Guidelines for the use of Insulin Sensitizing Drugs in the management of PCOS-associated Infertility

Clinical Practice Guidelines

Middle East Fertility Society

1.0 INTRODUCTION

1.1.0 Definition

1.1.1 Increased insulin resistance is observed in 20-30% of non-obese and 70-80% of obese women with polycystic ovary syndrome (PCOS). Women affected by the syndrome tend to be more insulin resistant than weight-matched women in the general population. Although obesity is a recognized risk factor for decreased insulin sensitivity, at least one aspect of the insulin resistance hypothesis in the context of PCOS is thought to be largely obesity-independent.

1.1.2 Hyperinsulinemia is believed to stimulate ovarian androgen production by direct action on theca cells and by potentiating LH effect. The local build-up in follicular androgenic signal has been shown to promote premature follicular atresia, primary and pre-antral follicle arrest, and impaired follicle dominance leading to anovulation. High insulin state potentiates adrenal androgen secretion by enhancing adrenal response to ACTH. Insulin has further been implicated in impairing progesterone inhibition of the Gonadotropin Releasing Hormone pulse generator and suppression of liver sex hormone-binding globulins.

1.2.0 Insulin sensitizing drugs

1.2.1 The management of PCOS has traditionally focused on the initial complaint at the time of presentation. Interest in the role of insulin sensitizing drugs (ISDs) as a means of reducing compensatory hyperinsulinemia in the hope of improving metabolic and reproductive functions in women with PCOS has grown measurably over the past decade.

1.2.2 Metformin is an FDA-approved biguanide for the management of type 2 diabetes mellitus. It is believed to lower fasting serum insulin levels in insulin-resistant states without inducing hypoglycemia.

1.2.3 Metformin is a Class B drug with no proven teratogenic risks in animals, and no reported untoward effects in humans. It is the only ISD recommended for use in women planning to conceive.

1.2.4 The main limitations to the use of Metformin remain nevertheless its side effects, causing about 30% of patients to discontinue treatment. These are predominantly gastrointestinal in nature, consisting of bloating, abdominal discomfort, nausea, vomiting and diarrhea (OR 4.27, 95% CI 2.4 to 7.59; 5 trials; 318 women).

1.2.5 A rare but serious complication of Metformin therapy is lactic acidosis.

1.2.6 Thiazolidinediones belong to another group of ISDs, and include rosiglitazone and poiglitazone.

1.2.7 The use of Thiazolidinediones presents several limitations to daily practice, nonetheless. This class of ISDs increases the incidence of weight gain among users by promoting adiposity, a counter-intuitive feature in the context of PCOS management.

1.2.8 Thiazolidinediones are also associated with increased cardiovascular risks, namely coronary artery disease, myocardial infarction and non-fatal heart failure.

1.2.9 More recently, an increased risk of bladder cancer has raised additional concern; further constraining Thiazolidinediones use in healthy individuals.

1.2.10 Rosiglitazone and Poiglitazone are classified as category C drugs with proven teratogenicity in animals and therefore limited use in humans, namely women planning for conception.

1.2.11 It is therefore unlikely that Thiazolidinediones may play a significant role in the management of PCOS in the future.

1.3.0 General considerations

1.3.1 Although the role of insulin resistance in the pathogenesis of PCOS is now well established, confusion exists in common daily practice regarding the role of ISDs in the management of this condition.

1.3.2 This document has been produced to formulate practice points on the value of ISDs in improving pregnancy outcomes in view of available evidence.

1.3.3 Clearly, there is a lack of high quality evidence about effectiveness of ISDs at reproductive outcome endpoints.

2.0 RECOMMENDATIONS for women with PCOS-associated subfertility

2.1.0 Non-obese women (BMI <30kg/m2) with PCOS-associated subfertility

2.1.1 For this category of women, there is moderate quality evidence demonstrating that **Metformin monotherapy** improves the odds of ovulation and increases clinical pregnancies.

2.1.2 Metformin monotherapy as a first-line treatment may be reserved for those in this group of women who may be reluctant to initiate ovulation induction using Clomiphene citrate (CC) during the first six months of attempting to conceive.

2.1.3 There is moderate quality evidence demonstrating the absence of reproductive benefit when Metformin is combined with CC therapy in non-obese women with PCOS-related subfertility.

2.1.4 **CC alone therapy** remains the mainstay pharmacological therapy for this group of women.

2.2.0 Obese women (BMI ≥30kg/m2) with PCOS-associated subfertility

2.2.1 For this category of women, there is low quality evidence showing the failure of Metformin monotherapy to improve reproductive endpoints.

2.2.2 In view of the considerable side effect profile, Metformin monotherapy may not be recommended for fertility management in this group of women.

2.2.3 There is moderate quality evidence to support a beneficial effect of **Metformin in combination with CC therapy** in increasing the likelihood of ovulation and clinical pregnancies.

2.3.0 Women with CC-resistant PCOS-associated subfertility

2.3.1 For this category of women, there is moderate quality evidence to support that Metformin co-treatment increases ovulation rates.

2.3.2 There is also low quality evidence demonstrating that **Metformin/CC combination** therapy may be associated with higher live births than laparoscopic ovarian drilling (LOD).

2.3.3 Women with CC-resistant PCOS may be given the benefit of a trial of medical ovulation induction using combination therapy prior to committing to the more invasive and expensive alternative of LOD.

3.0 RECOMMENDATIONS for women with PCOS undergoing assisted reproductive techniques

3.1.1 For women with PCOS undergoing IVF/ICSI treatments, there is moderate evidence to support the failure of Metformin co-administration to improve the clinical outcomes of live births, clinical pregnancies, or miscarriages.

3.1.2 There is moderate evidence demonstrating a significant reduction in the risk of ovarian hyperstimulation syndrome (OHSS) with Metformin co-treatment, when human chorionic gonadotropin (hCG) is used to trigger final oocyte maturation.

3.1.3 This benefit is however marginalized when appropriate ovarian stimulation protocols are utilized for women hyper-responders, namely gonadotropin-releasing hormone (GnRH) agonist trigger of ovulation.

4.0 CONCLUDING REMARKS

4.1.1 It should be emphasized that the strengths of the conclusions in this management protocol remain limited by severe weaknesses related to the quality of evidence available. Despite the availability of numerous meta-analyses, most suffer from major heterogeneity and poorly-powered trials.

4.1.2 Sources of heterogeneity were caused by differences in ethnic backgrounds, geographic locations, diagnostic criteria, presence of infertility confounders, and influence of fertility co-treatments. They were also caused by inconsistencies in methodology of ISD administration, outcome end-points, study design and follow-up periods.

4.1.3 It is therefore important to interpret current findings cautiously as more evidence accrues. The suggested recommendations were based on the current state of evidence, and may be subject to constant updating as more data are in the process of being generated.

Prepared by	**Name**	**Date**
Head, REI Division Professor of Obstetrics and Gynecology	Johnny Awwad, MD	January 3, 2013
Associate Professor of Clinical Obstetrics and Gynecology	Ghina Ghazeeri Abiad, MD	January 3, 2013
Reviewed and Concurred by	**Name**	**Date**
Professor of Clinical Obstetrics and Gynecology	Antoine Abu Musa, MD, PhD	February 1, 2013
Professor of Clinical Obstetrics and Gynecology	Antoine Hannoun, MD	February 1, 2013
Approved by	**Name**	**Date**
Head, REI Division	Johnny Awwad, MD	March 1, 2013
Department Interim chairperson	Anwar Nassar, MD	March 1, 2013