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Prevalence of primary infertility caused by chromosomal abnormalities and assessment of clinical manifestations in Rwandan patients

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A B S T R A C T

INTRODUCTION: Infertility affects millions of couples worldwide causing psycho-social problems and conflicts in families. Despite the establishment of multiple causes of infertility in both males and females, there have been no studies carried out in Rwanda about primary infertility caused by chromosomal abnormalities. Thus, the aim of this study is to determine the prevalence of primary infertility caused by chromosomal abnormalities and to assess the clinical manifestations in Rwandan patients.

METHODS: We performed a cross-sectional retrospective assessment of the data extracted from medical files and OpenClinic (an electronic data recording system) of patients transferred to one genetic lab in Huye that works with three main referral hospitals: Kigali University Teaching Hospital (CHUK), Huye University Teaching Hospital (CHUB) and Rwanda Military Hospital (RMH) from June 2009 to June 2019.

RESULTS: This study showed that the overall prevalence of primary infertility caused by chromosomal abnormalities was 25.4% (N=15/59) among the patients who consulted the genetic department. Females were more affected than males with 32% (N=8/25) of females being primarily infertile due to chromosomal abnormalities and 20.58% (N=7/34) of males respectively. Our study also found that the majority (66.1%) of infertile patients had a normal karyotype in both genders with 40.7% of the males (46, XY) and 25.4% of the females (46,XX).

CONCLUSION: Chromosomal abnormalities contribute significantly to primary infertility in the Rwandan population. Thus, clinicians should consider these chromosomal abnormalities in patients attending fertility clinics.

Keywords: Infertility; Primary; Chromosomal Abnormalitie; Prevalence; Rwanda

INTRODUCTION

Infertility is a global health burden that affects more than 186 million couples worldwide [1]. By definition, it is a disease of the reproductive system characterized by the inability to conceive naturally for a couple, despite one year of regular unprotected sex [2]. It causes many psycho-social problems such as conflicts in families, divorce or separation of partners, loss of social security and emotional distress [3]. Infertility is classified into primary and secondary infertility [4]. Primary infertility, also named sterility, is a term used for women who have never been pregnant and for men who have never impregnated a woman despite one year of regular unprotected sex. The term secondary infertility refers to the inability to conceive in a couple who have had at least one successful conception in the past [4].

There are multiple causes of infertility in both males and females. According to the World Health Organization (WHO), the most common identifiable female factors were menstruation and ovulatory disorders (32%), fallopian tube abnormalities secondary to pelvic adhesions and infections (34%), and endometriosis (15%) [3]. There are also other factors such as genetic disorders, as well as uterine and cervical factors. Male causes of infertility include genetic factors, abnormal sperm production and motility, anatomical defects, endocrine disorders and sexual dysfunction [5].

The statistics from the European Journal of Human Genetics re-

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vealed that genetic abnormalities could be the cause of infertility in 10% of female infertile patients and 15% of male infertile patients [4]. These genetic abnormalities include chromosome aberrations, micro deletions, duplications, single gene mutations, complex conditions and epigenetic disorders.

A study in Iran performed at a government centre for infertility in Fatemieh Hospital during 2010 to 2011, found that genetic factors were amongst the dominant causes of infertility in 29.8% of males [2]. Other male causes of infertility that were found were semen disorders (44.6%), vascular disorders such as varicoceles (17.2%), and anti-spermatogenesis agents (8.4%) [6].

Despite the prevalence of infertility and the growing need of using assisted reproduction treatment such as In Vitro Fertilization (IVF) and Intra-cytoplasmic Sperm Injection (ICSI), many researchers are not examining the genetic factors of infertility in Africa, and Rwanda in particular. And yet, research has found that gametes that contain chromosomal aberrations have a high probability of failing to enter in fertilization. There is also a concern nowadays about assisted reproductive techniques, which might force the formation of a zygote by dominating hidden chromosomal changes in parents, thereby transmitting genetic abnormalities to the next generation or increasing the number of early abortions or foetal abnormalities due to parental genetic defects [7].
Furthermore, the consequences of infertility for couples is very significant in Rwanda and other African countries because children are highly valued for economic and socio-cultural reasons.

Since there have been no studies carried out in Rwanda surrounding these issues, our study aimed to determine the prevalence of primary infertility caused by chromosomal abnormalities and assess the clinical manifestations in Rwandan patients who consulted the genetic department. We believe this study will bring new knowledge and evidence needed to improve the management of infertile patients in Rwandan hospitals.

