A Stepwise Approach to Mono-Ovulation in Women with Polycystic Ovary Syndrome: A Clinical Review on Ovulation Induction

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Objective: The purpose of this clinical review was to determine the most efficient, evidence-based method to achieve mono-ovulation in women diagnosed with polycystic ovary syndrome (PCOS).
Background: PCOS affects 5-10% of women of reproductive age and is the most common cause of anovulatory infertility. There are several approaches to ovulation induction treatment that varies in efficacy, time consumption and patient compliance.
Data Sources: Sources included Medline, Embase, Cochrane Library and reference lists on cited articles to May 2015. **Study Selection**: Eligible studies were in English, with information on treatment, efficacy and complication rates. Data were extracted describing level of evidence, treatment efficacy and multiple births. Systematic reviews, meta-analyses and randomized controlled trials were favored over cohort and retrospective studies.
Results: Ovulation rate is improved by lifestyle intervention (LI) in overweight women. Therefore, the primary consultation should focus on LI, such as dietary advice and exercise. LI improves body composition (BMI, body weight and waist-to-hip ratio), hyperandrogenism, and insulin resistance in women with PCOS. The efficacy of metformin in PCOS patients is related to the BMI. Metformin may regulate the menstrual cycle within 1–3 months of treatment. Pregnancy rates are higher for metformin compared to placebo (OR 2.31, 95%CI (1.52–3.51)). However, metformin does not improve the life birth rate (LBR) whether used alone (OR 1.80, 95%CI ((0.52– 6.16)) or in combination with clomiphene citrate (CC) vs. CC as monotherapy (OR 1.16, 95%CI (0.85–1.56). CC is recommended as primary treatment for PCOS related infertility. CC induces ovulation in three out of four patients, the risk of multiple pregnancies is modest, and the treatment is simple and inexpensive. It is not recommended to increase the dose above 150 mg/day. The starting dose of CC may be increased to 100 or 150 mg/day depending on the BMI. If ovulation is achieved on CC, up to six treatment cycles is suggested. The cumulative pregnancy rate is 46% after four cycles and 65% after six cycles. Exogenous gonadotropins (FSH) may be used as an alternative first line treatment or for CC resistant women. In order to reduce the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS), a step-up protocol with a low starting dose is recommended. If no response can be detected after at least seven days of stimulation, the dose can be increased by 25 to 37.5 IU/day. One study has shown a cumulative LBR of 47.4% after three FSH ovulation induction cycles compared with 36.9% in patients treated with CC (P = 0.03). Laparoscopic ovarian drilling is an alternative treatment, and should be considered in women with a history of CC resistance, previous OHSS or uncontrollable stimulation cycles. Conclusion: More than half of the women diagnosed with PCOS are overweight or obese. This implies the need for individualized treatment to carefully balance the advantages and disadvantages of the different ovulation induction strategies. This review suggests a stepwise approach to induce mono-ovulation in PCOS patients.

Figure 1: Treatment strategy to ovulation induction in women diagnosed with PCOS

Treatment strategy to ovulation induction in women diagnosed with PCOS			
Recommendations:	Consider:		
1. Clomifene citrate, 50–100 mg*	**Lifestyle interventions**	**Metformin*** **	**Ovarian drilling**
2. Gonadotropins. Low dose step-up protocol**			
*A starting dose of 100 mg is recommended to obese women with BMI>30 kg/m^2, hyperandrogenism, amenorrhea or women with a large ovarian volume			
** Women with increased BMI and amenorrhea often have a higher threshold value			
*** No effect on life birth rate. Treatment with metformin is controversial			

Figure 2: Evaluation of treatment modalities in ovulation induction in relation to efficacy, advantages and disadvantages.

Treatment modalities in ovulation induction for women diagnosed with PCOS – graded with pros (green) and cons (yellow, red)						
	Ovulation	Multiple pregnancies	Time to pregnancy	Ultrasound examinations	Side effects	Patient compliance
Lifestyle interventions	↑					
Metformin	↑					
Clomifene citrate	↑↑					
Gonadotropins	↑↑↑					
Ovarian drilling	↑					
↑ Indication of efficacy in relation to ovulation induction						