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Mini Review

How do we Manage Obese PCOS Infertile Patients

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Abstract

Poly cystic ovary syndrome (PCOS) is primarily a disorder of clinical and biochemical androgen excess plus either chronic anovulation and/or polycystic ovaries with exclusion of hyperprolactinaemia and 21 hydroxylase deficiency. Over 60% of PCOS patients seen in clinical settings are obese and it becomes challenging to Manage these obese infertile PCOS patients. Importance of life style interventions, role of bariatric surgery when required, various ovulation induction agents with primarily clomiphene citrate and letrozole along with role of anti-obesity drugs and insulin sensitizers like metformin is discussed. Second line treatment include gonadotropins, IVF, electroacupuncture and management according to BMI groups is discussed which needs individualized treatment.

Keywords: *Obese; PCOS; Bariatric Surgery; Anti-Obesity Drugs; Metformin; Letrozole; cc*

Introduction

PCOS is an evolving concept, as shown by the changing definitions. In 2004, definition of PCOS in women changed from the classic National Institute of Health (NIH) definition [1], i.e. clinical and/or biochemical androgen excess plus oligo anovulation with exclusion of specific etiologies like hyperprolactinemia, and 21 hydroxylase deficiency to the more inclusive Rotterdam's criteria [2] (any two of the following three criteria after similar exclusion, clinical and/or biochemical androgen excess, oligo or anovulation and polycystic morphology on ultrasonology. In 2009 the androgen excess society launched a new definition that considered PCOS primarily as a disorder of clinical and biochemical androgen excess plus either chronic anovulation and/or polycystic ovaries, still with exclusion of specific etiologies [3]. Further changes and updates till date in definition from time to time are depicted in table 1 [4-7].

Organization Group Year	Criteria
National Institute of Health(NIH) [1] 1990	Both hyperandrogenism and chronic anovulation
Rotterdam European Society For Human [2] 2003 Reproduction/American Society of Reproductive Medicine (ASRM)-sponsored PCOS census workshop group Androgen Excess Society [3] 2009	Two of the following conditions: hyperandrogenism, chronic anovulation, polycystic ovary Hyperandrogenism (central feature; biochemical or clinical) and ovarian dysfunction including infrequent or irregular ovulation or anovulation and/or polycystic ovary
Asterdam ESHRE/ASRM sponsored [4] 2011 [4] PCOS consensus workshop [4] NIH endorsed based workshop [5] 2012 European Society of Endocrinology [6] 2014 Practice Guidelines of Endocrine [7] 2013 Society	Different phenotypes separated by hyperandrogenism and chronic anovulation from those by ovulatory dysfunction and PCOM. Maintain broad Rotterdam criteria along with specific PCOS phenotypes for each single patient esp from metabolic point of view [6] confirmed by Eur society of endocrinology. Use of Rotterdam criteria for PCOS diagnosis Confirmed although characteristics of specific phenotypes at diagnosis was not considered clinically needed.

Management of obese PCOS infertile patient

Ovulation Induction in PCOS depends on patients BMI, insulin resistance etc.

Role of Diet

Lower carbohydrate 41:19:40 x 8 weeks has been shown to significantly increase insulin sensitivity and basal β cell response and be effective in reducing circulating testosterone as assessed by C peptide response to glucose during a liquid meal test and HOMA IR in 30 PCOS patients [8]. Mindful based stress reduction has been found to be an adjunct treatment in reducing BP, blood glucose, psychological distress and quality of life in PCOS who are overweight or obese [9].

Role of Bariatric Surgery

Bariatric Surgery is offered if diet and exercise doesn't effect weight loss in morbidly obese. In an analysis of 566 morbidly obese women undergoing Roux-en-Y-gastric bypass 31 (5.5%) had PCOS and Jamal., *et al*. found a 100% conception rate in those desiring conception in the morbidly obese group with mean BMI 52.8+-9.08 Kg/m^2 (37 - 76 kg/m^2) before surgery with excellent amelioration of PCOS manifestations like menstrual irregularities, hirsutism [10]. Similarly Escobar Morrealle advised metabolic surgery depending on fertility desire and to weigh pros and cons of surgical complications with that of metabolic complications and chances of spontaneous conceptions with so much weight loss achieved in such morbidly obese patients [11,12].

