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Assessment of cytogenetics and physiological parameter of polycystic ovary

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Abstract
Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 5-10% of women of reproductive age. The present study is to detect the effect of chromosomal abnormalities and cytogenetic study in cases of polycystic ovary syndrome (PCOS). In the study 100 females were selected from out patients clinic of El Galaa teaching hospital, all cases will be subjected to history taking, radiological examination in addition to hormonal profile and chromosomal study. The obtained results showed some patients with PCOS are a significant change in LH, T test., F test. And PRL were observed. And there no cytogenetic abnormalities has been confirmed in this study.

Keywords: polycystic ovary syndrome (PCOS), cytogenetics, physiological parameter

Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women of reproductive age. It is a heterogeneous disorder of uncertain etiology, but there is strong evidence that complex interactions between genetic, environmental, and behavioral factors contribute to causing this syndrome (Bargiota A., *et al*. 2012) [3]. PCOS affects as many as 10% of reproductive-age women when using the NIH criteria for diagnosis, and up to 18% of reproductive-age women are diagnosed with PCOS as per the Rotterdam criteria (March *et al*., 2010) [12]. Nevertheless, at least 70% of PCOS cases remain undiagnosed in primary care (Tomlinson *et al*., 2013) [15]. Polycystic ovary syndrome (PCOS) is a long-term recognized, complex heterogeneous familial disorder (Azziz *et al*., 2011; Unluturk *et al*., 2016) [2, 16]. Yet, despite decades of research, the etiology of PCOS remains elusive (Azziz *et al*., 2016). It is characterized by hyperandrogenism, enlarged cystic ovaries and chronic anovulation (Ciampelli *et al*., 1998) [5].
Genetic studies of PCOS are also confounded by variability between different investigators, especially if the study design or diagnostic criteria used across studies are not the same. The group of Ewens *et al*., has used standard diagnostic criteria throughout their studies (oligo-amenorrhea and increased testosterone levels) to distinguish cases from controls. A potential problem is that any variability in diagnostic criteria between investigators may impact the ability of putative candidate genes identified in one population to be replicated in other populations if the initial population studied was phenotypically dissimilar, as a result of different diagnostic criteria (Ewens *et al*., 2010) [7].
In 2015, results from a number of studies added to our understanding of the genetic basis of the disorder. Hayes and colleagues reported on genome-wide association study (GWAS) involving 984 patients with PCOS diagnosed by the NIH 1990 criteria (Shim *et al*., 2015).

Etiology of Pcos
A number of hereditary and environmental factors contribute to ovarian hyperandrogenism and/or insulin resistance. Polycystic ovaries, androgen levels, and insulin resistance have hereditary components. Environmental factors may be congenital or acquired and include intrauterine factors such as androgen exposure and prenatal nutrition, whereas acquired obesity is a major postnatal factor influencing the phenotype (Vink *et al*., 2006) [17] about half of sisters are hyperandrogenic, and half of these also have oligo-amenorrhea and thus PCOS and polycystic ovaries appear to be inherited as an autosomal dominant trait (Franks *et al*., 2008) [8]. Although estimates vary widely, 3%–35% of mothers of women with PCOS also have PCOS, as do about 25% of sisters and metabolic syndrome prevalence is high in parents and siblings (Legro *et al*., 2005; Coviello *et al*., 2009) [6]. The syndrome's phenotypic diversity is affected by ethnic diversity (Louwers *et al*., 2013) [11].

Diagnosis of PCOS
The clinical spectrum is broad and extends from relatively normal menses to chronic oligomenorrhea, and amenorrhea, some patients with PCOS are obese while others are not. Some experience no hirsutism while others show mild or more severe virilization (Kovacs and Wood, 2001).

Epigenetics and PCOS
In particular, epidemiologic and clinical studies conducted largely in adult human populations suggest a link between foetal growth restriction, and subsequent risk of type 2 Diabetes Mellitus (DM) and cardiovascular disease (Barker *et al*., 1993; Hales *et al*., 2001) [4, 9].