This study aimed at investigating somatic and sex chromosomal abnormalities that cause primary infertility in Rwandan patients evaluating the contribution of chromosomal abnormalities to decreased fertility in humans and describing the clinical manifestations of patients with primary infertility who consulted the genetic department in Rwanda

METHODOLOGY

Study design: This study used a cross-sectional retrospective assessment of the data extracted from patients' files and OpenClinic (electronic data recording system used in hospitals).
Study population: The study population included 59 patients, both male and female, with primary infertility who consulted the genetic department between June 2009 and June 2019.
Study site: The study was conducted in three referrals hospitals (CHUK, RMH, CHUB) which work with the Genetic Lab located in Huye.
Inclusion criteria: All patients with primary infertility as well as those with associated different forms of Disorders of Sex Development (DSD) who consulted the genetic department and whose files were available were included in this study. Symptoms considered for females were: the inability to conceive for one year despite unprotected and regular sexual intercourses and abnormal menstrual cycles. Symptoms considered for males were: the inability to induce pregnancy regardless of multiple unprotected sexual intercourses.
Exclusion criteria: Patients with incomplete files whose address, hospital identification and karyotype results were missing.
Data collection tool: We used a well-structured paper and electronic questionnaire. Questions were extracted from reliable and valid questionnaires released by different institutions including the American Society for Reproductive Medicine, UNC Fertility and Johns Hopkins Medical Centre.
Data analysis: Data was entered, stored and analysed in IBM SPSS Statistics software version 23. The data is presented in tables and figures and interpreted in percentages and frequencies.
Ethical consideration: Data security, privacy and confidentiality were taken into account based on recommendations from the Research Ethical Committee (REC).

RESULTS

Baseline details of data: In our study, we found 59 patients whose records met the inclusion criteria. They consulted the genetic department for primary infertility on suspicion of chromosomal abnormalities as a cause in a period of 10 years from June 2009 to June 2019.
The majority of patients (57.6%) were males whilst 42.4% of patients were females and the mean age was 32.81. The majority of the patients were aged between 20-34 years and the peak age group was 56 years. We found that most of the patients 52.5% (N=31) came from Kigali City, followed by Eastern Province with 18.6% (N=11). Western Province represented 13.6% (N=8) of patients, Southern Province with 5.1% (N=3) and the last being the Northern Province with no patients. 23.7% (N=14), of patients were from the Kicukiro district, followed by Gasabo having 20.3% (N=12) of patients and Nyarugenge and Kayonza having 8.5% (N=5) of patients each (Table 1).
Clinical features of patients with infertility: In our study, the most predominant clinical feature found in men was gynecomastia (14.7%) followed by micropenis (11.8%). Ejaculatory problems and abnormal reproductive organs were represented by 8.8% of patients whilst ambiguous genitalia were found in 2.9% (Figure 1).

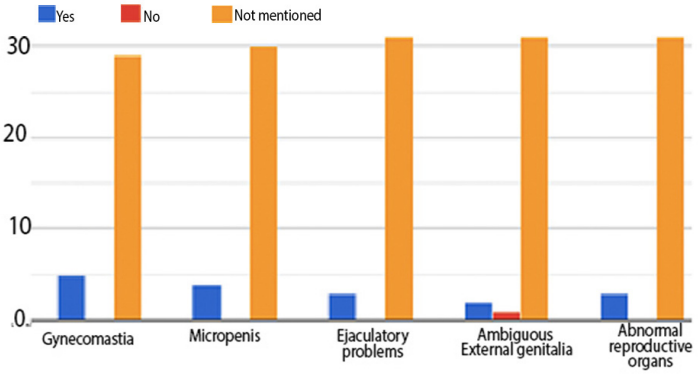

Figure 1: Clinical presentation of men with infertility

Table 1: Baseline details of patients showing gender and age distribution

Gender	Frequency	Percentage (%)
Male	34	57.6
Female	25	42.4
Age range	**Frequency**	**Percentage (%)**
20 to 34 years	39	66.1
35 to 50 years	18	30.5
51 to 65 years	2	3.4
Province	**Frequency**	**Percentage (%)**
Kigali City	31	52.5
Eastern Province	11	18.6
Western Province	8	13.6
Southern Province	3	5.1
Not Recorded	6	10.2
Province	**Frequency**	**Percentage (%)**
Bugesera	2	3.4
Gasabo	12	20.3
Gatsibo	2	3.4
Huye	1	1.7
Karongi	2	3.4
Kayonza	5	8.5
Kicukiro	14	23.7
Ngoma	1	1.7
Nyabihu	3	5.1
Nyamagabe	1	1.7
Nyamasheke	1	1.7
Nyanza	1	1.7
Nyarugenge	5	8.5
Rubavu	1	1.7
Rusizi	1	1.7
Rwamagana	1	1.7

Primary amenorrhea was the most common clinical feature (28%) in women, followed by abnormal reproductive organs (16%). Absent or delayed secondary characteristics were seen in 12% of women, followed by short stature at 8%. Ambiguous external genitalia were found in 4% of female patients (Figure 2).

