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Systematic Review of Epidemiology and Etiology of Male Infertility

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Abstract: **Infertility affects an estimated 15% of couples globally, amounting to 48.5 million couples. Males are found to be solely responsible for 20-30% of infertility cases and contribute to 50% of cases overall. However, this number does not accurately represent all regions of the world. We performed a systematic review in accordance with the PRISMA guidelines. PubMed, Embase, and the Cochrane Library were searched for articles published before August 1, 2016, using the MeSH terms for a variety of epdimeiology, Etiology, causes and Male infertility, to demonstrate the evidence based for an enhanced understanding of male factor infertility prevalence in the world, and to review the different causes of fertility among men. We concluded, as such, data from a significant number of infertile individuals is never included, which may bias the data. Genetic factors that impact male factor infertility will provide valuable insights into the creation of targeted treatments for patients and the determination of the causes of idiopathic infertility. Male subfertility occurs commonly in patients that endocrinologists see in their practice: men with obesity, diabetes mellitus, Klinefelter syndrome and hypogonadotropism due hyperprolactinemia, opiates, or corticosteroids.**

Keywords: **Infertility affects, epdimeiology, Etiology, causes and Male infertility.**

1. INTRODUCTION

Male infertility is a multifactorial syndrome encompassing a wide variety of disorders. In more than half of infertile men, the cause of their infertility is unknown (idiopathic) and could be congenital or acquired [1]. The clinical definition of infertility used by the World Health Organization (WHO) is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" [2]

According to Sharlip, 50% of infertility cases are due to a solely female factor, pure male factor accounts for 20-30% of the problem, and the remaining 20-30% is due to a combination of both male and female factors [3]. The observed prevalence of infertility will evidently depend on the definition used. Whilst common clinical practice, and many studies, are based on a definition of failure to conceive after 12 months of unprotected intercourse, many authorities, based upon the distribution of fecundity observed in a 'normal' population, have defined infertility as the failure of a couple to conceive after 2 years of unprotected regular coital exposure[4]. It should be clear; however, that such a definition of 'infertility' serves to obscure the true complexity of the clinical situation. In reality, those couples who fail to achieve a pregnancy within 12-24 months include those who can be considered sterile (and who will never achieve a spontaneous pregnancy) and those who are more properly termed subfertile, and who have reduced fecundability (probability of achieving a pregnancy within one menstrual cycle) and hence a prolonged time to pregnancy [5,6]

Infertility in men can be diagnosed initially by semen analysis. Seminograms of infertile men may reveal many abnormal conditions, which include azoospermia, oligozoospermia, teratozoospermia, asthenozoospermia, necrospermia and pyospermia. The etiology of impaired sperm production and function can be related to factors acting at pre-testicular, post-testicular or directly at the testicular level. Primary testicular failure accounts for about 75% of all male factor

infertility. Genetic factors can be identified in about 15% of cases (congenital hypogonadotrophic hypogonadism, congenital absence of vas deferens, primitive testicular failure) [1]. In this review we overview the epidemiology, causes and most common clinical diagnosis of male infertility.

Objective:

We conducted this study which aimed to demonstrate the evidence based for an enhanced understanding of male factor infertility prevalence in the world, and to review the different causes of fertility among men.

2. METHODOLOGY

We performed a systematic review in accordance with the PRISMA guidelines. PubMed, Embase, and the Cochrane Library were searched for articles published before August 1, 2016, using the MeSH terms for a variety of epdimeiology, Etiology, causes and Male infertility. The search was restricted to human studies performed in men and published in English. Studies were included if they contained original data on a possible cause and prevalence of male infertility worldwide. Studies were considered only if they included an appropriate control group and/or comprehensive laboratory data. Due to heterogeneity in the literature, a qualitative analysis was performed.