Genetic factors
Increasing evidences over many years point to familial aggregation of women with PCOS, hyperandrogenism and metabolic alterations the model of inheritance of PCOS has not yet been defined. Some researchers have postulated autosomal dominant transmission linked to a single genetic defect, but most authors define PCOS as a polygenic pathology. It is also possible that a particular gene in a given

family may have a predominant effect, influencing the phenotypic manifestations of the syndrome. The main candidate genes are those encoding for factors involved in the synthesis, transport, regulation and effects of androgens. Other candidate genes are those encoding for factors involved in insulin metabolism, such as insulin receptors, signaling cascade proteins responsible for binding of insulin to its receptor, IGF system, other growth factors and the gene encoding for Calpain-10 enzyme, responsible for insulin secretion and action (Franks *et al*., 2004).

Chromosomal abnormalities

A relation between PCOS with the X chromosome aneuploidies and polyploidies in addition to other cytogenetic abnormalities has been confirmed. Some of the cases of PCOS may represent an intermediate condition in a spectrum that extends from the streak gonad of Turners syndrome to the normal ovary. The concept is that at least some cases of PCOS may be due to X chromosomal factors causing an abnormal follicular apparatus (Hickey *et al*., 2002). In addition, large deletion of the long arm of chromosome 11 was seen in some of the PCOS cases (Meyer *et al*., 2000) [13]. However, there is no large cytogenetic study to identify karyotype abnormalities (Sheikhha *et al*., 2006) [14].

Material and Methods

The current study was conducted in the infertility units and Physiotherapy Unit of El-Galaa Teaching Maternity Hospital during the period from January 2014 to September 2016.This prospective, randomized clinical trial was carried out on 100 infertile Egyptian patients with polycystic ovarian syndrome (PCOS).

The diagnosis of PCOS was based on the revised criteria of the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine in 2003 (two out of three criteria): (i) oligoand/or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenism; and (iii) polycystic ovaries; and exclusion of other etiologies (e.g. congenital adrenal hyperplasia, androgen-secreting tumours and Cushing syndrome).

Investigations

To diagnose polycystic ovarian syndrome we may need special Investigations, the aim of which is to confirm the diagnosis suspected from the clinical data and to assess the relative contribution of both the ovary and the adrenal to the disease process. 'These investigations include laboratory, radiology, endoscopic and pathological ones.

1. **Laboratory Investigations**
   - A- Androgens
     - Serum Testosterone Total & Free
     - Dihydrotestosterone (DHT)
     - Serum Androstendione
   - B- Gonadotropins
     - Luteinizing Hormone (LH)
     - Follicle Stimulating Hormone (FSH) and LH/FSH ratio
   - C- Estrogens
     - Estrone (E1) and Estradiol (E2)
   - D- Prolactin (PRL)
   - E- Growth Hormone (GH)
   - F- Serum Insulin level
2. **Radiological investigations**
3. **Laparoscopic examination**

The patients were allocated according to the following selection criteria:

1) Primary infertility of whatever duration.
2) Age: between 18-35Yrs.
3) An ovulation was the only confined factor of their infertility problem as detected by the basic infertility investigations.

Results

In the current study, one hundred women with non-ovulatory polycystic ovarian syndrome were randomly allocated from out patient's clinic of El Galaa teaching hospital.

Table 1: FSH (mIU/ml)-LH (mIU/ml)- PRL(ng/ml)-Total Test.(ng/ml)-Free Test. (pg/ml)

	N	Min - Max	Mean ± S.D
Age	100	18.0 - 35.0	25.0 ± 4.0
FSH	100	3.6 - 12.5	7.0 ± 1.7
LH	100	9.3 - 28.1	16.6 ± 3.2
PRL	100	14.3 - 28.6	22.1± 3.3
T. Testosterone	100	0.1 - 10.5	0.8 ± 1.0
F. Testosterone	100	4.2 - 10.2	7.6 ± 1.3

