REVIEW ARTICLE

Causes and Risk Factors for Male-Factor Infertility in Nigeria: A Review

Sunny O. Abarikwu

Department of Chemical Sciences, Redeemer's University, Redemption Camp, Ogun State Nigeria

***For correspondence:** *Email: abarikwus@run.edu.ng; abarikwus@yahoo.com; Phone:* +234-80-30505464

Abstract

In recent times there has been a decline in the semen quality of young healthy men worldwide, with similar findings being reported in Nigeria. Although little is known about what is responsible for the decline in male sperm count worldwide, significant associations have been reported between impaired semen quality including sperm count, motility as well as morphology and exposures to heavy metals such as cadmium and lead, mycotoxins such as aflatoxins, pesticides, industrial chemicals and endocrine factors. In Nigeria, the problem is further compounded by a variety of factors such as sexually transmitted infections, genito-urinary tract infections/inflammations and deficiencies of dietary antioxidant nutrients, thereby increasing male-factor contribution to infertility in the population. In this article, we analyze data from different sources and present evidence of the possible etiology and risk factors for male-factor infertility in Nigeria. *(Afr J Reprod Health 2013; 17[4]: 150-166).*

Keywords: Semen quality, Nigeria, Male infertility, etiology, men

Résumé

Récemment, il y a eu une baisse de la qualité du sperme des jeunes hommes en bonne santé dans le monde et les résultats similaires ont été rapportés au Nigeria. Bien qu'on sache peu de ce qui est responsable de la baisse du nombre de spermatozoïdes chez les hommes dans le monde entier, l'on a rapporté des associations significatives entre la qualité du sperme affaibli, y compris le nombre de spermatozoïdes, la motilité aussi bien que la morphologie et l'exposition à des métaux lourds comme le cadmium et le plomb, les mycotoxines telles que les aflatoxines, les pesticides,les produits chimiques industriels et les facteurs endocriniens . En Afrique tropicale, comme le Nigeria, le problème est encore aggravé par une variété de facteurs tels que les infections sexuellement transmissibles, les infections des voies urogénitales / inflammations et les carences de nutriments antioxydants alimentaires, augmentant ainsi la contribution masculine à la stérilité chez la population nigériane. Dans cet article, nous essayons d'analyser les données provenant de nombreuses sources différentes sur l'étiologie de la stérilité masculine due à des paramètres du sperme affaibli chez les hommes nigérians. *(Afr J Reprod Health 2013; 17[4]: 150-166).*

Mots-clés: qualité de la semence, Nigeria, stérilité masculine, étiologie, hommes

Introduction

Male-factor infertility is a well-known health issue all over the world including Africa and other developing countries; it presents a particularly vexing clinical problem. It has been estimated that infertility of couples affects 10-15% of the general population[1]. The prevalent rate varies between and within countries. For instance, in the United Kingdom and the United States of America it is estimated to be 6% and 10% respectively[2]. In Denmark, it is estimated to be in the region of 15.7% (Schmidt et al., 1995)[3]. In Nigeria and some parts of sub-Saharan Africa including the Republic of Sudan and Cameroon, infertility rate could exceed 30%[4,5,6]. Some studies reported in South-eastern Nigeria, have demonstrated a 65% and 35% prevalent rate for primary and secondary infertility respectively (Table 1)[7]. Similarly, some countries, most notably Kenya, Gabon, Botswana, Zimbabwe and many other African countries, have shown a trend toward lower fertility[4,8,910]. The high

level of infertility in Africa is due largely to reproductive tract infections which may be associated with abnormal semen parameters and low sperm count[2,7,8]. In about 60% of all couples experiencing infertility, male factor is responsible in about 40% of the couples[9]. The male factor is associated with a greater percentage of cases of primary rather than secondary infertility[9]. This was reported to be as high as 59% in France[11], 35% in Nigeria[1], 26%–32 % in the UK and Kashmir Valley in India, and about 36% in South Africa, Indonesia and Finland[12,13].

Infertility is a problem of public health importance in Nigeria and many other developing nations because of its high prevalence and its serious social implications on affected couples and families. The public health implications are even greater when one considers that these conditions represent the consequence of other disease problems, each of which may have additional risks to personal health for both couples and place additional burdens on the health service[8]. In addition, infertility leading to depopulation of some areas limits the social and economic development of a region. When efforts to have children by infertile couples are unsuccessful, feelings of helplessness, frustration and despair are common; it can be a major life crisis for many couples. They go through enormous emotional crisis and psychological distress, as their friends and peers begin to have children. It is now generally accepted that male factor infertility is equally as important as the female factor. In this review article on male factor infertility among Nigeria males, the causes of infertility in the male population are analyzed.

Table 1: Type of infertility according to aetiological factors in infertile Nigerian couples

Aetiological factor	Primary infertility no. (%)	Secondary infertility no. (%)	Total no. (%)
Male only	91 (68.4%)	42 (31.6%)	133 (42.4%)
Female only	49 (60.5%)	32 (39.5%)	81 (25.8%)
Both partners	43 (66.2%)	22 (33.8%)	65 (20.7%)
Unexplained	21 (60.0%)	14 (40.0%)	35 (11.1%)
Total	204 (65.0%)	110 (35.0%)	314 (100.0%)

Source: Ikechebelu et al[7]

Evidence for Impaired Male Reproductive Health Worldwide

Historic data showed that the bulk of young men in the 1940s had sperm counts far above 40 million per ml with averages higher than 100 million per ml. A semen sample should ideally contain more than 40 million sperm per ml in order to be considered normal[14]. World Health Organization guidelines suggest that the cut off value for a normal semen sample should be 20 million sperm per ejaculate, with 50% motility and 60% normal morphology. These indicate that if the concentration is less than 20 million sperm per milliliter of ejaculate, fertility may be impaired. Notwithstanding, if the sperm show adequate forward motility concentrations as low as 5 to 10 million can produce a pregnancy[15]. Hence, some andrologists have suggested a lower limit of normal of 10-15 million per mil[14]. On the contrary, others have suggested 48 million per ml and 55 million per ml, as the lowest values of the normal range for sperm counts[14] .Based on data available in the literature on sperm count, only a small proportion of males will have sperm values that satisfy these ideal figures in today's Western industrialized countries. Not only are sperm counts decreasing, the proportion of sperm with abnormal morphology and reduced motility is also increasing. For example, the proportion of sperm with abnormal morphology increased (from 26% to 45%) and sperm motility decreased[16] in a Danish study while in Oslo, Norway, the proportion of abnormal sperm rose from 40% to 59% between 1966 and 1986[17]. A Belgian study also found that the proportion of sperm with normal morphology decreased from 39.2% in the period 1977-1980 to 26.6% in 1990-1995 and their mean percentage motility decreased from 52.7 to 31.7%[18]. Some studies have suggested that the semen quality of sperm of young men in Northern Europe is declining[19]. Other reports have confirmed the presence of extraordinarily poor semen quality among otherwise healthy young men in the general population[20].

Carlsen and colleagues first raised the possibility of a substantial fall in male fertility levels in 1992. They reported that sperm concentration in healthy men appeared to have

dropped from 113 million/ml in 1940 to 66 million/ml in 1990[21]. Carlsen data showed that sperm count declined to 71.2 million/ml in Ibadan, Nigeria,[22] 54.6 million/ml in Lagos, Nigeria,[23] 65.0 million/ml in Salem, Libya,[24] 66.9 million/ml in Dar Es salaam, Tanzania[25] and 57.4 million/ml in Copenhagen, Denmark[26]. Subsequent studies have confirmed and strengthened Carlsen's findings (Table 2).

