European Journal of Obstetrics & Gynecology and Reproductive Biology 222 (2018) 126–133

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Tumor necrosis factor alpha versus LH and androstendione as a reliable predictor of spontaneous ovulation after laparoscopic ovarian drilling for women with clomiphene citrate resistance polycystic ovarian disease

Emaduldin Seyam[a,*], Enas Hefzy[b]

[a] Obstetrics and Gynecology Department, Minia University College of Medicine, Minia, Egypt
[b] Microbiology and Immunology Department, Fayoum University College of Medicine, Fayoum, Egypt

ARTICLE INFO

Article history:
Received 6 May 2017
Received in revised form 5 November 2017
Accepted 10 January 2018
Available online xxx

Keywords:
Polycystic ovary syndrome
Clomiphene citrate
Tumor necrosis factor alpha (TNF-α)
BMI
Inflammatory markers
Insulin resistance and hyperinsulinism

ABSTRACT

Objective: Laparoscopic ovarian drilling (LOD) is still a controversial decision; due to the long term hazards; so short and long term predictors after the procedure should be taken in consideration. The aim of this work was to investigate the role of the serum level of tumor necrosis factor alpha (TNF-α) and other polycystic ovarian disease (PCOD) relevant clinical and biochemical factors as a predictor of spontaneous ovulation after laparoscopic ovarian drilling (LOD) in women with clomiphene citrate resistant polycystic ovarian disease (CCR-PCOD).

Methods: It was a prospective research work, where 150 infertile women with CCR-PCOD had been recruited. TNF-α serum level, which is an inflammatory biomarker, was investigated in addition to other PCOD relevant clinical and biochemical parameters as possible predictors of successful spontaneous ovulation and subsequent pregnancy after LOD.

Results: Recruited women with higher preoperative levels of TNF-α, LH, and androstenedione had significantly higher rates of spontaneous ovulation within the first three months follow up after LOD, in contrast to obese women with BMI ≥ 25 kg/m2, long duration of infertility ≥3 years, marked biochemical hyperandrogenism (testosterone levels ≥4.5 nmol/L, free androgen index ≥15), and high insulin resistance (IR). Ninty five (95 = 63.3%) women in between women regularly menstruated (105 = 70%) had spontaneous ovulation, and of those spontaneously ovulated, 35(36.8%) women got pregnant spontaneously during the first 3 months follow up. Extended follow up for 12 months period revealed that 61 women got pregnant, with cumulative pregnancy rate of 58%. Logistic regression showed that the best cut-off values for spontaneous ovulation after LOD were 65.1 pg/ml, 11.5 IU/l, and 3.1 ng/ml and with a sensitivity of 91%, 88%, 55%, and with a specificity of 85%, 79%, 78%, for TNF-α, LH, androstenedione serum level respectively.

Conclusion: TNF-α, LH, and Androstenedione could be considered as reliable predictors to depend on for recruiting the ideal women candidates with CCR-PCOD; to have the maximum benefits after LOD treatment option.

Introduction

Polycystic ovary disease (PCOD) is a predominant cause of anovulatory infertility, and considered the commonest endocrine disorder during the women reproductive age. Epidemiologically, it has a prevalence rate of 20% based on the Rotterdam diagnostic criteria recently reported. This means that one in five infertile women attending infertility clinics would have PCOD. The etiology

Abbreviations: TN-α, tumor necrosis factor alpha; PCOD, polycystic ovarian disease; LOD, laparoscopic ovarian drilling; CCR-PCOD, clomiphene citrate resistant polycystic ovarian disease; BMI, Body Mass Index; LH, lutienzing hormone; FSH, follicle stimulating syndrome; CRP, C Reactive Protein; IGF1, insulin growth factor 1; DHEAS, dehydroepiandrosterone sulfate; 17α-OH-P, 17 alpha-hydroxyprogesterone; FAI, free androgen index; HOMA-IR, homeostasis model assessment formula for insulin resistance; SHBG, sex hormone binding globulin; Ir, insulin resistance; AMH, antimullerian hormone; E2, Estrogen2; OGTT, oral glucose tolerance test.

* Corresponding author.
E-mail addresses: eemsseyam@yahoo.com (E. Seyam), emhefzy@yahoo.com (E. Hefzy).

https://doi.org/10.1016/j.ejogrb.2018.01.011
0301-2115/

and pathophysiology of PCOD still remain a complicated issue with a strong evidence linking this common syndrome with hyperandrogenesim, insulin resistance and compensatory hyperinsulinemia [1–5].

Polycystic ovary disease have been proved to be a proinflammatory disorder and several publications on PCOD have show increased levels of circulatory inflammatory markers such as plasminogen activator inhibitor-1, TNF-α, Il-6, Il-18, and C Reactive Protein (CRP). The reason of increased inflammation in PCOD has not been clarified yet, and it remains uncertain whether it is associated with PCOD itself or the accompanying obesity. Upcoming results put those biomarkers as dependant factors in the pathogenesis of PCOD [6–8].

