New trends in induction of ovulation in patients with polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is the major cause of infertility in developed countries (***Guzick, 2007***), While it is diagnosed in 4–10% of women attending gynaecology clinics in developing countries (***Dunaif, 1997***). It is a common female disorder of fertile age. The pathogenesis remains still today not completely clear. However the syndrome is characterized by an increased frequency of LH pulse over FSH favouring the androgen production by ovarian theca cells and the increase of 17β- estradiol conversion in granulosa cells. Insulin plays also a key role in the pathogenesis of PCOS acting sinergically with LH on theca cells, and reducing the sex hormone binding globulin (SHBG) and thus increasing the biologically active androgen levels. In addition, several paracrine and autocrine factors mediate the effect of LH and insulin (***Stefano et al***, **2006**).

Polycystic ovary syndrome (PCOS) is a syndrome of ovarian dysfunction showing cardinal features of hyperandrogenism and polycystic ovarian morphology (**The Rotterdam *consensus workshop, 2004***). It is one of the most common reproductive endocrine disorders in

young adult women who exhibit clinical signs of menstrual disorder, anovulation, hirsutism, acne, and obesity. Approximately 15% of patients with PCOS remain anovulatory despite treatment with clomiphene citrate (CC), and half of patients with PCOS who became ovulatory on this treatment fail to conceive (***Nugent, et al, 2000***).

Traditional and well validated treatments used for ovulation induction in women with PCOS are administration of clomiphene citrate (CC) and gonadotropins, and the surgical ovulation induction with the use of laparoscopic ovarian diathermy (LOD). New treatments, which have been gaining a lot of popularity in clinical practice, are the use of insulin sensitizing drugs such as metformin and specific lifestyle programs for obese women with PCOS ***(Palomba. et al, 2004***).

Women with polycystic ovary syndrome (PCOS) have a myriad of phenotypic and clinical features that may guide therapeutic options for metabolic protection and ovulation induction. The primary etiology of PCOS is unknown; however, insulin resistance with compensatory hyperinsulinemia is a prominent feature of the syndrome

and appears to have a pathophysiologic role in the hyperandrogenism of the disorder for both lean and obese women with PCOS (***Dunaif et al., 1989***). Hyperinsulinemia results in increased ovarian androgen biosynthesis (***Adashi et al., 1985***) and decreased sex hormone–binding globulin synthesis from the liver (***Nestler et al., 1991***), which leads to increased bioavailability of free androgens. Previous research clarified the relationship between PCOS and insulin resistance and led to the use of insulin-sensitizing medicines to treat women with PCOS for ovulation induction. Among the insulin-sensitizing medicines, metformin has been widely accepted for use and has the most reassuring safety profile (***Nestler et al., 2002***). Metformin reduces the insulin response by decreasing hepatic gluconeogenesis and reducing androgen levels, which allows resumption of normal menstrual cyclicity. By increasing insulin sensitivity, metformin ***reduces*** insulin resistance, insulin secretion, and hyperinsulinemia (***Dunn and Peters, 1995***).

Gonadotropin therapy is widely used as the second-line treatment for induction of ovulation after failure of CC to achieve a pregnancy in anovulatory women with PCOS. Theoretically, pure FSH is advantageous over human menopausal gonadotropins (hMG) in view of the high

levels of endogenous LH in women with PCOS. However, both preparations have been used successfully for ovulation induction in these women with comparable results ***(Howles et al., 2010).*** Before ovulation induction with gonadotropins, patients should be counselled about the risks of OHSS and higher-order multiple pregnancies. Serial ovarian ultrasound scans and measurements of serum oestradiol (E2) concentrations during gonadotropin ovarian stimulation are necessary to predict these risks (***Engmann et al., 2008).***

Aim of the study:-

The aim of the study is to highlight the new trends in ovulation induction among polycystic ovary patients.

Chapter I

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. It is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can to a large degree be classified as a genetic disease ***(Simon .et al, 2011).*** It produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility and the most frequent endocrine problem in women of reproductive age (***Moran, 2010)***.

Definitions

The diagnosis of PCOS remains controversial and is based on various signs, symptoms, and/or laboratory findings that are not universally accepted. The four most common definitions of the syndrome are presented in Table (1). The 1990 National Institutes of Health (NIH) definition requires the simultaneous presence of hyperandrogenism (clinical and/or biochemical) and menstrual dysfunction in the absence of other causes highlighting the importance of hyperandrogenism in the syndrome's etiology ***(Dunaif A,***

1992). In contrast, the 2003 Rotterdam [European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM)] definition requires only two of the following three criteria: (1) Hyperandrogenism (clinical and/or biochemical), (2) ovulatory dysfunction (oligo- or anovulation), and (3) ultrasonographic evidence of polycystic ovaries in the absence of other cause ***(Rotterdam , 2004***). Importantly, the Rotterdam criteria broadened the PCOS phenotype to include women with ovulatory dysfunction and polycystic ovaries but without hyperandrogenism, and eumenorrheic women with hyperandrogenism and polycystic ovaries (often called ‘‘ovulatory’’ PCOS ***(Panidis , 2007).*** However, the 2006 Androgen Excess Society (AES) definition reemphasized the importance of hyperandrogenism in the etiology of PCOS, requiring: (1) The absence of other hyperandrogen-causing disorders, syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia, (2) hyperandrogenism (clinical and/or biochemical), and (3) ovulatory dysfunction (oligo- or anovulation) or polycystic ovarian morphology ***(Azziz et al ., 2006).*** The 2009 Androgen Excess and Polycystic Ovary Syndrome Society’s definition also emphasized the importance of hyperandrogenism in the syndrome’s