Table 2: Reports on the sperm counts of fertile men in different countries of the world in five (5) decades

Author and Year of study/publication	Country of Study	No. of men included	Mean sperm concentration (× 10^6 per ml)
Hotchkiss et al[104]	US	200	120.6
Macleod and Heim[105]	US	100	134.0
Macleod and Gold[106]	US	1000	107.0
Nelson and Bunge[107]	US	340	40.1
Rehan et al[108]	US	1300	79.0
Sturde et al[109]	Germany	100	74.4
Bahamondes et al[110]	Brazil	185	67.6
Ladipo[223]	Nigeria	53	71.2
Aabyholm[111]	Norway	51	89.0
Sheriff [24]	Libya	1500	65.0
Wang et al [112]	Hong Kong	1239	83.0
Osegbe et al[23]	Nigeria	100	54.7
Chan and Wang[113]	Hong Kong	36	62.4
Kirei[25]	Tanzania	120	66.9
Barrat et al[114]	UK	49	73.0
Pol et al [115]	France	1222	77.7
Rehan[108]	Pakistan	200	58.21
Fisch et al[116]	US	221	72.7
Fisch et al[116]	US	662	100.8
Benshushan et al[117]	Israel	188	69.9
Anderson et al[118]	Denmark	708	57.4
Selevan et al[119]	Czech Republic	272	61.2

A survey of 1,350 sperm donors in Paris found a decline in sperm counts by around 2% each year over the past 23 years with total decline of 32% and with younger men having the poorest-quality semen[27]. Similar studies have also found that sperm counts in the United States dropped by about 25% during the 1980s[28] and in Denmark dropped by about 25% between 1952 and 1972[29]. In another study at the University Hospital in Ghent, Belgium, researchers found that sperm counts among sperm donors had declined to about 10 million per ml between 1977 and 1994[18]. Similarly at the Scotland's Centre for Reproductive Biology in Edinburgh, Stewart Irvine reported a 40% decline among sperm donors when sperm counts of men born in the 1940s was compared with men born in the late 1960s[29]. In a more extensive re-analysis of the Carlsen data, Swan et al. confirmed a significant mean sperm count decline of 1.5% per year in USA between 1938 and 1988, and of 3.1% per year in Europe between 1971 and 1990[30]. The incidence of male reproductive disorders such as testicular cancer, cryptochidism, hypospadias have increased as much as 3 or 4 times since the 1940s[31]. The concern about this adverse trend in male reproductive health is that semen samples where the concentration of sperms is below 40 million per ml may be associated with longer time to conception or even subfertility, and low sperm count where the concentration of sperms is below 15 million per ml may be associated with higher risk of infertility. This downward trend in sperm quality does not augur well for male fertility in future.

Defining Infertility

Infertility is typically defined as failure to conceive within a certain period of time. For the male, this definition is particularly problematic, as it relies on an outcome for his female partner, who may have reproductive issues of her own. *Fecundability is* the term used for the probability of a woman in a sexually active couple becoming pregnant per menstrual cycle without contraception. It is customary to define infertility clinically as the inability of a couple trying to conceive to do so within one year. Infertility can be classified as primary infertility when no pregnancy has ever occurred or secondary if it occurred after one or more pregnancies. Approximately 15% of couples attempting their first conception meet with a failure, and another 10% face secondary infertility[32]. Data available over the past 20 years reveal that in approximately 30%-50% of the cases of infertility, the cause is found in the man alone, and in another 20%, the causes are found in both[33] and in 50%-70%, the causes are found in the female alone[1]. Experience shows that many of these supposedly "infertile" couples will eventually conceive, even without

treatment. For example, 38% of couples attending an infertility clinic in India conceived before any treatment began, and another 27% conceived before their treatment was completed[34]. The difficulty inherent in defining infertility in this manner is obvious: some couples without reproductive dysfunction who wish to conceive fail to do so probably due to inadequate coital exposure or timing, while others have reproductive-system dysfunction that prevents conception (Table 3). If a good assay were available for male reproductive function, independent of the female, a practical definition of male infertility would be "the condition of the subset of males with a positive assay within the set of couples that fail to conceive within one year." Such an assay does not currently exist.

Table 3: Causes of infertility among male and female partners of infertile Nigerian marriages over a five-year period (2001-2005)

Female causes of infertility and associated findings	Number of patients (%)	Male causes of infertility and associated findings	Number of patients (%)
Tubular damage/Chronic pelvic inflammatory disease	196 (45.1)	Genital infections	78 (34.7)
Unexplained infertility	109 (25.1)	Testicular failure	73 (32.4)
Failure of ovulation	63 (14.5)	Varicoceles	46 (20.4)
Co-existing uterine fibroids	32 (7.4)	Coital failure	15 (6.7)
Co-existing ovarian cysts	16 (3.7)	Congenital causes	8 (3.6)
Non-specific endometritis	9 (2.1)	Testicular torsion	4 (1.8)
Tuberculous endometritis	5 (1.1)	Heat atrophy	1 (0.4)
Endometriosis	5 (1.1)	Antisperm antibodies	22 out of 50*
Male/Female causes	90 (12) (out of 750)		
Antisperm antibodies	1 out of 5 (20%)		

Adapted from Ekwere et al[1]
* Positive by Slide Agglutination Techniques (SAT), and Gelatin Agglutination Technique (GAT)

Male-factor infertility in Nigeria: What could be responsible for Seminal Quality Abnormality?

The rate of infertility in Nigeria was put at 11%[9]. The true figure could be much higher because Nigerian gynecologists frequently report that infertility cases constitute between 60 and 70% of their consultations in tertiary health institutions[35]. It is reported that up to 30% of Nigerian couples may have difficulty in conceiving a child after two years of regular unprotected sexual intercourse[6]. The most comprehensive study of infertility[36] a WHO study of 5,800 infertile couples seeking help at 33 medical centers in 22 developed and developing countries-found that female causes accounted for between 25 to 37% of infertility worldwide (with larger proportions in sub-Saharan Africa and Southeast Asia), male causes accounted for between 8 to 22%, and both male and female causes accounted for between 21 to 38%. In contrast to the results reported in the WHO study, a positive male factor alone was found in 42.4% of the couples in the Nigerian cohort, and in 25.8%, the female alone appeared to be responsible. A combination of male and female factors was found in 20.7% of the couples, while the cause of infertility was unexplained in 11.1% (Table 1)[7]. In another study, 42.5% (171) of the subjects had a sperm count of less than 20 million per ml; 13.9% (56) of the subjects had azoospermia, while 53.2% (214) had sperm motility of less than 50%[37]. The male factor contribution to infertility in these Nigerian populations seems to be very high. Similarly, at the Gynaecologic Out-patient Clinic of Ogun State University Teaching Hospital, Sagamu, Southwest Nigeria, the male factor contribution to the incidence of infertility was 26.8%, female factor was 51.8% and both male

and female factors were contributory in 21.4% cases and the incidence of infertility was found to be 14.8%[38]. The results of the semen analysis of one thousand, one hundred and ten (1,110) males attending an infertility clinic at the University of Nigeria Teaching Hospital (UNTH) Enugu, Eastern Nigeria showed that the aetiology of male infertility in the population seem to be unrelated to sperm volume but related to sperm count, motility and morphology[39].

A follow-up community-based study of 17 males, whose female partners had been reported as being infertile, showed that eight males (47%) had severe semen abnormalities that could have been responsible for the infertility reported in their female partners[40]. Other studies have also shown that azoospermia was present in 6.6% of males attending a general infertility clinic and 35% in those attending male infertility clinics[41]. The failure of spermatogenesis and obstruction of the ductal system particularly the vas deferens were reported as the causes of the azoospermia and that the obstruction of the vas deferens was not a major cause of azoospermia[42]. It was reported that infection of the seminal fluid was the major cause of azoospermia in infertile males as infection is known to damage the vas deferens and seminiferous tubules thereby affecting the circulating levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone[43]. One study in an African nation reported that azoospermia was present in 31% (192) and oligospermia in 69.40% (413) infertile African males (595) attending male infertility clinics. The azoospermia was caused by obstruction to the vas deferens and/or epididymis in 44% of cases and testicular lesions in the remaining 56% of cases, whilst the oligospermia was caused by obstruction to the vas deferens and/or epididymis in 4.7% of cases and testicular lesions in 85.3%[44]. A similar result was observed in an infertility clinic in Lagos and Ibadan, Southwestern Nigeria as reported in Ogunbanjo et al.[45] It is now thought that post bacterial infections and idiopathic testicular pathology are common causes of azoospermia in Nigeria[43]. Additionally, a descriptive analysis of the seminal patterns of infertile males at the University College Hospital, Ibadan, in South-west Nigeria showed that asthenozoospermia was the most common seminal quality abnormality[46]. The study that was done at the Nnamdi Azikiwe University Teaching Hospital in South-east Nigeria showed that oligozoospermia (35.9%) and asthenozoospermia (32.3%) were the most common aetiological factors responsible for male infertility (Table 4)[7]. Similarly, 70% of the study population (170) in a study conducted in a private fertility clinic in Abakaliki, Eastern Nigeria, had low sperm count with significantly high defective parameters (64%). Asthenozoospermia and teratozoospermia were the major abnormal parameters recorded. Higher prevalence of oligospermia was found in the civil servants and the oligospermic semen (38%) was associated with bacterial infection[2]. These data seem to suggest that abnormal semen quality remains a significant contribution to overall infertility in the Nigerian environment may be associated with genital infections.