3. RESULTS

- **Epidemiology of male infertility in worldwide:**

Our search has identified global study by **Ashok et al, 2015** [7] that overviewed the male infertility worldwide and they calculated global data that shows the percent of infertility that is attributable to males ranged between 20-70% (**Table 1**). Additionally, the percentage of infertile males in these countries varied from 2.5-12% (**Table 1**). The largest pockets of male infertility occurred in Central and Eastern Europe (8% to 12%) and Australia (8% to 9%). North America demonstrates rates of male infertility 4.5-6% [8]. While a calculated percentage reveals 4.5-6% of North American males are infertile, the Centers for Disease Control (CDC) estimates that 9.4% of males in the United States are infertile (**Table 1**) [8]. Sub-Saharan Africa is typically thought to have high rates of infertility; however, possibly due to underreporting, the rates shown in **Table 1** appear low.

Table.1: This table shows male infertility, based on various studies reported by Ashok et al,2015 [7] including male or female infertility globally

	Males that are reported infertile	Couples that are reported infertile	Couples in which the male factor is one of multiple factors involved
North America	4.5-6%[a]	15%	50%
Middle East	Unknown	Unknown	60%-70%[b]
Sub-Saharan Africa	2.5%-4.8%[a]	12.5%-16%	20-40%
Europe	7.5%[a]	15%	50% of all infertile couples
Australia	8%; 9%[b]	15%	40%
Central/Eastern Europe	8%-12%	20%	56%
Asia	Unknown	Unknown	37%
Latin America	Unknown	Unknown	52%
Africa	Unknown	Unknown	43%

[a]Percentages were calculated from data reported on female infertility, using the assumption that 50% of infertility cases are due to females only, and 20-30% are due to male factor only.

[b]Study states that 60-70% of all men presenting to IVF clinics in the Middle East have some involvement in the cause of infertility.

Table 4 extrapolates male data from pre-existing female data reported in a systematic analysis conducted by the WHO [10]. The rates of primary infertility, as reported by women, ranged from 1.5% to 2.6%, which were much lower than those reported over the course of 12 or more months. The male contribution to these rates of infertility ranged from 0.4% to

1.82% according to WHO estimates. Secondary infertility reported by women ranged from 7.2% to 18%, with the highest rates in Central and Eastern Europe, followed by South Asia at 12.2% and Sub-Saharan Africa at 11.65%[9]. This data consolidated information between 1990 and 2010, providing a 5-year projection of infertility. According to this data, the highest rates of infertility were concentrated through Africa and Central/Eastern Europe[9].

Table.2: A 5 year extrapolation as reported by a Systematic Analysis of 277 Health Surveys on Female infertility by Maya et al, 2012 [9]

	Primary infertility		Secondary infertility	
	Total 5 year infertility rate as reported by females a,b	**5 year Male factor infertility rate (calculated)**	**Total 5 year infertility rate as reported by females a,b**	**5 year Male factor infertility rate (calculated)**
Latin America	1.5%	0.78%[c]	7.5%	3.9%[c]
North	2.6%	1.56-1.82%[c]	7.2%	4.32-5.04%[c]
Sub-Saharan Africa	2%	0.4-0.8%[c]	11.6%	2.32-4.4%[c]
Central/Eastern Europe	2.2%	1.23%[c]	18%	10.03%[c]
South Asia	2.2%	0.81%[c]	12.2%	4.51%[c]
East Asia/Pacific	1.5%	0.56%[c]	11%	4.07%[c]
World	1.9%	0.38-0.57%[d]	10.5%	2.1-3.15%[d]

[a]Percentage of child-seeking women.

[b]Measured in 2010.

[c]Male data was calculated based on the various reported rates of male factor contribution to infertility cases in multiple studies.

[d]Male data for world was calculated based on the argument that while 50% of infertility is due to females, 20-30% is due to males.

Since we do not know the actual rates of infertility, most of the numbers shown are based on self-report, thus cover a wide range. Overall, by examining the available literature and consolidating the information, our data indicates that global rates of male infertility range from 2.5% to 12%, **Fig1** shows regions and estiated percantage of male infertlity [7].