All parameters are represented as mean ± SD

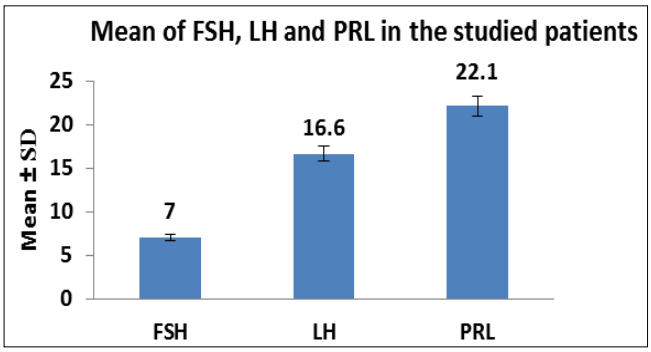

Fig 1: Mean of Follicular Stimulating Hormone, Luteinizing Hormone and Prolactin Hormone

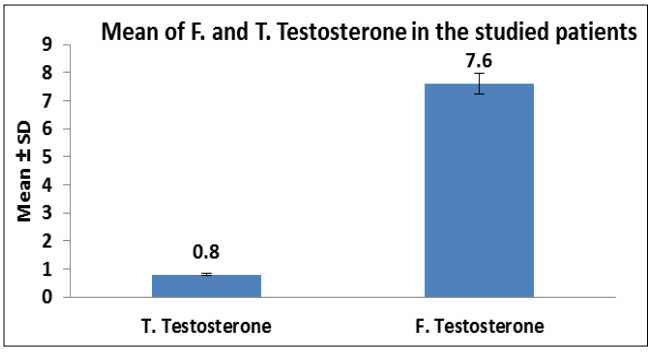

Fig 2: Mean of Total and Free Testosterone in the studied patients

Table 2: Correlation study

Pearson Correlation	FSH		LH		PRL		T. Test		F. Test	
	r	P. value	r	P. value	r	P. value	r	P. value	r	P. value
Age	-0.094	0.351	-0.024	0.815	0.047	0.646	-0.050	0.618	0.038	0.711
FSH			0.387**	0.001	0.137	0.175	0.081	0.421	0.129	0.201
LH					0.277**	0.005	0.094	0.354	0.059	0.558
PRL							0.176	0.080	0.162	0.108
T. Test.									0.135	0.181
F. Test.										

**. Correlation is significant at the 0.01 level (2-tailed).

LH / FSH Ratio

LH/FSH	2.4 : 1

Although previous studies suggest that the ratio between Luteinizing hormone and follicular stimulating hormone is 3: 1 but this study suggests that the ratio is 2.4: 1 in Egyptian population.

Karyotype

	N	%	P. value
Normal	100	100.0%	0.001**
Abnormal	0	0.0%	

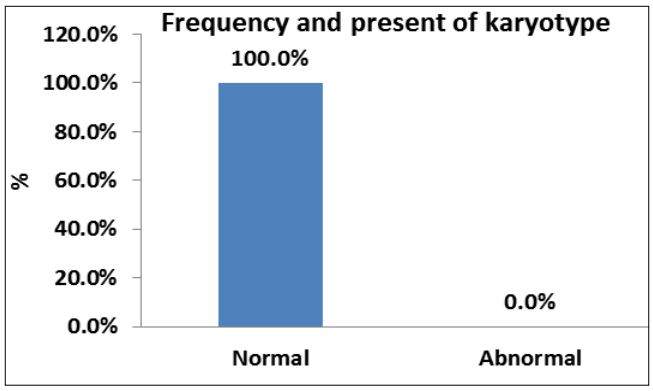

Fig 3: Frequency and present of karyotype

Discussion

The most common endocrine disorder affecting women of reproductive age is the polycystic ovary syndrome (PCOS). It affects approximately 10% of this population (Franks, 1995; Marx and Mehta, 2003). This disease is characterized by chronic anovulation and hyperandrogenism as broadly speaking (Homburg *et al*., 1996; Dunaif, 1997; Vandermolen *et al*., 2001; Barbieri *et al*., 2003), together with enlarged ovary with multiple small non-growing follicles often with obesity, hyperinsulinemia and insulin resistance (Giampelli and Lanzone, 1998) [5]. Obesity, in PCOS women is rather high, ranging from 30% to 60% (Franks, 1995).