Table 4: Semen abnormality of the infertile Nigerian male partners

Male Factor	**Number of cases N =198**	**%**
Azoospermia	34	17.2
Oligozoospermia (< 20 million sperms per ml)	71	35.9
Asthenozoospermia (Motility < 60% with normal count)	64	32.3
Mixed pathology (Oligo ± astheno ± teratozoospermia)	29	14.6

Source: Ikechebelu et al[7]

The role Infections play in male infertility in the Nigerian Environment

Studies have observed that testicular biopsies from infertile Nigerian men showed a variety of pathological conditions; the most prevalent was hypospermatogenesis. Patients without testicular biopsies had clinically detectable testicular or epididymal abnormalities. There was a higher incidence of inflammatory testicular or prostatic conditions as compared with those found in Europeans, suggesting that inflammatory conditions contribute more to male infertility in Nigeria and other developing African nations[45]. In the study by Ogunbanjo et al.[45]. The seminal fluid

from 782 infertile Nigerian males (Table 5) were examined over a period of ten years with respect to infective agents and indices such as sperm count, motility and the presence of a significant number of pus cells. Various infective agents were recovered from 7% of the patients, while in 25% of the remaining patients, a significant number of pus cells were present, with associated abnormal seminal fluid indices. The authors suggested that seminal fluids constituted an important medium for the spread of various infective agents, and that genital infections by these infective agents, sexually and non-sexually transmitted, may be responsible for a good percentage of infertility cases in Nigerian males.

Table 5: Results of Seminal fluid examination from infertile men over a 10-year study period

No. examined	782
No. found with infective agents	54
No. with evidence of infection* (i.e. pus cells ≥ 5/HPF)	221
No. with < 20 x 10^6/ ml count	562
No. with < 50% motility	622
No. with infective agent but no pus cell	1
No. with no pus cells at all	30

Source: Ogunbanjo et al[45]
At ≥ 5/HPF, 72% and 86% showed < 50% sperm motility and a sperm count of < 20 x 10^6/ ml, respectively. * *Candida spp*

Another study reported that testicular cancers accounted for 0.14% of the male biopsies in patients with suspected cases of testicular malignancies in Ilorin, Southwest Nigeria and may not be major contributory factors in male infertility in Nigeria[47]. In another study of 456 men who attended the sexually transmitted diseases clinic of the University of Ilorin Teaching Hospital, Ilorin because of infertility, it was found that 159 (34.8%) and 297 (65.2%), presented with primary and secondary infertility respectively and that the 7% bacteriospermia observed in the study may have contributed to the male infertility[48]. Similarly, at the fertility clinic of Olabisi Onabanjo University Teaching Hospital, Sagamu, in Western Nigeria, the overall prevalence of HIV infection among 110 women and 49 of their male partners was 8.2%, which was more than double the reported prevalence among the general population in Ogun State, Nigeria between January 2001 and December 2002. This has significant effect on the seminal volume while the other variable of semen quality was not affected. It appears that a higher prevalence of HIV infection is common among the infertile couples in the Western Nigeria and it may be advisable to have infertile couples screened for HIV based on the prevalence of HIV in sub-Saharan Africa[49]. It was also observed that sexually transmitted infections (STIs) had significant effects on the seminal quality of male partners of infertile couples during a five year study period (1993-1997) at the Gynecological and Urological units of Ife State Hospital branch of Obafemi Awolowo University Teaching Hospital complex Ile-Ife, Nigeria[50]. The association of STDs and urinary tract infections to the high rate of oligospermia and azoospermia was also reported in Onitsha, eastern Nigeria. In this study, Obiechina et al[51]. Analyzed the seminal fluid of 628 men attending an infertility clinic at St. Charles Borromeo Hospital, Onitsha between 1994-1998. The authors reported that 63% had normal sperm density, while 37% of the men, had sperm density less than 20 million per ml ejaculate. 6.2% of the patients were azoospermic. 44% of the patients had sperm motility that was less than 50% while 21% of the samples contained pathogens, with the most common pathogen being staphylococcus aureus in 46% (n = 60). Furthermore, in Calabar, Southern Nigeria, nearly 70% of all infertile men attending an infertility clinic gave a history of current or previous exposure to STIs and accounted for nearly 40% of all cases of azoospermia[52]. Additionally, mycoplasma and ureaplasma species were isolated in the semen samples of 54 married men in their fourth decade of life (30-39) and having problems of infertility and with sperm counts less than 20 million/ml[53]. In view of the potential role of ureaplasma urealyticum in reproductive failure, samples of semen from 100 Nigerian males were cultured in oxoid mycoplasma broth. In 39% of the patients, Ureaplasma urealyticum was cultured. Of those with positive culture, 92.3% were infertile patients. Five sub fertile males with sperm concentrations of 20-35 million/ml achieved pregnancy with their partners after eradication of the ureaplasma urealyticum by a course of tetracycline[54]. Apparently, ureaplasma urealyticum

could attach to sperm cells and this may have an inhibitory effect on fertilization. The aetiology of male infertility in the Nigerian population studied seems to be related to the influence of genital mycoplasma and ureaplasma species on sperm count. Infections in the male genito-urinary tract including infections of the epididymis, seminal vesicles, prostate, bladder and urethra are known to play a major role in many cases of infertility[55]. The exact extent of the role they play is largely unknown because of the lack of suitable diagnostic criteria coupled with the asymptomatic nature of many infections. The presence of antisperm antibodies is considered to be a good indicator of a chronic infection in the absence of other clinical findings.

There are also a wide variety of bacteria, viruses, and other organisms which can infect the male genito-urinary system. Chlamydia is now recognized as the most common and the most critical of infection in the male genitourinary tract[55]. In men chlamydia is a major cause of acute non-bacterial prostatitis and urethritis. It is estimated that 28 to 71% of infertile men have evidence of a chlamydial infection[55]. Furthermore, a recent five year case-control study 150 fertile and infertile Nigerian men reported that 42.7% of the infertile men had sperm count < 5 million/ml (Table 6). The abnormal semen parameters were significantly associated with bacteria in cultures. The most common organisms grown were *Staphylococcus aureus, Streptococcus fecalis, Trichomonas vaginalis* and *Candida albicans*. The authors further observed that the infertile men were more likely to have bacterial organisms in semen cultures than fertile men[56]. Sexually transmitted infections (STIs) may be important local factors for male infertility in Nigeria, and has been poorly investigated for its association with male infertility in Nigeria. Several sexually transmitted bacteria such as *Neisseria gonorrheae* and *Chlamydia trachomatis* are also highly prevalent in Nigeria[56], which are known to damage the male genital tract. The number of infertile men attending STI clinics in Nigeria is also high[56]. This would be relevant in relationship between previous exposure to STIs and infertility in Nigerian men. In conclusion, infection play an important role in the aetiology of male infertility and the high prevalence of male infertility in Nigeria is often compounded by infection of the genital area particularly STIs.

Table 6: Results of Semen analysis of fertile and infertile Nigerian men over a period of four (4) years (1999-2003)

Variables	Fertile		Infertile		P
	N	%	N	%	
Semen concentration					
> 20 million/mL	145	96.7	12	8.0	
> 10-20 million/mL	5	3.3	15	10.0	
> 5-10 million/mL	-		17	11.3	
< 5 million/mL	-		64	42.7	
Azoospermia	-		42	28.0	< 0.001
Sperm motility					
> 50%	147	98.0	26	17.3	
30-50%	3	2.0	23	15.3	
< 30%	-		59	39.4	
Azoospermia	-		42	28.0	< 0.001
Viable form					
0	-		13	8.7	
> 50%	132	88	25	16.7	
30-50%	17	11.3	35	23.3	
< 30%	1	0.7	35	23.3	
Azoospermia			42	28.0	< 0.001
Semen culture					
No bacteria growth	113	75.3	82	55.0	
Positive bacterial growth	37	24.7	68	45.0	< 0.001

Source: Okonofua et al[56]

