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J. Wanyoike-Gichuhi, MBChB, MMed, Senior Lecturer, R. Parkar, MBChB, MMed,Professor, B. Kihara, MBChB, MMed, Lecturer and D. K. Ondieki, MBChB, MMed, Lecturer, Department of Obstetrics and Gynaecology, College of Health Sciences, University of Nairobi, P. O. Box19676-00100, Nairobi

Request for reprint to: Dr. J. Wanyoike-Gichuhi, Department of Obstetrics and Gynaecology, College of Health Sciences, University of Nairobi, P. O. Box19676-00100, Nairobi

PREMATURE OVARIAN FAILURE IN TWINS: CASE REPORT

J. WANYOIKE-GICHUHI, R. PARKAR, B. KIHARA and D. K. ONDIEKI

SUMMARY

Premature ovarian failure (POF)is a serious life-changing condition that affects young women, remains an enigma and the researchers' challenge. POF, premature ovarian insufficiency (POI), premature menopause, premature dysfunction (POD), or hypergonadotropic hypogonadism is one of the most perplexing disorders with aheterogeneous origin. Infertility, social and psychological stress are common consequences of this entity. This paper presents a rare condition where both twins had presented with POF.

INTRODUCTION

Premature ovarian failure (POF), affects 0.1% and 1-2% of women younger than 30 years and those younger than 40 years respectively, and is a significant insidious aetiology of female infertility due to atypical ovarian reserve (1-3). POF clinically presents with amenorrhoea of at least four months and features of hypoestrogenism with an increased follicle stimulating hormones of more than 20 IU/l in women under age of 40years (1-3). POF origin is mainly idiopathic, however, probably genetic in most cases, with other causes being environmental factors, viral infection, autoimmune and metabolic disorders and iatrogenic (3). This paper presents twins, both with premature ovarian failure (POF), discuss the aetiology, clinical presentation and management of this condition, which has poor prognosis.

CASE REPORT

Twenty nine years old who presented with primary infertility and secondary ammenorrhoe for four years. Menarche was at 13 years. There was no history of utilisation of contraceptive or any other medication and no previous surgery. On a family history, she was a twin and had four siblings (3 sisters and a brother). Interestingly, her twin sister also had infertility and ammenorhoea. On general examination, there was no goitre, galactorrhoe and no hirsutism. Systemic examination revealed no significant. The external genitalia and uterus were normal.

Investigations
Follicle stimulating hormone: 32.84 mIU/ml
Antimullerian Hormone: 1.2pmol/ml.
Prolactin: 120 mIU/L
Luteinising hormone: 22mIU/ml.
Estradiol: 18pmol/L.
Testosterone: 0.5nmol/L.
TSH: 3.4mU/L

Ultrasound: Uterus was normal but the ovaries were bilaterally atrophic.The diagnosis of premature ovarian failure was made. Out of scientific curiosity, the other twin patient was requested to be clerked and investigated to ascertain her diagnosis.

Second twin: She also had primary infertility and secondary ammenorrhoe for 18 months. Menarche was at 13 years. There was no history of contraceptive use and no other medication use. No previous surgery. On general examination, there was no goitre, galactorrhoe and no hirsutism. Systemic examination revealed no significant. The external genitalia and uterus were normal.

Investigations
Follicle stimulating hormone: 28.12 mIU/ml
Antimullerian Hormone: 1.2pmol/ml
Prolactin: 126mIU/L
Luteinising hormone: 22mIU/L
Estradiol: 42pmol/L
Testosterone: O.6nmol/L
TSH: 4.1mU/L

Ultrasound: Uterus was normal but the ovaries were bilateral atrophic. The diagnosis of premature ovarian failure was made.It was not possible to ascertain whether these twins were fraternal or identical.

Premature june 2016.indd 258 10/08/2016 1:06 PM

None of the other female sibling had ammenorhoe or difficult in conception.

DISCUSSION

Infertility, a highly complex disease of the reproductive system with multifactorial aetiology, has a prevalence of 15% in the reproductive population (4). Primary female infertility, which includes POF, affects germ cell structure or physiology, causing arrest of germ cell development and ultimate cell death. Premature ovarian failure (POF) not only truncates the fertile lifespan but also has an impact on women's long-term health and well-being, notably the risks of infertility, cardiovascular disease and osteoporosis (5). POF is commonly, if arbitrarily, defined for clinical purposes as the spontaneous and irreversible cessation of menses before 40 years of age: it is a consequence of the failure of follicles to reach maturity, either because the store of primordial follicles is exhausted or because they are refractory to growth stimuli (6).

Many factors are responsible for POF, including abnormal karyotype, translocations, point mutations, ovarian autoimmunity, pelvic infection, cytotoxic drugs and destructive ovarian surgery (6).