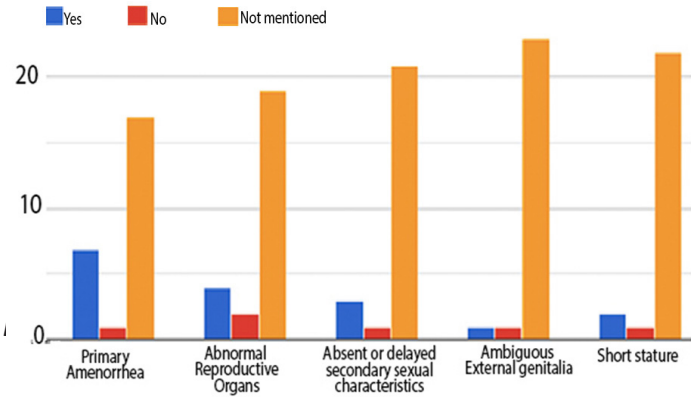

Figure 2: Clinical presentation of women with infertility

Our study results showed that 14.7% of male patients had low testosterone levels, 2.9% (N=1) had low oestradiol levels , whilst LH and FSH were both high in 5.9% of male patients (Figure 3).

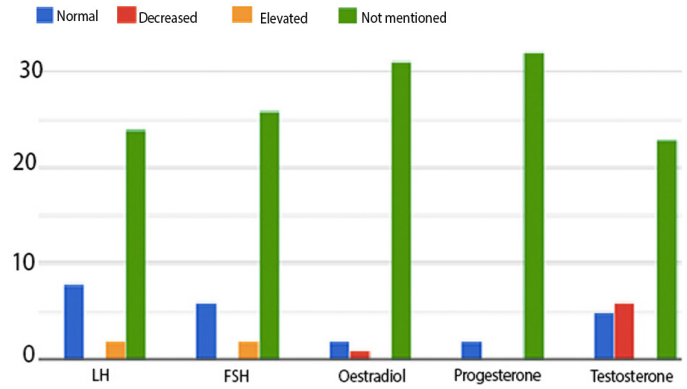

Figure 3: Hormonal studies in male patients

As shown in figure 4, FSH and oestradiol were both abnormal in 16% of female patients. 12% of female patients had abnormal LH and Testosterone levels, whilst progesterone was low in 4% (Figure 4).

We found that 46.9% of male patients had abnormal semen with azoospermia being the most common cause (29.4%), followed by oligospermia at 8.8%(N=3/34). Necrospermia, hypospermia and oligoasthenoteratozoospermia were found in 2.9% of male patients each (Table 2).

Table 3: Karyotype results according to gender

			Semen Analysis							Total
Azoospermia Oligospermia			Necrospermia	Hypo-speemia	Oligoasthe-noteratozo-ospermia	Normal	Not Re-corded			
Gender	Male	Count	10	3	1	1	1	3	15	34
		% of Total	29.4%	8.8%	2.9%	2.9%	2.9%	8.8%	44.1%	100.0%
Total		Count	10	3	1	1	1	3	15	34
% of Total			29.4%	8.8%	2.9%	2.9%	8.8%	44.1%	100.0%	

In our karyotype results, we found that the abnormal karyotype counted for 25.4% of patients, amongst which numerical abnormalities are responsible for 11.9% (N=7).

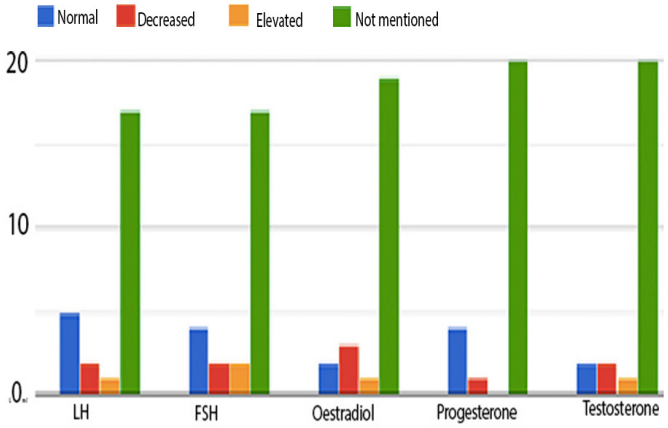

Figure 4: Hormonal studies in female patients

Turner syndrome and Klinefelter syndrome (Figure 5) affected 6.8% and 5.1% of patients respectively, whilst abnormal sex chromosomes equivalently counted for 11.9%. Structural abnormalities were the least prevalent found only in 1.7% of patients. Our study found that 66.1% had a normal karyotype in both genders with 40.7% male 46, XY and 25.4% female 46,XX (Table 3).