The prevalence of endocrinopathy among infertile Nigerian men

Endocrinopathy is the presence of an abnormality in the serum hormonal panel without necessarily implying a primary endocrine cause of infertility. To determine the pattern of hormonal abnormalities and testicular pathology in azoospermic male Nigerians in Kano, Northern Nigeria, semen samples from consecutive azoospermic infertile males attending the fertility clinic at Aminu Kano Teaching Hospital, Kano, were analyzed over a period of six months, after which serum FSH, LH, testosterone and prolactin were assayed, and histological examination of testicular biopsies done. Of the 80 subjects studied, 32 (40%) had abnormal hormonal levels, 48 (60%) had normal hormonal values and 36 (45%) had evidence of testicular pathology. In another study, the same authors analyzed these hormones in a total of five hundred males, aged between 28 and 56 years over a period of 4 years (2001-2004). Hormonal abnormalities were detected in 22% of oligospermic, 41% of severely oligospermic, and 43% azoospermic subjects[57]. Similarly, an observational, retrospective study[32] conducted on 1,201 men (mean age of 35.7 years) in Northern Nigeria investigated for infertility at the University of Maiduguri Teaching Hospital, over a two-year period, (2004-2006) showed that 96 (7.9%), underwent hormonal assessment because of abnormalities of their sperm counts. 68 (71%) patients had primary infertility and 72 (75%) had azoospermia. 88 (92%) patients had abnormal hormonal assays, giving a prevalence of endocrine abnormality of 7.3% (Table 7). Therefore, endocrinopathy is also common among infertile Nigerian men as with their counterparts elsewhere. However, the prevalence of endocrinopathy of 7.3% was lower than that reported from Kenya[58], an African country, but higher than that reported from Brazil a developing country like Nigeria[59]. However, it was within the range reported in the literature[60]. The majority (71%) of the patients in the study population were found to have primary infertility, which was similar to the study from the Southeastern part of Nigeria[7] and another study conducted in the United Kingdom[61] However, a report from Ile-Ife in Southwestern Nigeria showed a preponderance of secondary infertility[62]. This may be related to the adverse effects of lifestyle factors in Southwestern Nigeria. The azoospermia reported in Geidam et al[32] was higher than that reported in a previous study in the same hospital[62], a Southwestern Nigerian study[50] and another study conducted in Ghana[44]. The study population consisted of only patients with azoospermia and severe oligospermia and that could be the reason for the high percentage of azoospermics observed in their study. Overall, these data suggest that endocrine abnormalities are common in azoospermic infertile Nigerian males.

Table 7: Age group, type of infertility, sperm counts and endocrinological diagnosis of subjects evaluated for infertility in Northern Nigeria.

Demographical profile	No. (%) (n= 96)
Age group (years)	
< 25	4 (4.2)
25-40	73 (76.0)
> 40	19 (19.8)
Mean (range)	35.7 (22-52)
Type of infertility	
Primary	68 (70.8)
Secondary	28 (29.2)
Sperm count (million/ml)	
0 (azoospermia)	72 (75)
< 5	24 (25)
Endocrinological diagnosis	
Hypergonadotropic hypogonadism	40 (41.7)
Hypogonadotropic hypogonadism	4 (4.20)
Partial androgen resistance	12 (12.5)
Germinal epithelial failure	24 (25.0)
Hyperprolactinaemia	8 (8.30)
Normal	8 (8.30)

Source: Geidam et al[32]

Risk Factors that may be Responsible for the Decreasing Male Fertility

Effects of Toxic Metals Exposure and smoking on Male Fertility

A number of epidemiological studies provided equivocal results concerning the effects of lead and cadmium on hormone concentration, male infertility and sperm parameters[63]. Geographic differences in the amount of naturally occurring cadmium have been correlated with incidence rates of prostate cancer[64]. Major changes in the levels of toxic elements in seminal fluid have been related

to abnormal spermatozoa function and fertilizing capacity[65]. Cadmium has been detected in significantly high level in serum of men who were smokers and implicated this metal as one of the causes of asthenoteratozoospermia[65]. Nigerian environments have been reported to be highly polluted by toxic metals, especially lead and cadmium[66]. Cigarette smoking is an important variable when considering the effect of both lead and cadmium exposure on human health. A single cigarette has been reported to contain 1.5 µg of cadmium. Moreover, one tenth of the metal content of a cigarette is inhaled[67]. The incidence of unwilling exposure to second-hand cigarette smoke is very high in Nigeria. Unlike in most developed countries, there are no smoking restrictions in public places in Nigeria except hazardous areas such as petrochemical filling stations. In a recent study, the relationship between Cd levels and spermatograms or the hypothalamic-pituitary-gonadal (HPG)–axis and the correlation of serum and seminal plasma Cd levels with semen characteristics and hormone levels was evaluated in 60 infertile Nigerian men. The serum and seminal plasma Cd levels were increased in azoospermic men in comparison to oligozoospermic and control subjects while a significant negative correlation was observed between serum Cd level and all examined biophysical semen characteristics except sperm volume. A positive correlation between seminal plasma Cd and FSH was also observed. The results demonstrate the role of cadmium in infertility in male Nigerians[66]. Cumulative evidence suggests that cigarette smoking may have a deleterious effect on male fertility by reducing sperm production, motility and increasing the number of abnormal sperm[68]. Smokers are 60% more likely to be infertile than non-smokers. Cigarette smokers were also shown to have higher levels of circulating estradiol and decreased levels of LH, FSH and prolactin than non-smokers, all of which can negatively impact spermatogenesis[68]. Smokers with low prolactin levels also demonstrated defects in sperm motility[68]. Other heavy metals including mercury and chromium may have implications for reproductive dysfunction (Table 8) but there is limited evidence to show that human exposure to mercury and chromium has deleterious effects on the male reproductive system, therefore available data in this regards appear inconclusive and need further study[69,70].

Table 8: Effects of exposure to chemical agents on male fertility

Substance	Effect		References
Metals	Lead	Reduced sperm count and motility	Roy Chowdhury et al[69]
		Spontaneous abortions, Birth defects	Telisman et al[120]
		Reduction in fertility	Matthies et al[121]
		Spermatogenesis impairment	Kumal[122]
	Cadmium	Reduced semen quality	Telisman et al[120]
	Chromium	Changes in semen quality	Li et al[70]
		Testicular atrophy	Kumal[122]
	Mercury	Decreased sperm count, terato/astheno	Kumal[122]
	zoospermia		Matthies et al[121]
		Impaired fertility index	
Pesticides	DBCP	Decreased sperm count, Azoospermia	Potashnik et al [123]
		High serum LH and FSH and infertility	Kumal[122]
			Slutsky et al[71]
		Testicular dysfunction	Kumal[122]
	2, 4-D	Astheno/teratozoospermia	Lerda and Rizzi[73]
	Carbaryl	Decreased sperm function	Petrelli[124]
Plasticizers	DPrP, DPP	Decreased fertility, testicular atrophy	Foster et al[84]
Mycotoxins	Aflatoxins	Astheno/teratozoospermia	Ibeh et al[85]
Alcohol		Changes in hormone production	Emanuele and Emanuele[94]

Exposure to Pesticides, Industrial Chemicals and mycotoxins

The spermatotoxic effects of dibromochloropropane (DBCP), a nematocide widely used in agriculture was reported in the early 1960's in rodents by animal toxicologist but their reports went essentially unnoticed until the late 1970's when oligospermia and azoospermia were reported in manufacturing plant workers and pesticides applicators[71]. It was noted that there was limited childbearing among the workers after they started working in DBCP production. About half of the DBCP-exposed azoospermic men remained that way for many years suggesting that all of the stem spermatogonia may have been compromised. 71 Others experienced a recovery in their sperm count, but in some cases the recovery did not occur until 3 to 6 years later[71]. Furthermore, the men had high levels of FSH and LH in serum indicating that DBCP action is directly on the Leydig cells causing alterations in androgen production and action[71].

Other pesticides such as Dichloro-diphenyl-trichloroethane (DDT), endosulphan; and organophosphorus pesticides i.e. malathion, methyl-parathion, dimethoate, monocrotophos, phosphamidon and quinalphos; synthetic pyrethroids such as fenvelrate and cypermethrin have been reported to show male-mediated adverse reproductive outcome such as abortion, stillbirths, neonatal deaths, congenital defects, e.t.c. among occupationally exposed workers[72]. A significantly higher level of asthenozoospermia and teratozoospermia was found in 2, 4-dichlorophenoxy acetic acid exposed workers as compared to unexposed control subjects[73]. Pesticides with oestrogen-mimetic properties including dichlorodiphenyldichloroethylene, a major metabolite of DDT, dieldrin, lindane and pentachlorophenol have been shown to decrease sperm counts in man[74]. Atrazine, a widely used chloro-s-triazine herbicide, has also been reported to reduce semen quality in men[75] and also in animal models[76]. The direct effect of atrazine on rat testicular cells has also been demonstrated *in vitro* and was reported as the mechanism responsible for spermatogenesis abnormality in rats[77-79]. Although DDT production has been banned in the United States for more than two decades, new factories are still being built to produce DDT in some developing nations. The presence of these chemicals in some developing countries is of concern since they are probably accumulating to harmful levels. Because of its persistence (it has a half-life of about 100 years) and it's recycling in food chains especially in fats, DDT is detectable in the body fat of most people[80]. Vinclozolin, a fungicide used on many types of fruits and vegetables, has been shown to be a potent anti-androgen, blocking the effects of the male sex hormones and resulting in demasculinisation of male offsprings which is accompanied by a decrease in sperm count in the exposed[81]. Dioxin (2,3,7,8-Tetrachlorodibenzo-*p*-dioxin), the most toxic man-made chemical, can block the action of estrogens under certain conditions and thus decrease Sertoli cell number[82]. There is a significant relationship between the number of Sertoli cells and the number of spermatozoa[83]. Therefore any factor that could alter the Sertoli cell multiplication and differentiation during testis development, during fetal life or before puberty, or irreversibly damage the Sertoli cells after puberty, will reduce the number of spermatozoa produced by the testis.