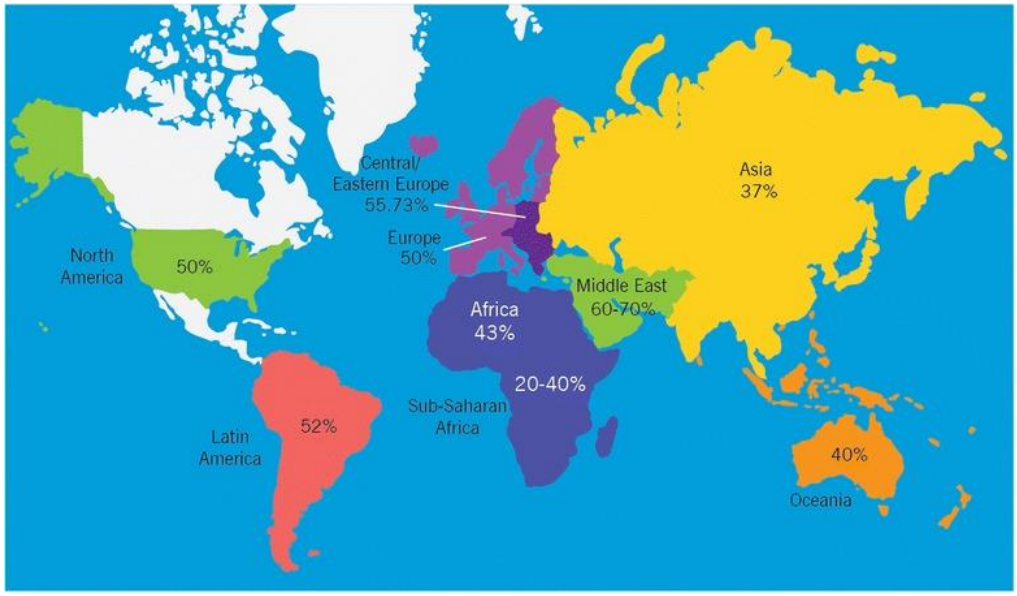

Fig.1: World map containing percentages of infertility cases per region that are due to male factor. This figure demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement [7].

- **Etiology of Male infertility:**

Genetic or molecular causes of male infertility:

In our systematic review we identified very important study [11] that demonstrated the genetics disorders causing Male infertility which they defined as a multifactorial syndrome encompassing a wide variety of disorders. In more than half of infertile men, the cause of their infertility is unknown (idiopathic) and could be congenital or acquired. Up to 10% of infertility cannot be explained medically **Fig.2** [11]

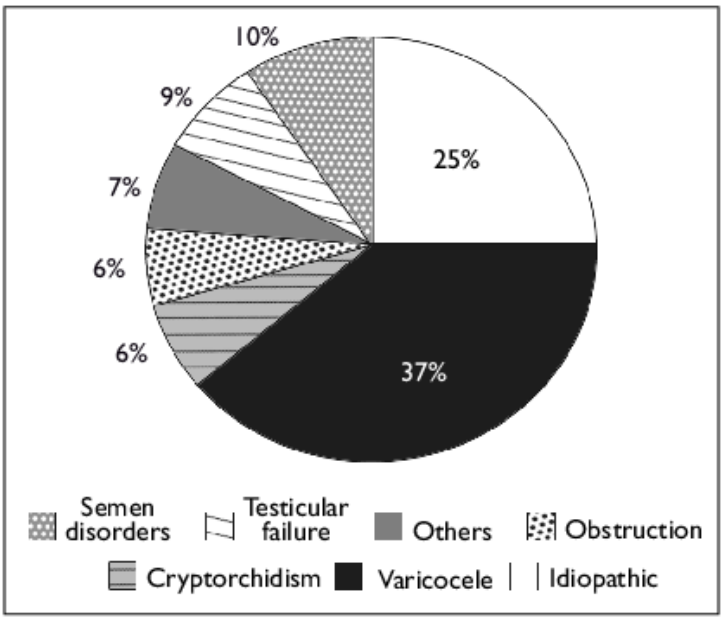

Fig.2: chart shows the distribution of male infertility disorders[11]

Genetic abnormalities have been identified in men with unexplained oligozoospermia and azoospermia, including numerical and structural chromosomal abnormalities [12]. Genetic factors involved in male infertility manifest as chromosomal disorders, mitochondrial DNA (mtDNA) mutations, monogenic disorders, multifactorial disorders and endocrine disorders of genetic origin.