Role of Ovulation Induction (OI) agents

CC, an estrogen receptor antagonist acting by increasing serum FSH remains the first line of treatment. Its limitations remain in patients with BMI > 30 KG/M2 and advanced age with although ovulation rate in 70 - 80%, but pregnancy rates only in 22% because of its anti-estrogenic effect on endometrium and poor cervical mucus [13].

Gharib., *et al*. found comparing letrozole 2.5 mg (n = 30) with tamoxifen (Tmx) 20 mg 0d x 5d (n = 30) (BMI-20 - 30 Kg/m^2) found DF >= 18 mm in letrozole grp was > Tmx. Ovulation was 23.3% in letro vs 8.89% Tmx grp and preg occurred in 5.56% in letro vs 2.2% in Tmx grp showing letro superior although both can be used In CC resistant patients [14].

Role of Aromatase Inhibitors

Although both letrozole and anastrozole are banned in India they were approved for OI in 2001 and special interest was for getting mono folliculogenesis [15] but a recent review and comment s by Kasper., *et al*. show right from heading how under the false impression as many as sixtuplets [16,17] got born with 3rd cycle of 7.5 mg letrozole and hence careful monitoring is needed even when planning an IUI. In a double blind multicentre trial Legro., *et al*. studied 750 women in a 1:1 ratio randomized to receive either letrozole or CC and basal characteristics were similar with basal BMI in all women in letrozole group being 35.2 +- 9.5 and in CC 35.1 +- 9 and without any life style intervention that found cumulative live birth was higher in letrozole group 103/374 (27.5%) vs 72/376 (19.1%) in CC group respectively. Similarly cumulative ovulation rate was 834/1352 treatment cycles (61.6%) vs 688/1488 treatment cycles (48.3%) in CC, although statistically significant difference in the pregnancy losses in both groups as well as congenital malformations [18].

Glucocorticoids-prednisolone/dexamethasone-used to induce by adding high dose short course to CC resistant PCOS with normal DHEAS is associated with no androgenic effects on endometrium and higher ovulation and pregnancy rates in significant number of cases. Dexa 0.25, 0.5 mg at bedtime [19] - Addition of 2 mg dexa from 3 - 5 days is associated with higher ovulation rates and cumulative rates in 230 patients who failed to ovulate to 200 mg CC X 5 days [20]. Enthusiasm has dampened by potential adverse effects on insulin sensitivity, therefore prolonged use is to be discouraged.

Role of Insulin Sensitizers

Metformin a biguanide commonly used as an oral hypoglycaemic was utilized for its effects of tackling IR in patients with type 2 DM and had been found to improve menstrual cyclicity, improve anovulation by reducing insulin levels and altering the effects of insulin on androgen biosynthesis, also potentially inhibits through a direct effect on inhibiting ovarian gluconeogenesis. Further Genazzani., *et al.* 2010 studying allopregnanolone response to ACTH in 22 overweight patients with PCOS with hyperinsulinemia found that allopregnanolone secretion is altered with no change in progesterone secretion in obese patients with PCOS which gets corrected by metformin and restores normal steroid synthesis both from the ovary as well as the adrenal gland [21]. Dosage-Starting with 500 mg od with food, increased gradually upto 1500 mg weekly. Target dose is 500 - 850 mg t.id. If patient does not respond to 1500 mg, unlikely that she will respond to 2000 mg. Nausea, vomiting diarrhea are the commonest side effects, besides Lactic acidosis occurring mainly in patients with renal impairment.