The anti-fertility effects of phthalate esters (Table 8) have been demonstrated in animal and human studies and were associated with decreased weight of the testis and epididymis, decreased epididymal sperm concentration, and increased seminiferous tubule atrophy[84]. Ibeh et al.[85] first reported higher concentrations of aflatoxin B1 (AFB1) in the semen of infertile Nigerian men than those in fertile controls and concluded that the consumption of AFB1 contaminated diets may predispose to male infertility in Nigeria[85]. Over 5 billion people in developing countries worldwide are at risk of chronic exposure to AFB1 through food products contaminated by the fungal molds. The Infertile men with aflatoxin in their semen showed a higher percentage of spermatozoal abnormalities (50%) than the fertile men (10-15.0%). In animals fed with AFB1 contaminated feeds, the deleterious effects on the spermatozoa of affected rats, produced features that resemble those seen in semen of infertile men exposed to aflatoxin[85]. From the above data, it is plausible that

pesticides, industrial chemicals, and contaminants of food such as aflatoxins might produce some adverse reproductive health effects in humans, and might be implicated in the declining fertility of the males. In developing nations such as in Nigeria, where regulations on the use and disposal of these chemicals are less restricted than in developed nations, exposure may be greater, and risks may be higher. Furthermore, locally endemic factors such the consumption of aflatoxin contaminated food products may be important in the causation of male infertility in Nigeria.

Nutritional Considerations

Numerous antioxidants nutrients such as vitamin C, vitamin E, glutathione and coenzyme Q_{10} have been documented in several studies as having modulatory effects on sperm parameters[86]. These positive effects may not be observed in Nigeria because of the well-recognized deficiency of protective micronutrients in this sub-region[87]. Studies have shown that the concentration of ascorbic acid in seminal plasma directly reflects dietary intake, and lower levels of vitamin C may lead to infertility and increased damage to the sperm genetic material[88]. Very little is known about vitamin C status in Nigerian males with impaired fertility.

Ebesunun et al.[89] determined ascorbate levels in the plasma of 27 Nigerian males with inadequate spermatogenesis. There were significant decreases in the seminal and plasma ascorbic acid concentrations in the males who had inadequate spermatogenesis compared with the control values. The plasma low density lipoprotein and triglyceride concentrations were significantly high in all the patients. However, the plasma lipid and lipoprotein levels did not demonstrate any definite pattern with respect to sperm characteristics. The authors concluded that semen ascorbate levels may play a significant role in reduced sperm characteristics in these patients[89]. Selenium and glutathione are essential to the formation of phospholipid gluthathione peroxidase, an enzyme present in spermatids, which becomes a structural protein comprising over 50% of the mitochondrial capsule in the midpiece of mature spermatozoa. Deficiencies of either substance can lead to instability of the mid-piece, resulting in defective motility[86]. It was reported that normospermic infertile patients from Nigerian male partners of infertile marriages, exhibited higher serum manganese levels when compared with oligospermic and azoospermic men which may have effects on sperm count concentration[90]. Akinloye et al.[91] correlated the selenium concentrations in oligo/azoospermic men with the spermatogram and hormonal levels in order to determine their relationship and significance in male infertility. The serum levels of selenium were found to be significantly increased in oligospermic compared to azoospermic subjects and controls whereas the seminal plasma levels were significantly higher in azoospermic compared to oligospermic subjects and controls. A significant inverse correlation was also observed between serum selenium level and sperm count. Similarly, seminal plasma selenium correlated with spermatozoa motility, viability, and morphology. Serum selenium levels show positive correlation with the serum testosterone levels. There appears to be a physiological balance in the distribution of selenium in serum and seminal plasma compartment of control males which might have a significant influence on spermatogenesis if compromised.

Other risk factors for male-factor infertility

Other risk factors for male infertility include chemotherapeutic agents, radiation exposure, and a variety of pharmaceutical agents that act either as direct spermatotoxins or through a steroidal pathway. Other equally important factors with high prevalence in Nigeria include previous exposure to drugs, concurrent medical illnesses, as well as surgical procedures, such as hernia repairs and the use of native medications. Common drugs known to impair male fertility include cimetidine, sulfasalazine, nitrofurantoin, cannabis, and androgenic steroids[92]. Men and women around the world are exposed to the effects of nicotine, alcohol, caffeine, and other chemically active substances every time they smoke a cigarette, have a beer, or drink a cup of coffee. These habits may pose a problem for men with borderline fertility[93]. Several studies reported that alcohol is the

principal cause of hypogonadism seen in alcoholic men and could cause testicular failure[94]. Therefore it is possible that the increased consumption of alcohol among men today could be a contributory factor to the global fertility crisis the human species is facing. Whether nicotine results in impaired male fertility is controversial; however, because of its negative effect on erectile function, nicotine use is discouraged in men attempting to conceive with their partners[95]. There is also the risk of STI, which are either not treated or treatment by sufferers not adequate, this result in poor spermatogenesis later.

A number of occupations are being reported as risk factors for male infertility. For example, an insult to spermatogenesis has been reported among professional drivers who are exposed to the products of fuel consumption, noise, vibration, emotional stress, physical load on the pelvic organs, and increased temperature in the pelvis because of prolonged sitting[96]. Intense exposure to heat in the workplace (for example, Nigerian men working in furnaces or in bakeries), long soaks in the bath tub, use of laptops, and excessive bicycling can cause the temperature in the scrotum to increase enough to impair sperm production. Another example is that of welders, who are exposed to heat, solvents, heavy metals and noise[96]. Also vulnerable to this risk are men who wear tight pants which hold the testes close to the body[97]. Noticeable improvement in sperm count has been observed when the tight underwear is discarded[97]. Skin tight underwears are very popular among adolescent Nigerian males. Poor semen quality such as low sperm count and decreased sperm function has been reported in men exposed to occupational agents in the workplace. Occupational chemical agents with negative effect on fertility include heavy metals, pesticides and other agricultural agents, industrial chemicals, estrogens and estrogen derivatives are shown in (Table 8). Furthermore, global warming and increased temperatures may be affecting normal sperm production, as it is known that testicles are anatomically positioned on the exterior of males because sperm production is highly temperature dependent, particularly because spermatozoa which are susceptible to denaturation at high temperatures. However in countries with hot climates the theory is not supported as birth rates are relatively high, e.g. India and Africa, so this factor has not been supported by evidence. With increasing ozone layer depletion due to the use of aerosols in the past and currently in some countries, more radiation is reaching the earth. Exposure to radiation has further increased with the invention of televisions, microwaves, x-rays, nuclear weapons and the construction of power stations. It has been demonstrated that radiation reduces sperm production in adult males[98]. The effects of radiation on sperm production are more pronounced in children and the effects are seen at lower doses than those seen in adults. Mumps viral infections in adolescent and adult males carry an up to 30% risk that the testes may become infected resulting in orchitis, epididymitis or epididymo-orchitis, which can be quite painful; about half of these infections result in testicular atrophy, and in rare cases sterility can follow[99] Congenital abnormalities (cryptorchidism and testicular dysgenesis, congenital absence of the vas deferens); acquired urogenital abnormalities (obstructions, testicular torsion, testicular tumour, orchitis, urogenital tract infections; increased scrotal temperature (e.g. as a consequence of varicocele); and immunological factors are also widely accepted as causes of infertility.