Chromosomal disorders, Human male infertility is often related to chromosome abnormalities. Klinefelter syndrome (XXY) and specific translocations are well-established causes of male infertility[13]. Two important gene defects conclusively associated with spermatogenic failure are the point mutations in the androgen receptor and the cystic fibrosis transmembrane conductance regulator (CFTR) gene commonly associated with congenital vas deferens abnormalities[14]. The most frequent sperm chromosome anomaly in infertile males is diploidy, originated from either meiotic mutations or by a compromised testicular environment.

(a) Microdeletion of the Y chromosome:

One of the most significant pathogenetic defects associated with male infertility is microdeletions of the long arm of the Y chromosome (Yq). 13% of azoospermic men, 1%–7% of severely oligozoospermia men, 5% of men with severe primary testicular failure and with a sperm density of less than 5 million/ml showed Y chromosome microdeletion[13]. De novo deletions of Yq are one of the most frequently-occurring chromosomal abnormalities in men and are believed to arise from recombination events between long stretches of highly repetitive DNA sequences during meiosis or early pre-implantation development[15]. Accordingly, Y chromosome microdeletions contribute only marginally to the totality of human male infertility, but when present, the introduction of ICSI as an artificial reproduction technique may allow for the transmission of such mutations to the next generation[16].

(b) Mitochondrial DNA mutations:

Apart from some nuclear genes, mitochondria have their own genome, capable of producing many essential components of the respiratory chain that have a profound impact on sperm motility. The quality and quantity of sperm production may be affected greatly by both environmental and genetic factors. Sperm mitochondria play an important role in spermatozoa because of the high adenosine triphosphate (ATP) demand of these cells[17].

(c) Multifactorial disorders:

Multifactorial disorders result from mutations in multiple genes, often coupled with environmental causes. A mutation (C677T) in the gene, methylenetetrahydrofolate reductase (MTHFR), is known to increase susceptibility to various multifactorial disorders[18].

ABNORMALITIES OF SPERM COUNT AND MORPHOLOGY:

Various studies have been published supporting a decline in sperm quality or dismissing the same[19,20,21,22,23]. Analysis of retrospective data indicates that sperm counts may have declined in some parts of the world, but there seems to be geographical variations in the semen quality [24,25,26]. The reason for geographic variations in semen characteristics is not clear, but it may be due to environmental, nutritional, socioeconomic, or other unknown causes[27]. The decline in the semen quality coincides with an increasing incidence of abnormalities of the male genital tract including testicular cancer and cryptorchidism in various countries [28,29].

Sperm abnormalities are a critical factor in male infertility. These abnormalities include:

Abnormalities related to sperm count:

Azoospermia: Absence of sperm in seminal plasma

Low sperm count (oligozoospermia: <15 million sperms/mL) [30].

Abnormalities related to sperm motility:

The efficient passage of spermatozoa through the cervical mucus depends on rapid progressive motility, [31,32] that is, spermatozoa with a forward progression of at least 25 μm/s. A normal semen analysis must contain at least 50% grade A and B, progressively motile spermatozoa. Persistent poor motility is a predictor of failure in fertilization[33].

Abnormal sperm structure and shape (teratozoospermia):

For morphology of sperms, smears can be scored using the WHO classification, or by Kruger's strict criteria classification[34]. Morphology should be used along with other parameters, and not as an isolated parameter when determining clinical implications [35,36].

Defects in sperm transportation:

Defects in sperm transportation include obstruction of the ejaculatory tract and ejaculatory dysfunction such as retrograde ejaculation or anejaculation. An important cause of ejaculatory tract obstruction is congenital bilateral absence of the vasa deferentia (CBAVD). The majority (50–80%) of men with CBAVD have mutations of the cystic fibrosis transmembrane conductance regulator [37,38]. Although nearly all men with cystic fibrosis have CBAVD, CBAVD may be the only clinical manifestation of a CFTR gene mutation. All men with CBAVD should be tested for CFTR gene mutations.