PCOD has been surgically managed with ovarian wedge resection in the 1930s. This procedure has been replaced by laparoscopic ovarian drilling (LOD) which is considered a minimally invasive alternative, and recently recommended by the second ESHRE/ASRM PCOS consensus workshop as a second line intervention management for CCR-PCOD women. A recent Cochrane review found that LOD resulted in a pregnancy rate of 39.7% and a live birth rate of 33.9% in this subset of women without an increased risk of multiple pregnancy or OHSS [9–12].

The mechanism of LOD action still remains unclear. Its effect might be through re-adjusting the ovarian pituitary feedback mechanism. Another explanation is that damage of ovarian follicles and parts of the ovarian stroma could result in local and systemic reduction of androgens and inhibin levels, which would be followed with increased FSH levels; thus promoting follicular maturation and subsequent ovulation. Others believe that postoperative intra-ovarian inflammatory changes might lead to release of local of growth factors such as IGF1 that interacts with FSH ending in follicular growth and ovulation, in addition to postoperative improved insulin sensitivity [8,10,13].

Around 30% of PCOD women fail to ovulate after LOD, which known as LOD non-responders, diagnosed with lack of regular menstruation and absence of ovulation ≥8 weeks following the procedure. Detection of reliable predictors for LOD success is considered an important issue to improve the procedure outcome and avoiding unnecessary surgical intervention with possible risks of decreasing the ovarian reserve. And so, the aim of this work is to investigate TNF-α, which is an inflammatory biomarker versus other different clinical, biochemical parameters that help in predicting spontaneous ovulation and pregnancy after LOD.

Patients and methods

In this cohort study, 150 women who are CCR-PCOD, and underwent LOD at a private fertility care centre had been recruited between January 2014 and December 2016. PCOD had been diagnosed according to the revised announcement of the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) criteria of 2004 which had been based on the Rotterdam criteria [4,5].

Clomiphene citrate resistance (CCR) had been diagnosed with the absence of growing follicles after ovarian induction with 150 mg clomiphene citrate/dayily, starting from the 2nd to 5th day of the menstrual cycle, and for 3 successive cycles. A total of 150 patients who had met those criteria and underwent LOD were recruited. The details of the recruited women could be seen in Table 1. The sample size had been chosen after statistical consultation; to get the highest statistical power for the work. The recruited women for this work had shared before in a preliminary study, which investigated the role of TNF-α in different PCOD phenotypes.

The exclusion criteria adopted during subject selection were: other causes of irregular menstrual cycles and/or androgen excess (i.e., Cushing's syndrome, hyperprolactinemia, congenital adrenal hyperplasia, or other diseases of the adrenal gland, thyroid disorders, galactorrhea, breastfeeding and pregnancy), impaired glucose tolerance or type 1/type 2 diabetes, hypertension, hyperlipidemia, active or chronic liver or renal failure, or congestive heart failure, a history of coronary artery disease, and gestational diabetes mellitus (GDM).

Table 1
Preoperative clinical and biochemical parameters.

Variable	Group A (responders) (n = 105)	Group B (non-responders) n = (45)	P
Clinical Factors			
Age (years)	26.2 ± 1.1	25.4 ± 2.3	0.37
BMI (Kg/m)	26.4 ± 2.3	27.2 ± 1.3	0.42
Menstrual Regularity	20(13.13%)	17(11.3%)	0.57
Infertility duration	3.2 ± 1.3	3.5 ± 2.4	0.34
Type of infertility			
Primary	54(36%)	96(64%)	0.33
Secondary	26(32%)	32(34%)	
Biochemical factors			
TNF-α (pg/ml)	81.4 ± 9.8	78.2 ± 6.5	0.001
LH (IU/l)	10.6 ± 3.2	11.1 ± 2.1	0.001
FSH (IU/l)	5.4 ± 2.4	4.9 ± 2-5	0.001
Prolactin (ng/l)	22.2 ± 6.7	21.1 ± 7.5	0.001
Testosterone (ng/dl)	3.8 ± 3.1	3.6 ± 205	0.55
DHEAS-SO4 (umol/ml)	7.7 ± 2.4	6.8 ± 3.1	0.97
SHBG (nmol/l)	36.2 ± 1.5	34.3 ± 2.1	0.09
Androstendione (ng/l)	2.3 ± 3.2	2.9 ± 2.8	0.02
Fasting insulin (IU/l)	22.5 ± 3.9	20.13 ± 2.45	0.002
HOMA-Ir	2.8 ± 5.2	3.1 ± 1.1	0.001
Ovarian Volume (cm)	12.6 ± 3.2	11.9 ± 6.6	0.14

BMI, body mass index; CC, clomiphene citrate; FSH, follicle stimulating hormone; IQR, interquartile range; LH, luteinizing hormone; SD, standard deviation; SHBG, sex hormone binding globulin; US, ultrasonographic. Data are presented as mean SD, median (interquartile range, IQR) and number (%) as appropriate.* Statistical significance ($P < 0.05$).