Furthermore, in male infertility, the frequency of genetic factors is high and may be responsible for about 15% of infertile male subjects[100,101]. The possible relationship between androgen receptor gene CAG and GGN polymorphisms and reduced spermatogenesis have been reported in infertile Nigerian men (Table 9)[102]. The unique distribution in the polymorphism of the (GGN) repeats in the Nigerian population could suggest the possibility of a geographical diversity on male-factor contribution to infertility in the Nigerian population[102]. Other causes of male infertility includes, societal pressures leading to psychological problems. Psychological factors and stress-induced changes in heart rate and cortisol are predictive of a decreased probability of achieving a viable pregnancy[96]. Since stress is the brain-body connection, this raises the possibility that a history of high levels of cumulative stress associated with recurrent depression or anxiety may be an important causative factor. The pressure

even is more when the infertile couples see their friends and peers begin to have children while they are unable to have their own. This may push them to turn to infertility treatments. These treatments, whether done by traditional healers or medical professionals, can put additional stress especially on the woman. The stress is greatest when the couple has great faith that the treatments are going to work but then fail. Thus, psychological stress can represent part of the aetiology of male infertility and can also be a result of the infertility itself. The significance of psychological stress as an independent aetiological factor in the current global male fertility crisis is increasingly being recognized but has not been supported by good studies[96,103].

Table 9: Group statistics of clinical parameters evaluated in patient and control Nigerian males

Parameters	**Azoospermia (No =20)**	**Oligozoospermia (No =40)**	**Control (No =38)**	**F/chi-q**	**p**
[a]Age (yr)	36.4±5.34	38.65±6.13	35.92±6.37	2.15	0.123
[b]Spermiogram					
Semen volume (mL)	3.0 (1.5-10)	2.8 (1-6)	3.0 (1-6)	0.18	0.912
Sperm count (10^6/vol)	0	17 (0.05-96)	124 (44-320)	95.55	0.000
Sperm concentration (10^6/mL)	0	6.9 (0.01-16.3)	41.35 (20-167)	84.69	0.000
% motility	0	22.5 (0-80)	70 (50-90)	72.44	0.000
Morphology (%)	0	42.5 (10-70)	72.5 (50-90)	75.65	0.000
[b]Hormones					
LH (U/l)	13.35 (4.2-29.9)	5.3 (0.9-16)	4.4 (1.1-11.5)	19.48	0.000
FSH (U/l)	5.7 (0.9-20.4)	3.9 (1-18.8)	27.62	0.000	
Testosterone (nmol/l)	22.9 (2.8-53.5)	13.7 (1.4-37.3)	17.9 (2.9-46.5)	1.99	0.368
	17.55 (1.5-75)				
[a]Androgen Receptor					
CAG	20 (17-26)	20.5 (14-26)	19.5 (14-28)	1.67	0.452
GGN	20 (19-24)	21 (17-24)	20 (18-23)	1.18	0.555

[a]Values expressed as mean±SD, statistical analysis by analysis of variance; [b]values expressed as median (range), statistical analysis by Kruskal-Wallis-Test.
Source: Akinloye et al[102]

Conclusions

The Male factor contribution to infertility has become relevant in Nigeria constituting about 50% of all infertility cases. This confirms international research on the high prevalence of infertility around the world in recent times. In tropical Africa such as in Nigeria, the problem is further compounded by a variety of factors including higher exposure risk to toxic chemicals such as agrochemicals, cadmium, lead and aflatoxins as well as the high prevalence of sexually transmitted infections which are often not properly treated and as such now assuming epidemic proportions in many areas.

Clearly any effort to reduce the prevalence of male infertility in Nigeria must largely focus on the prevention and prompt treatment of sexually transmitted infections. Other important risk factors include tobacco smoking, excessive alcohol intake, use of native medications and drugs, low socio-economic status and having multiple sexual partners amongst others. The exploration of psychological factors is also an important factor to consider in the management of this devastating problem which has both cultural and social impact on infertile Nigerian couples. Efforts by the Nigerian government through the Nigerian Federal Ministry of Health and related governmental and non-governmental health-care providers through various program initiatives to address these problems could be beneficial in reducing the rate of male infertility in Nigeria. Such programs should include measures to reduce smoking in public places and the level of alcohol consumption, information on responsible sexual habits, or 'safer sex' strategies for people having multiple sex partners, including mutual

monogamy, non-penetrative sex, and consistent use of barrier contraceptive methods. However, as most of the studies conducted so far in Nigeria do not prove a cause and effect relationship between infertility and the risk factors, it is necessary to conduct epidemiological studies to identify the causative factors for male infertility in Nigeria. Such information is needed, as it would enable the design of programs to prevent male infertility in the country. There is also an urgent need to look at the indiscriminate use and disposal of environmental chemicals especially pesticides, industrial chemicals as the chemicals enter the food chains and surface and ground water and could be potential for exposure during the critical period of development. It is also important to educate the Nigerian populace about the safe use of chemicals, and their effects on reproductive function. Furthermore, if the hypothesis of fetal origin of male infertility is true, then getting more information on estrogenic toxic chemicals and understanding how they control the reproductive system should be a priority for active investigation/future research.

Declaration

The author conceived and designed the study, collected and analyzed the data as well as prepared the manuscript.

References

1. Ekwere PD, Archibong EE, Bassey EE et al. Infertility among Nigerian couples as seen in Calabar. Port Harcourt Med J 2007; 2:35-40.
2. Ugwuja E1, Ugwu NC, Ejikeme BN. Prevalence of Low Sperm Count and Abnormal Semen Parameters in Male Partners of Women Consulting at Infertility Clinic in Abakaliki, Nigeria. Afr Reprod Health 2008; 12:67-73.
3. Schmidt L, Minister K, Helm P. Infertility and the seeking of infertility treatment in a representative population. Br J Obstet Gynaecol 1995; **102:** 978-984.
4. Larsen U. Primary and secondary infertility in sub-Saharan Africa. Int J Epidemiol 2000; 29: 285-291.
5. Okonofua EF, Harris D, Odebiyi A et al. The social meaning of infertility in Southwest Nigeria. Health Trans Rev1997; 7: 205-220.
6. Adetoro OO, Ebomoyi EW. The prevalence of infertility in a rural Nigerian community. Afr J Med Med Sci. 1991; 20:23-27.
7. Ikechebelu JI, Adinma JI, Orie EF, Ikegwonu SO. High prevalence of male infertility in South-eastern Nigeria. J Obstet Gynaecol. 2003; 23: 657-659.
8. Okonofua FE. Infertility in Sub-Saharan Africa. In: Okonofua F, and L Odunsi, eds. Contemporary Obstetrics and Gynaecology for Developing Countries. Women's Health and Action Research Centre. 2003: 128-156.
9. Araoye MO. Epidemiology of infertility: social problems of the infertile couples. WAJM, 2003; 22: 190-196.
10. Agyei-Mensah S. New perspective on the fertility situation in Sub-Saharan Africa NorskGeografiskTidsskrift - Norwegian J Geo.1996; 50:101 – 112.
11. Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J et al. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988-1989). Hum Reprod 1991; 6: 811–816.
12. Mehta RH, Makwana S, Ranga GR, et al. Prevalences of oligozoospermia and azoospermia in male partners of infertile couples from different parts of India. Asian J Androl 2006; 8: 89–93
13. Fisch H, Goluboff ET. Geographic variations in sperm counts: a potential cause of bias in studies of semen quality. Fertil Steril 1996; 65: 1009–14.
14. Guzick DS, Overstreet JW, Factor-Litvak P et al. Sperm morphology, motility, and concentration in fertile and infertile men. New England J Med 2001; 34: 1388-1393.
15. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 4th edition, Geneva, World Health Organization 1999.
16. Bostoffe E, Serup J, Reba H. Has the fertility of Danish men declined through the years in terms of semen quality? A comparison of semen qualifies between 1952 and 1972. Int J Fert 1983; 28: 91-95.
17. Bendvold E. Semen quality in Norwegian men over a 20-year period. Intl J Fert 1989; 34: 401-404.
18. Van Waeleghem K, De Clercq N, Vermeulen L et al. Deterioration of sperm quality in young Belgian men during recent decades. Hum Reprod 1994; 9: 73.
19. Jørgensen N, Carlsen E, Vierula M et al. Recent increase in testis cancer incidence among young Finnish men in associated with a decreasing trend in semen quality. Int J Androl 2011; 34: 37-48.
20. Jørgensen N, Asklund C, Carlsen E et al. Coordinated European investigations of semen quality: result from studies of Scandinavian young men is a matter of concern. Int J Androl 2006; 29: 54–61.
21. Carlsen E, Giwercman A, Keiding N et al. Evidence for decreasing quality of semen during past 50 years. Brit Med J 1992; 305:609–613.
22. Ladipo OA. Seminal analysis in fertile and infertile Nigerian men. J Nat Med Assoc 1980; 72:785-789.
23. Osegbe DN, Amaku EO, Nnatu SN. Are changing semen parameters a universal phenomenon? EurUrol 1986; 12: 164–168.

