

Assessment and Predictive Test of anti-Mullerian Hormone on Ovarian Responsiveness in PCOS Patients Undergoing Intracytoplasmic sperm injection

Thesis

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List of Abbreviations

ACTH	Adrenocorticotrophic hormone
AFC	Antral follicles count
AMH	Anti-Müllerian hormone
AR	Androgen receptors
ART	Assisted reproductive technology
BMI	Body mass index
cAMP	Cyclic adenosinemonophoshate
COH	Controlled ovarian hyperstimulation
DHEA	Dehydroepiandrosterone
E₂	Estradiol
FSH	Follicle-stimulating hormone
Gn-RH	Gonadotrophin Releasing Hormone
hMG	Human menopausal gonadotrophin
HP-hMG	Highly purified human menopausal gonadotrophin
HPG	Hypothalamus pituitary gonadal
ICSI	Intracytoplasmic sperm injection

 List of Abbreviations

IGF	Insulin-like growth factor
IVF	In vitro fertilization
LH	Luteinizing hormone
LOD	Laparoscopic ovarian drilling
NCAH	Non-classic congenital adrenal hyperplasia
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovary syndrome
PGT	Preimplantation genetic testing
rFSH	Recombinant follicle-stimulating hormone
SHBG	Sex hormone binding globulin
TSH	Thyroid stimulating hormone
TVUS	Transvaginal ultrasound

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INTRODUCTION

The polycystic ovary syndrome (PCOS) is a common condition affecting up to 7% of women of fertile age and is associated with 75% of the causes of anovulatory infertility (*Kousta et al., 1997*).

The number of follicles of 2 – 9 mm in the polycystic ovary seems to be key in determining the severity of the syndrome (*Piouka et al., 2009*) and the AMH produced by these follicles could be marked to reflect this. However, up to 20% of the female population of fertile age have been reported to have polycystic ovaries on ultrasound examination, but only 5 – 8% actually suffer from symptoms such as oligo/amenorrhoea or hyperandrogenism (clinical or biochemical), including hirsutism, persistent acne or hyperandrogenemia (*Balen et al., 2009*). The question has been raised whether polycystic ovarian morphology (PCOM) alone is simply a normal variant of ovarian morphology or is a precursor of the syndrome.

As FSH is responsible for the follicular development leading to ovulation, the oligo/anovulation, characteristic of PCOS, could be due to abnormalities of FSH which may be quantitative, or qualitative or both. The reported

property of AMH to oppose the actions of FSH imply that the high production of AMH by the polycystic ovary may have an important role in the pathophysiology of the syndrome (*Pellatt et al., 2011*).

Since AMH performs equally well, if not better, than AFC in predicting ovarian response and that it is both operator- and menstrual cycle-independent, there has been a growing trend to determine AMH assay as the first line ovarian reserve test (*Nelson et al., 2012*).

The emergence of a single unified assay for the measurement of AMH has added a new facet to the medicines, equipment, and techniques of those investigating PCOS (*Wallace et al., 2011*).

In addition, a positive correlation between AMH and both LH and testosterone serum concentrations in PCOS has been found (*Rosenfield et al., 2012*).

It has been demonstrated that the relatively good chance of success in women with potential for being high-responders could be increased by using a GnRH antagonist protocol with a starting gonadotropin dose of 150 IU daily (*Yates et al., 2011*)

But it is not confirmed if the type of gonadotropin preparation should be taken into consideration to further modulate the ovarian response. Indeed, highly purified menotropin (HP-hMG) and recombinant follicle-stimulating hormone (rFSH) are associated with differential follicular growth (**Devroey et al., 2012**), which may be attributed to differences in FSH isoforms and overall profile of isoforms, as well as the luteinizing hormone (LH)-activity component in HP-hMG (**Wolfenson et al., 2005**).

Further, a high basal concentration of AMH has been shown to be linked with excessive response to gonadotropin stimulation (**Arce et al., 2013**).

The overexpression of AMH and its receptors in oligo/anovulatory PCOS women could be due to elevated LH levels and/or inhibition of its repressive action. This dysregulation is observed in oligo/anovulatory, but not in normo-ovulatory, PCOS women and this implicates LH in the follicular arrest of PCOS (**Pierre et al., 2013**).

Research hypothesis:

In women with PCOS and undergoing ICSI, baseline AMH level may predict ovarian response accurately.

Research Question:

In women with PCOS and undergoing ICSI, does baseline AMH level may predict ovarian response accurately?

Aim of the Work

The aim of this study is to assess the accuracy of baseline AMH level for ovarian responsiveness in PCOS women undergoing Intracytoplasmic sperm injection (ICSI).

Patients and Methods

- **Study design:**

A prospective observational study.

- **Study Site:**

Maternity Hospital Ain Shams University, assisted reproductive technology Unit.

- **Study population**

The study population comprises women with PCOS, fulfilling the inclusion criteria, attending to Ain Shams University Maternity Hospital, assisted reproductive technology (ART) Unit, during the study period, who are planning for Intracytoplasmic sperm injection (ICSI).

- **Sample size**

A total number of 50 cases of women with PCOS will receive induction with human menopausal gonadotrophin (hMG) for Intracytoplasmic sperm injection (ICSI).

The Sample size was calculated using PASS 11.0 sample size calculation program, and based on the finding of a previous study carried out by *Amer et al., 2013* who stated that “Of the 34 cycles of hMG stimulation included in this study, 19 (56%) resulted in a good response

(defined as 3 or more follicles after hMG stimulation). The remaining 15 cycles were considered poor response (defined as either less than 3 follicles ($n = 6$) or no follicles after hMg stimulation ($n = 9$)). Group sample size of 50 patients will be included to achieve 81% power to detect a difference between the group proportion of 0.4400. The proportion in group one (the treatment group) is assumed to be 0.5600 under the null hypothesis and 1.0000 under the alternative hypothesis. The proportion in group two (the control group) is 0.5600. The test statistics used is the two-sided Fisher's Exact test. The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is 0.0184.

Inclusion criteria:

1. Women of age 18 - 35 years.
2. BMI 20 - 30 kg/m²
3. Diagnosis of PCOS based on Rotterdam consensus criteria 2003 (two of three criteria: Oligo/anovulation, hyperandrogenaemia and sonographic appearance of polycystic ovaries).
 - Hyperandrogenaemia may present clinically as hirsutism, acne, and/or pattern alopecia.