Ejaculatory dysfunction disorders are common in men with neuropathy due to systemic disease such as diabetes mellitus or central nervous system diseases including spinal cord lesions [39]. Retrograde ejaculation into the bladder may cause male infertility [39]. It is often due to medications (eg, α-adrenergic blockers) dysautonomia, bladder neck surgery, or any disorder that affects the neuroregulation of the bladder neck and results in failure to close the bladder neck during ejaculation. Anejaculation is usually due to neurological disorders, but it is also associated with serotonin reuptake inhibitors used for the treatment of depression [40].

Endocrinopathies that are associated with reduced spermatogenesis:

Hypothalamopituitary disorders are the most common cause of male subfertility due to an endocrinopathy. Because normal secretion of both FSH and LH is required for quantitatively and qualitatively normal spermatogenesis, any disease that affects hypothalamic secretion of GnRH or pituitary secretion of FSH or LH will impair spermatogenesis. Tumors and infiltrative diseases of the hypothalamus, hyperprolactinemia, hemochromatosis, Kallmann syndrome, and idiopathic hypogonadotropic hypogonadism are classic endocrine causes of male subfertility. Opioids and anabolic androgenic steroids may also cause hypogonadotropism and subfertility.

Hypothyroidism and hyperthyroidism may disrupt normal spermatogenesis, but these disorders are usually clinically obvious when thyroid dysfunction is the sole or primary cause of male subfertility [41]. Adrenal disorders also may cause male subfertility via a variety of mechanisms. Cushing syndrome of any etiology may result in impaired testicular

steroidogenesis and spermatogenesis. Congenital adrenal hyperplasia is often associated with male subfertility due to disruption of normal GnRH and gonadotropin secretion and hypertrophy of testicular adrenal rests. Testicular adrenal rests represent embryological remnants of nests of adrenal cells that co-migrate with the gonad during fetal development. In men with undertreated congenital adrenal hyperplasia, continuously increased ACTH secretion causes adrenal rest hypertrophy. Large adrenal rests decrease spermatogenesis and sperm transport directly (via compression of the seminiferous tubules) and indirectly (by local testicular production of corticosteroids that impair testicular sex steroidogenesis and therefore impair spermatogenesis) [42].

Obesity may also contribute to hypogonadotropism and male subfertility [43,44,45]. Although data exist that obesity might inhibit normal testicular function directly or via insulin resistance, most of the evidence suggests that the primary mechanism of hypogonadism in obesity is the suppression of LH and FSH. Obesity-induced hypogonadotropic hypogonadism and subfertility might be due to increased aromatization of T to estradiol in the peripheral fat of obese men; estradiol is a potent inhibitor of LH secretion. Leptin resistance might contribute to obesity-induced hypogonadotropic hypogonadism. There is strong evidence from animal studies and some confirmation from a small number of human studies of leptin-deficient men that leptin is essential for normal male reproduction [46]. Specifically, leptin appears to act via the kisspeptin pathway to stimulate hypothalamic release of GnRH that in turn stimulates FSH and LH secretion from the pituitary. Because obesity is commonly associated with leptin resistance, it is likely that functional leptin deficiency contributes to obesity-induced hypogonadism.

4. CONCLUSION

Calculating regionally based male infertility rates is challenging for a number of reasons. First, population surveys generally interview couples or female partners of a couple who have unprotected intercourse and wish to have children. This is a very specific population. As such, data from a significant number of infertile individuals is never included, which may bias the data. Genetic factors that impact male factor infertility will provide valuable insights into the creation of targeted treatments for patients and the determination of the causes of idiopathic infertility. Male subfertility occurs commonly in patients that endocrinologists see in their practice: men with obesity, diabetes mellitus, Klinefelter syndrome and hypogonadotropism due hyperprolactinemia, opiates, or corticosteroids.

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