DISCUSSION

In our study, we found that the overall prevalence of chromosomal abnormalities was 25.4% of the total number of male and female patients with primary infertility who consulted the genetic department in Rwanda. Our study showed that 20.58% (N=7/34) of all the patients with chromosomal abnormalities were male, whereas 32% were females. A study performed in Croatia also showed a higher proportion of chromosomal abnormalities in infertile females compared to males at 26.4% and 17.7% respectively [8].

Analysis showed that the most common genetic diseases found in the patients had different prevalence in each gender.

In males, we found that the most prevalent chromosomal abnormality is 46, XX DSD, affecting 11.76% of patients. This is a type of DSD where a person appears male phenotypically but the karyotype test reveals a female genotype (masculinized female). The second most common chromosomal abnormality was Klinefelter syndrome which was seen in 8.82% of male patients. There were no males with a structural karyotype abnormality or a Y chromosome micro-deletion.

Our findings are not very different from a study that was carried out in the USA where Klinefelter syndrome was found to be the most common chromosomal aberration in 14% of infertile patients with azoospermia [9].

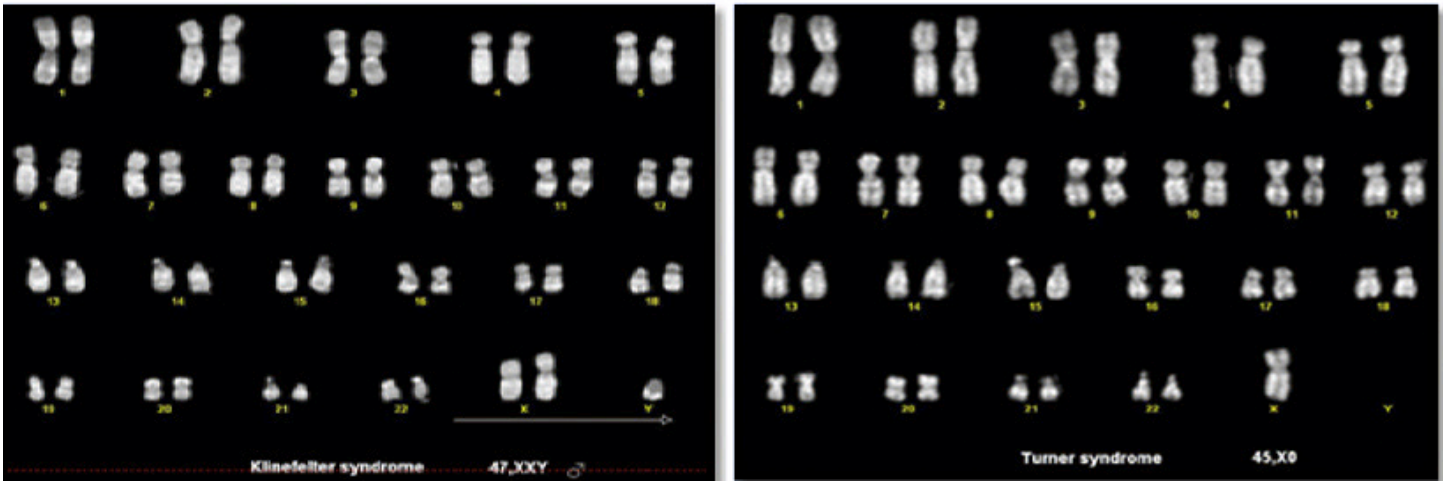

Figure 5: Klinefelter (Left) and Turner (Right) syndrome Karyotypes

Table 3: Karyotype results according to gender

Gender 46, XY 46, XY DSD		Karyotype 46, XX	46, XX DSD	45, X0	47, XXY	46, X del (Xq)	Not Recorded			Total
Male	Count	24	0	0	4	0	3	0	3	34
	% of Total	40.7%	0.0%	0.0%	6.8%	0.0%	5.1%	0.0%	5.1%	57.6%
Female	Count	0	3	15	0	4	0	1	2	25
	% of Total	0.0%	5.1%	25.4%	0.0%	6.8%	0.0%	1.7%	3.4%	42.4%

In females, we found that most prevalent chromosomal abnormality was Turner syndrome 45, X0 which accounted for 16% of female patients who consulted the genetic department in Rwanda. The least common genetic defect in females was 46, X del (Xq) that accounted for 1.7% of patients.

Semen analysis is one of the cornerstone investigations for an infertile couple. Our study revealed that 46.9% of male patients had abnormal semen, gynecomastia, micropenis, ejaculatory problems and abnormal reproductive organs. In a study by Dohle GR et al, 40-60% also had abnormal semen, gynecomastia and hypogonadism [10].

In conclusion, this study revealed that chromosomal abnormalities contribute significantly to primary infertility in the Rwandan population. Thus, clinicians should consider these abnormalities in patients attending the fertility clinic. This study highlights the need for patients to consult as a couple, since infertility is a shared problem that affects both men and women.

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