The numbers of follicles in the human ovary decline continuously throughout life; few remain at the time of the menopause and virtually none in post-menopausal ovaries (7,8). This transition normally occurs in mid-life and is conventionally defined retrospectively after 12 months of amenorrhea. The age distribution of natural menopause has been described for many populations worldwide. Despite differences and limitations in survey designs (retrospective, cohort and prospective), results have been remarkably consistent, at least for well-nourished populations, indicating that the menopause is determined primarily by biological factors with minor modifications because of environmental or lifestyle factors (9). The mean age of menopause is 50–52 years, and the median age is slightly higher because the distribution is negatively skewed. The prevalence of POF was correspondingly similar between surveys (17).

Prevalence of POF: Among mainly Caucasian women with an intact uterus and ovaries, the prevalence before 40 years of age was 0.9% in a survey from the Mayo Clinic, 1.0% from the Study of Women Across the Nation (SWAN) and 1.3% from the European Prospective Investigation into Cancer and Nutrition (EPIC) (10,11,12). When the 40- to 44-year-old group was included, the prevalence of POF rose to 5–8%. The SWAN study reported that POF by the 40- and 45-year thresholds was more frequent in African and Hispanic Americans than Caucasians and less so in Japanese (11). No literature was found the prevalence in black indigenous Africans. The twins have a significantly higher prevalence of POF than women in the general population (6).

Aetiology of POF: X chromosome abnormalities, which comprise of aneuploidy, monosomies, trisomies, deletions and translocations constitute of 13 % of POF cases (1,3).Oogenesis, with its complex multiple developmental stages, is essential for perpetuation of species. Each stage is dictated by unique network of molecules and regulatory genes, which impact on oocyte developmental potential, quality and genetic integrity (13). Deviation of ovarian genetic pathways and mutation of ovarian specific genes like FOXL2, BMP15, NOBOX AND FIGLA can result in premature ovarian failure (17). Turners Syndrome (45,XO) is one of the most frequent X chromosome abnormalities, with an incidence of 1:2000-2500 female births and is associated with POF (1,2,14,). Clinical presentation depends on the level of mosaicism, which influences the germinal cell atresia and ovarian failure (1,3).

Trisomy X with an occurrence of 1:1000 female births is one of the most frequent causes of POF (3,14). The chromosomal abnormality occurs during meiosis due to nondisjunction errors (14).

Fragile X Syndrome which has mutation of fragile X mental retardation I ($FMRI_1$) gene has also been associated with POF (15).

Defect of Hypothalamic –Pituitary –Ovarian Axislike Kallmans Syndrome and FSH & LH gene mutations have been associated with POF (14).

Autoimmune involvement in POF: POF can occur as a result of: a primitive reduced pool of oocytes; an accelerated follicular atresia; or an impaired folliculogenesis. An exaggerated autoimmune reaction involved in atretic acceleration, oocyte wastage or impaired folliculogenesis first described an association between an autoimmune adrenal deficiency and POF. Autoimmune attack might be general or in most instances, partial, reversible, and responsible for, in many cases, fluctuating course of the POF (17). Between 10 and 30% of women with POF have a concurrent autoimmune disease; the most commonly reported being hypothyroidism, and the most clinically important hypoadrenalism, as well as association with myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Crohn's disease (17).Spontaneously conception can occur in 5-10% 0f women with POF and these are the cases with autoimmune component (18). The thyroid function tests were normal in the twins presented.

Other cause of POF are environmental causes;viral infection, chemotherapy, radiotherapy, and pelvic surgery (17).

POF is extremely rare in healthy adolescents and young adults. In this case presentation, young twins have presented with POF. Ideally, potential cases of POF should be screened for karyotype, fragile

X permutations and skewed X-inactivation (19).It was not possible to perform chromosomal studies to ascertain the cause of the POF in these twins but it is most likely genetic in origin.

In discordant twins (one with POF and the other normal), POF has been reversed by sister → sister ovarian tissue transplantation, and a viable pregnancy established after natural conception(16). The procedure is performed laparoscopically in both the donor and the recipient. However the twins presented in this paper could not benefit from ovarian tissue transplantation as both had POF and their only options are either *in vitro* Fertilisation with egg donation or adoption.

Inconclusion,POFisacomplexheterogeneousdisorder, which has significantly higher prevalence in twins than the general population. It is difficult to identify the particular etiology of POF in developing country setup due to its strong links with genetics and immunology. Management of POF patients should be multidisciplinary and individualised, including the provision of proper counseling, nutrition supplement advice, hormone replacement therapy (HRT), immunosuppressive therapy in a selected population, and assisted conception techniques. The ideal treatment strategy for young women with POF poses a clear challenge and treatment should be tailored according to choice, different needs of these women and individual risk factors.

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Premature june 2016.indd 260 10/08/2016 1:06 PM