Previous studies suggest that genetic factors play a major role in the etiology of PCOS (Dunif, 1998; Govind A 1999). However, the mode of inheritance of PCOS remains unknown, and recent studies indicate that this disorder could be a complex trait (Crosignani PG, Nicolosi AE, 2001). This means that several genes are interacting with environmental factors to provoke the phenotype (Weiss KM, Terwilliger JD, 2000). In contrast, biochemical parameters, including fasting insulin levels or hyperandrogenemia, seem to be highly heritable parameters, suggesting that some clinical signs, symptoms, or biochemical parameters of PCOS could be transmitted as mendelian autosomal dominant (Carey AH, Chan KL, 1993) or X-linked traits (Legro RS, 2002), but the genetic studies have not as yet concluded the pattern of heredity (Diamanti-Kandarakis E, 2005). While studies, so far, are unable to exclude an autosomal or X-linked dominant mode of inheritance, the heritability of PCOS is probably more complex, similar to that of type 2 diabetes mellitus or cardiovascular disease.

However, a positive family history appears to be the most informative risk factor for the development of PCOS. Furthermore, environmental factors alter the clinical and biochemical presentation in those with genetic predisposition to PCOS.

The concept is that at least some cases of PCOS may be due to X chromosomal factors causing an abnormal follicular apparatus (Hickey T, Chandy A, Norman RJ, 2002). In addition, large deletion of the long arm of chromosome 11 was seen in some of the PCOS cases **(**Meyer MF, Gerresheim F, 2000) [13]. However, there is no large cytogenetic study to identify karyotype abnormalities.

Clinical characteristics

Before starting the study, all patients were found balanced regarding the mean age, mean duration of infertility, and mean body mass index (BMI); three parameters which could have effect on the results. Thus, the random allocation and random classification in this study was successful in this aspect.

Age

Koivunen reported that the prevalence of PCOS is more common in women younger than 36 years (Koivunen, 1999; Koivunen *et al*., 2001). In the current study, the mean age was 25.0 ± 4.0 years with a range of 18 to 35 years.

Obesity

The prevalence of obesity in PCOS is variable (Balen, 1999; Legro, 2000; Balen and Rajkowha, 2003). (Legro 2000), reported that 38.4% of PCOS patients as based on ultrasound diagnosis were overweight (BMI > 26 kg/m2), while Hoeger (2001), found that 60% of PCOS patients as defined by anovulation and elevated androgen levels, were obese (BMI > 30 kg/m2). However, at least 20% of women are lean. These women are more insulin resistant than their normal eumenorrheic, weight-matched counterparts (Dunaif *et al*., 1992; Morales *et al*.,)

Menstrual cyclicity

As stated by several authors, the menstrual pattern in PCOS women is variable. Oligomenorrheais present in 50% to 90% of cases. Amenorrhea is present in 26% to 51% while normal menstrual pattern constitutes 22%of the cycles

(Franks, 1995; Azziz *et al*., 1998; Futterweit, 1999; Ibanez *et al*., 2000; Pirwany *et al*., 2003). In the current study, all studied women were initially oligomenorrheic. The range of the length of spontaneous menstrual cycle was 44-112 days.

LH & LH/FSH

Several authors reported that 94% of PCOS patients had an elevated LH levels (LH>7mIU/ml) and elevated LH/FSH ratio ranging from 1.5 to 3 (Taylor *et al*., 2000a; Slowey and Concord, 2001; Lewis, 2001).

In the current study the LH/FSH ratio was 2.4: 1 thus this is followed by the second type of PCOS.

Karyotype (Chromosomal Analysis)

All Patients have normal female Karyotype 46, XX. Thus, the analysis of the numerical chromosomes is statistically non-significant.

Conclusion

Polycystic ovary syndrome (PCOS) is a common, highly heritable complex disorder of unknown etiology characterized by hyperandrogenism, chronic anovulation and defects in glucose homeostasis. Increased luteinizing hormone relative to follicle-stimulating hormone secretion, insulin resistance and developmental exposure to androgens are hypothesized to play a causal role in PCOS. Chromosomal abnormalities not observed in polycystic ovarian syndrome patients. All patients have normal female karyotype (46, XX) with G-Banding or Giemsa banding. All patients have LH/FSH ratio 2.4:1 (This ratio is specific to the Egyptian Population).

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