24. Sheriff DS. Setting standards of male fertility. I. Semen analyses in 1500 patients-a report. Andrologia 1983; 15: 687-692.
25. Kirei BR. Semen characteristics in 120 fertile Tanzanian men. East Afr Med J 1987; 64: 453-457.
26. Andersen AG, Jensen, TK et al. High frequency of sub-optimal semen quality in an unselected population of young men. Hum Reprod 2000; 15: 366–372.
27. Sharpe RM, Fisher JS, Millar MM et al. Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. Environ health perspect1995; 103: 1136-1143.
28. Itoh N, Kayama F, Tatsuki TJ et al. Have sperm counts deteriorated over the past 20 years in healthy young Japanese men? Results from the Sapporo area. J Androl 2001; 22: 40-44.
29. Irvine DS. Falling sperm quality. Brit Med J 1994; 309:476
30. Swan SH, Elkin EP, Fenster L. Have sperm densities declined? A reanalysis of global trend data. Environ Health Perspect 1997; 105:1228–1232.
31. Boisen K, Chellakooty M, Schmidt I et al. Hypospadias in a cohort of 1072 Danish newborn boys: prevalence and relationship to placental weight, anthropometrical measurements at birth, and reproductive hormone levels at 3 months of age. J Clin Endocrinol Met 2005; 90: 4041–4046.
32. Geidam AD, Yawe KDT, Adebayo AEA et al. Hormonal profile of men investigated for infertility at the University of Maiduguri in northern Nigeria. SingaporeMed J 2008; 49: 538-541.
33. Demetrius JP. Male Infertility: Diagnosis and Treatment. J Nurse Pract 2006; 2: 298-299.
34. Singh AJ. Support for infertile couples. World Health Forum 1996; 17:176-177.
35. Umeora OUJ, Ejikeme BN, Sunday-Adeoye I, Umeora MC. Sociocultural impediments to male factor infertility evaluation in rural South-east Nigeria. J ObstetGynaecol 2008; 28:323 –326.
36. Cates W, Farley TMM, Rowe PJ. Worldwide patterns of infertility: Is Africa Different? Lancet 1985; 596-598.
37. Loto OM. Profiles of the semen analyses of male partners of infertile couples in a Nigerian population. Int Congress Series 2004; 1271: 57-59.
38. Olatunji AO, Sule-Odu AO. The pattern of infertility cases at a university hospital. West Afr J Med 2003; 22: 205-207.
39. Nwafia WC, Igweh JC, Udebuani IN. Semen analysis of infertile Igbo males in Enugu, Eastern, Nigeria. Nig J Physiological Sci2006; 21: 67-70.
40. Snow R, Okonofua FE, Kane T et al. Prevalence of determinants of infertility in Ile-Ife, Nigeria. Contracep, Fert Sex 1995; 23:554.
41. Marinho AO. Aetiological factors in infertility-A review of 277 infertile Nigerian couples. West Afr J Med 1986; 5: 69-74.
42. Emokpae MA, Emokpae LA. Calcium concentration in semen of azoospermic Nigerians. J Med Lab Sci1997; 6: 42-43.
43. Megafu U. Seminal fluid infection and oligospermia. Trop J ObstetGynecol1991;9; 10-12.
44. Yeboah ED, Wadhwani JM, Wilson J. B. Etiological factors of male infertility in Africa. Int J Fert 1992; 37: 300-307.
45. Ogunbanjo BO, Osoba AO, Ochei J. Infective factors of male infertility among Nigerians. Afr J Med MedSci 1989; 18: 35-38.
46. Adeniji RA, Olayemi O, Okunlola MA et al. Pattern of semen analysis of male partners of infertile couples at the University College Hospital, Ibadan. West Afr J Med. 2003; 22:243-245.
47. Izegbu MC, Ojo MO, Shittu LA. Clinico-pathological patterns of testicular malignancies in Ilorin, Nigeria: a report of 8 cases. J Cancer Res Ther2005; 1: 229-231.
48. Nwabuisi C, Onile BA. Male infertility among sexually transmitted diseases clinic attendees in Ilorin, Nigeria. Nig J Med 2001; 10: 68-71.
49. Sule-Odu AO, Oladapo OT, Jagun OE et al. Microbial isolates and HIV infection in couples attending fertility clinics in Sagamu, Nigeria. J ObstetGynaecol2005; 25: 685-688.
50. Esimai OA, Orji EO, Lasisi AR. Male contribution to infertility in Ile-Ife, Nigeria. Nig J Med 2002; 11:70-72.
51. Obiechina NJ, Okoye RN, Emelife EC. Seminal fluid indices of men attending infertility clinic at St. Charles Borromeo Hospital, Onitsha, Nigeria (1994-1998). Nig J Med 2002; 11: 20-22.
52. Ekwere PD. Profile of sub-fertile Nigerian men in an infertility Clinic in Calabar, Nigeria. Nig J Surg 2004; 10:37-42.
53. Agbakoba NR, Adetosoye AI, Ikechebelu JI. Genital mycoplasmas in semen samples of males attending a tertiary care hospital in Nigeria: any role in sperm count reduction? Niger J ClinPract 2007; 10:169-173.
54. Ladipo OA, Osoba AO. Ureaplasmaurealyticum (T. mycoplasma) and male infertility in topical countries. Afr J Med Med Sci. 1978; 7:187-190.
55. Purvis K, Christiansen E. Review: Infection in the male reproductive tract. Impact, diagnosis and treatment in relation to male infertility. Int J Androl 1993; 16: 1-13.
56. Okonofua F, Menakaya U, Onemu SO et al. A case-control study of risk factors for male infertility in Nigeria. Asian J Androl 2005; 7:351-361.
57. Emokpae MA, Uadia PO, Omale-Itodo A et al. Male infertility and endocrinopathies in Kano, Northwestern Nigeria. Annals Afr Med 2007; 6: 64-67.
58. Muthuuri JM. Male infertility in a private Kenyan hospital. East African Medical Journal 2005; 82:362-366.
59. Pasqualotto FF, Pasqualotto EB, Sobreiro BP et al. Clinical diagnosis in men undergoing infertility investigation in a university hospital. UrolInt 2006; 76: 122 125.

