was observed to be effective in 74.6 % males. In a study done earlier, 32 subfertile men with BMI≥25kg/m^2 were treated with anastrazole and a significant improvement was seen in sperm concentration after 5 months of therapy. [3]

In one patient of acquired hypoandrogenemia with oligospermia, careful history taking revealed, that he was taking testosterone Injections for erectile dysfunction. This was interesting and should always be considered while interviewing subfertile males . This patient was treated with antioxidant and clomiphene citrate. The sperm concentration improved at 3 months and there was conception in the female partner as well.

Two men had hyperprolactinemia, who were treated with Cabergoline and showed marked improvement in seminal count.

Congenital hypogonadotropic hypogonadism was observed in one patient where low total testosterone level (28 ng/ml) was associated with LH and FSH <1miu/ml. In this patient on magnetic resonance imaging, no intracranial or pituitary focal lesion was found. This male did not have an olfactory abnormality and cytogenetics was normal(XY karyotype) . In this patient, puberty had been achieved earlier and had now come for management of azospermia. He was therefore considered for treatment with gonadotrophins, to improve semen parameters.

Treatment modalities for Congenital Hypogonadotropic Hypogonadism for inducing spermatogenesis.



- Human Chorionic Gonadotrophin (HCG) is the first line of treatment, given in a dose of 2000-5000 i.u, 2-3 times weekly.It acts on the leydig cells of testes and increases the testosterone level. Serum total testosterone is measured every month and dose is titrated to keep total testosterone in the range of 400-900ng/dl. Semen count is measured every month, after testosterone level becomes normal.
- Human menopausal gonadotrophin (HMG) or Pure Follicle stimulating hormone (FSH) in a dose 75-150 iu, twice a week is added to HCG after 6 months; if there is no improvement in spermatogenesis. These patients show improved seminal count in about 6-24 months of therapy
- GnRh can also be used in non responsive cases to deliver 2 hourly pulsatile doses, with a GnRh pump to enhance semen parameters .

Hypergonadotropic hypogonadism with primary testicular infertility was considered in 5 patients, where low testosterone was associated with elevated LH and FSH. Klinefelter (XXY) syndrome was observed in 2 of these patients, the incidence, being 1 in 500males, and is listed in the Orphanet journal of rare diseases.[6] However, in one patient with hypoandrogenemia , only raised LH and normal FSH, considered as having abnormal spermatogenesis was given antioxidant therapy . There was marked improvement in the seminal count, when determined at 3 months.

Testicular microlithiasis (TM) of scrotum was reported in one patient where hyperechoic opacities were seen in both testes on scrotal ultrasonogram. The initial sperm concentration in this male was 5million/ml and the testes were also suboptimal in size, measuring 5cc and 6 cc.

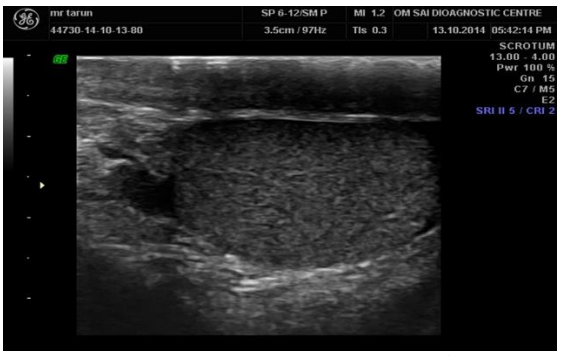


Fig5: Ultrasonogram showing Microlithiasis of Testes.

Microlithiasis of testes is a rare disorder with prevalence of 0.6%and 9%in symptomatic adults and 2.4%to 5.6% in adult males without symptoms.[4] Poor seminal counts are associated with TM in about 30-60%of patients, because of obstruction of seminferous ductules by calcium crystals with resulting secondary inflammation, increased intra-seminiferous pressure and an alteration in vascular supply to testicles. In a Chinese study, TM was associated with poor semen parameters in adult men with fertility intention. The extent of microlithiasis was found to be inversely correlating with semen parameters.[6]

TM was thought to have a propensity for future occurrence of malignancy and was analysed in a recent study. The authors analysed European data and concluded that regular follow up in TM is required in these patients , only when it is associated with other risk factors for testicular germ cell tumour.[7]

Mild varicocoele on ultrasonography was evident in 10 men. One person with clinically palpable varicocoele and confirmed on USG, was sent for laparoscopic ligation.

One patient had tuberculous lymphadenitis, with azospermia, thus suggesting that, in India tuberculosis is still relevant and should be inquired for during eliciting history in a subfertile male.

Five patients with suspected oxidative damage were treated with an antioxidant formulation containing Co-enzymeQ10 200mg (CoQ10), l-carnitine 1gm, superoxide dismutase, lycopene 5000i.u. as major constituents. The same formulation of antioxidant was used, whenever it

was administered. Four of the 5 patients with oxidative damage, when treated with antioxidants showed improvement in seminal count, which was very encouraging. In a recent analysis, data about benefits of antioxidants on sperm parameters was studied from papers published between 2004 – 2015. The authors concluded that a combination of antioxidants L- carnitine, CoQ10, Vitamin C and E, showed a definite improvement in semen parameters like concentration, motility and morphology.[8]

In the hypergonadotropic group, Klinefelter (XXY) syndrome was observed in 2 patients. Klinefelter has a potential risk for genetic transmission to the offspring and therefore these patients were advised donor intrauterine insemination of female partner or Intracytoplasmic sperm injection (ICSI) with donor semen. [10] Gene analysis was not included in the study; as it was a low budget analysis.

CONCLUSION

A simple algorithm as suggested in this study, has simplified the diagnosis and thereby management of infertility in the male partner, when a couple visits a gynaecologist. A specific diagnosis was attempted and treatment was provided depending upon the etiology. Medical treatment was offered to males with a treatable cause, such as those with an endocrinal dysfunction. Few selected patients with normal karyotype and sperm transport disorders were referred to a specific higher centre for therapies, such as sperm retrieval and storage. Males with abnormal karyotype were sent for donor insemination of female partner or ICSI. The study has been very reassuring in terms of eliciting the cause of subfertility, and improvement in semen count in a good percentage of patients, with a very minimal expense.

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AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

COMPETING INTERESTS

The authors declare no competing interests with this case.

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