60. Schlaff W. Integrating infertility evaluation and treatment into the general Ob/Gyn office. Postgrad Obstet Gynaecol 2006; 26: 1-8.
61. Aziz N, Agarwal A, Nallella, et al. Relationship between epidemiological features and aetiology of male infertility as diagnosed by a comprehensive infertility service provider. Reprod Biomed 2006; 12: 209-214
62. Idrisa A, Ojiyi E, Tomfafi O et al. Male contribution to infertility in Maiduguri, Nigeria. Trop J ObstetGynaecol2001; 18: 87-90.
63. Benoff S, Jacob A, Hurley IR. Male infertility and environmental exposure to lead and cadmium. Hum Reprod 2000; 6: 107–121.
64. Angwafo PF. Migration and prostate cancer: an international perspective. J Nat Med Assoc 1998; 90: S720-723
65. Omu AE, Dashtu H, Mohammed AT et al. Significance of trace elements in seminal of infertile men. Nutrition 1995; 11: 502-505.
66. Akinloye O, Arowojolu AO, Shittu OB et al. Cadmium toxicity: a possible cause of male infertility in Nigeria. Reprod Bio 2006; 6:17-30
67. Sram BI, Binkova B, Dejmek J et al. Teplice program-the impact of air pollution in human health. Environ Health Persp 1996; 104: 699-714
68. Olayemi FO. A review on some causes of male infertility. African J Biotechnol 2010; 20: 2834-2842
69. RoyChowdhury A, Mitra C. Spermatogenic and steroidogenic impairment after chromium treatment in rats. Indian J Exp Bio 1995; 33; 480-483.
70. Li H, Chen Q, Li S et al. Studies on male reproductive toxicity caused hexavalent chromium. Zhonghua Yu Fang XueZaZhi 1999; 33:351-353.
71. Slutsky M, Levin JL, Levy BS. Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries. Int J Occup Environ Health 1999; 5: 116-122
72. Rupa DS, Reddy PP, Reddy OS. Reproductive performance in population exposed to pesticides in cotton fields in India. Environ Res 1991; 55: 123-128.
73. Lerda D, Rizzi R. Study of reproduction function in persons occupationally exposed to 2, 4-dichloro phenoxyacetic acid (2, 4-D). Mutat Res 1991; 262: 47-50.
74. Beard AP, Bartlewski PM, Chandolia RK et al. Reproductive and endocrine function in rams exposed to the organochlorine pesticides Lindane and Pentachlorophenol from conception. J ReprodFert 1999; 115: 303-314.
75. Swan S, Kruse R, Liu F et al. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect2003; 111: 1478–1484.
76. Abarikwu SO, Adesiyan AC, Oyeloja TO, et al. Changes in Sperm Characteristics and Induction of Oxidative Stress in the Testis and Epididymis of Experimental Rats by a Herbicide, Atrazine. Arch Environ Contam Toxicol 2010; 58: 874-882.
77. Abarikwu SO, Farombi EO, Kashyap MP, et al.. Atrazine induces transcriptional changes in steroidogenesis marker genes in primary cultures of rat Leydig cells. Toxicol in Vitro 2011; 8:1588-1595.
78. Abarikwu SO, Pant AB, Farombi EO. The protective effects of quercetin on atrazine-induced cytotoxicity on rat Sertoli-germ cell co-culture. Int J Androl 2012; 35:590-600.
79. Abarikwu SO, Pant AB, Farombi EO. Effects of quercetin on mRNA expression of steroidogenesis genes in primary cultures of Leydig cells treated with atrazine. Toxicol inVitro 2012; 27: 700-707.
80. Sharpe RM, Skakkebaek NE. Are estrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993; 34: 1392-1395.
81. Birnbaum LS. Endocrine effects of prenatal exposure to PCBs, Dioxins, and other Xenobiotics: implications for policy and future research. Environ health prosp 1994; 102: 676-679.
82. Muller Andreas MF, Makropoulos V, Bolt HM. Toxicological aspects of oestrogen- mimetic Xenobiotics present in the environment. ToxicolEcotoxicol News 1995; 2: 68-73.
83. Johnson L, Zane RS, Petty CS, et al. Quantification of the human Sertoli cell population: its distribution, relation to germ cell numbers, and age-related decline. Biol Reprod 1984;31:785-795
84. Foster PM, Cattley RC, Mylchreest E. Effects of di-n-butyl (DBP) on male reproductive development in the rat: implications for human risk assessment. Food ChemToxicol 2000; 38: S97-99.
85. Ibeh IN, Uraih N, Ogonar JI. Dietary exposure to aflatoxin in human male infertility in Benin City, Nigeria. Int J Fert1994; 39: 208–214.
86. Sinclair S. Male infertility: Nutritional and environmental consideration. Altern Med Rev 2000; 5: 28-38.
87. Underwood BA, Smitasiri S. Micronutrients malnutrition: policies and programs for control and their implications. Ann Rev Nutr 1999; 19: 303-324.
88. Dabrowski K, Ciereszko A. Ascorbic acid protects against male infertility in a teleost fish. Experientia 1996; 52: 97-100.
89. Ebesunun MO, Solademi BA, Shittu OB et al. Plasma and semen ascorbic levels in spermatogenesis. West Afr J Med 2004; 23: 290-293.
90. Adejuwon CA, Ilesanmi AO, Ode EO et al. Biophysical and biochemical analysis of semen in infertile Nigerian males. Afr J Med Med Sci. 1996; 25:217-219.
91. Akinloye O, Arowojolu AO, Shittu OB et al. Selenium status of idiopathic infertile Nigerian males. Biological Trace Element Research 2005; 104: 9-18.
92. Sigman M, Lipshultz L, Howards SS. Evaluation of the subfertile male. In: Lipshultz LI, Howards SS (Eds.). Infertility in the male. St. Louis: Mosby-Year Book Inc., 1997, 1997; 173-93.
93. Kunzle R, Mueller MD, Hanggi Wet al. Semen quality of male smokers and nonsmokers in infertile couples.FertilSteril2003; 79: 287–291.
94. Emanuele MA, Emanuele NV. Alcohol and the male reproductive system. Alcohol Res Health 2001; 25:282-287.

95. Elhanbly S, Abdel-Gaber S, Fathy H et al. Erectile dysfunction in in smokers: a penile dynamic and vascular study. J Androl2004; 25:991-995.
96. Sheiner EK, Sheiner E, Hammel RD, et al. Effect of occupational exposures on male fertility: Literature Review. Industrial Health 2003; 41: 55-62.
97. Foster WJ, Rowley MJ. Testicular biopsy in the study of gorilla infertility. Am J Primatol2005; 3: 121 – 125.
98. Herrmann T. Radiation reactions in the gonad: importance in patient counseling. StrahlentherOnkol1997; 173: 493-501.
99. Senanayake SN. Mumps: a resurgent disease with protean manifestations. Med J Aust. 2008; 189: 456–459.
100. Samli H, Samli MM, Solak M, et al. Genetic anomalies detected in patients with non-obstructive azoospermia and oligozoospermia. Arch Androl 2006; 52: 263-267.
101. Foresta C, Ferlin A, Gianaroli L, et al. Guidelines for the appropriate use of genetic tests in infertile couples. Eur J Hum Genet 2002; 10: 303-312.
102. Akinloye O, Gromoll J, Nieschlag E, et al. Androgen receptor gene CAG and GGN polymorphisms in infertile Nigerian men. J. Endocrinol Invest 2009; 32:797-804.
103. Stoleru S, Teglas JP, SpiraA et al. Psychological characteristics of infertile patients: discriminating etiological factors from reactive changes. JPsycho ObstetGynecol1996; 17: 103-118.
104. Hotchkiss RS, Brunner EK, Grenley P. Semen analysis of two hundred fertile men. American J Med Sci 1938; 196: 362-384.
105. MacLeod J, Heim LM. Characteristics and variations in semen specimens in 100 normal young men. J Urol 1945; 54: 474-482.
106. MacLeod J, Gold RZ. The male factor in fertility and infertility. II. Spermatozoön counts in 1000 men of known fertility and in 1000 cases of infertile marriage. J Urol 1951; 66: 436–449.
107. Nelson CMK, Bunge RG. Semen analysis: evidence for changing parameters of male fertility potential. Fertil Steril 1974; 25: 503–507.
108. Rehan N. Semen characteristics of fertile Pakistani men**.** J Pakistan Med Asso1994; 44: 62-64.
109. Sturde HC, Glowania HJ, Bohm K. Comparative ejaculate studies in men from sterile and fertile marriages. Arch DermatolForsch. 1971; 241: 426-437.
110. Bahamondes L, Abdelmassih R, Dachs JN. Survey of 185 sperm analyses of fertile men in an infertility service. Int J Androl 1979; 2:526-533.
111. Aabyholm T, An andrological study of 51 fertile men. Int J Androl 1998; 1: 646-656.
112. Wang C, Chan SYW, Leung A et al. Cross sectional study of semen parameters in a large group of normal Chinese men. Int J Androl 1985; 8: 257-74.
113. Chan SYW, Wang C. Correlation between semen adenosine triphosphate and sperm fertilizing capacity. FertilSteril 1987; 47: 717-719.
114. Barratt CLR, Dunphy, BC, Thomas EJ et al. Semen characteristics of 49 fertile males. Andrologia 1988; 20: 264-269.
115. Pol PS, Beuscart R, Leroy-Martin B et al. Circannual rhythm of sperm parameters of fertile men. FertilSteril 1989; 51: 1030-1033.
116. Fisch H, Goluboff ET, Olson JH et al. Semen analyses in 1,283 men from the United States over a 25-year period: no decline in quality. FertiSter 1996; 65: 1009–1014.
117. Benshushan A, Shoshani O, Paltiel O et al. Is there really a decrease in sperm parameters among healthy young men? A survey of sperm donations during 15 years. J Ass Reprod Gen 1997; 14: 347–353.
118. Andersen AG, Jensen TK, Carlsen E et al. High frequency of sub-optimal semen quality in an unselected population of young men. Human Reprod 2000; 15: 366–372.
119. Selevan SG, Borkovec L, Slott VL et al. Semen quality and reproductive health of young Czech men exposed to seasonal air pollution. Environ Health Perspect 2000; 108:887–894.
120. Telisman S, Cvitkovic P, Jurasovic J et al. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc and copper in men. Environ health Perspect 2000; 108; 45-53.
121. Matthies VJ, Donat H, Schwarz I. Einfluss Von Schwarmetallionen auf die mannlichefertilitat. ZentralblGynakol 1989; 111: 155-166 (in German).
122. Kumar S. Occupational exposureassociated with reproductivedysfunction. J Occup Health. 2004 Jan; 46(1):1-19.
123. Potashnik G, Ben-Aderet N, Israel R et al. Suppressive effect of 1, 2-dibromo-3-chloropropane on human spermatogenesis. FertilSteril 1978; 30: 444-447.
124. Petrelli G, Montovani A. Environmental risk factors and male fertility and reproduction. Contraception 2002; 65: 297-300.