Thiazolidinediones (Th)-Th like troglitazione, rosiglitazone/pioglitazone, activate transcription of genes that affect glucose and lipid metabolism mediating decreased free fatty acid levels and decreased visceral fat mass [22]. Although troglitazone can improve ovulation it was abandoned because of hepatotoxicity. Rosiglitazone (4 mgbd) has been shown to enhance both spontaneous and clomiphene induced ovulations in PCOS women with a BMI of 35.5 - 38.5 kg/m^2. Liao., *et al*. showed in 58 patients where n = 29 received metformin alone or n = 29 metformin along with 4 mg bd rosiglitazone for 6months and BMI decreased significantly by 7.8% in metformin grp with no change in met +rosi although 6 pregnancies were achieved in the combination group although only 2 in metformin alone [23]. While Mohsen using CC alone n = 46 or CC with rosi (4 mgbd n = 45) for 12 weeks found enhancement of CC induced ovulation with rosi along with insulin sensitivity although no statistical difference was found in the cumulative pregnancy rates in the 2 grps (30.4 vs 28.8% respectively) [24]. Although both rosiglitazone and pioglitazone have very little short term risk they have been classified as pregnancy category C drugs, hence should be discontinued immediately after pregnancy although no adverse congenital effects were found in the above studies. Tang., *et al*. updated the Cochrane review about insulin sensitizing drugs from 2010 to 2012 and concluded that there is no evidence that metformin improves live birth rates, used alone or in combination with CC. Hence the use of metformin in improving reproductive outcomes in women with PCOS remains limited. Th group has been shown to improve IR but their safety in human foetus is not well established and hence metformin starting from 500 mg, titrating to a higher dose currently is recommended [25].

Role of IPG mediators of Insulin Action-Myoinositol and DCI

Growing attention has been given to the role of inositol phosphoglycans (IPG) mediators of insulin action and evidence suggests that deficiency of D-chiroinositol (DCI) containing IPG, might be at the basis of IR, frequent in PCOS patients. Based on these insulin sensitivity, hormonal parameters of 8 weeks treatment with Myo2g/d in (n = 42) obese PCOS patients. After treatment BMI and IR decreased along with LH/LH/FSH and insulin. On subdividing the patients according to the fasting insulin levels Grp A (n = 15), insulin < 12 µu/ml and Grp B (n = 27), insulin > 12 µu/ml. Myo treatment induced similar changes in both groups but only of Grp B showed significant decrease of both fasting In plasma levels from 20.3 to 12.9 +_ 1.8 µu/ml ($p < 0.00001$) and AUC of insulin under GTT. Thus M is more effective in obese patients with high fasting In plasma levels [26].

D-chiroinositol (DCI)- Using DCI 500 mg/day/12 weeks in patients with BMI > 26 kg/m^2 Gennazzanni., *et al*. 2014 found FSH/LH/androstenedione/insulin/in response to OGTT significantly improved along with GnRH induced (10µg bolus) LH response. This was associated with a decrease in BMI without requiring lifestyle intervention. Also PCOS patients having diabetic relatives showed greater improvement after DCI administration. Thus DCI administration is effective in restoring insulin sensitivity in obese hyper insulinemic patients especially those with diabetic relatives and BMI also decreased during therapy [27].

Myoinositol (M)- Kamanov., *et al*. used M (N = 50 with IR) and Myoinositol (M) alone led to ovulation in 29 (61.7%, 18 (38.3% resistant). Of the ovulatory women 11 (37.9%), became pregnant. Of 18 M resistant patients after CC 13 (72.2%) ovulated. Of the 13 ovulatory women 6 (42.6%) became pregnant and M ameliorated IR and body weight and improved ovarian activity in PCOS patients [28].

Gonadotrophins- 2nd line of action MOA-initiation of ovulation ii)maintain and promote optimal DF-Drawback-promote multiple folliculogenesis, thereby increasing risk of OHSS/multiple pregnancies regimen-stepup/stepdown-monitor to DF 16-17 and then hcg induction [29].

Role of IVF

IVF is the last possibility for achieving a full term pregnancy in women with PCOS [3]. Although several stimulation protocols have been identified including CC, HMG, Rfsh with GnRH agonist or antagonist either alone or in combination, the cycle cancellation rate was found to be high according to a metaanalysis conducted in 2006,when the duration of stimulation cycle was significantly longer. Using four different stimulation protocols, long protocol, super long protocol, short protocol and antagonist protocol Yin., *et al*. found in a retrospective study of 337 PCOS patients with 330 patients without PCOS undergoing IVF/ICSI-ET with PCOS women having significantly higher BMI, and testosterone levels, that although fertilization rate was lower in IVF with PCOS patients but on ICSI fertilization rates were higher and no significant differences between both groups in all stimulation protocols regarding embryo arrest and did not find any difference over testosterone levels [30]. Similarly Although Huang et al found a slighter better pregnancy rates in leaner PCOS as compared to those with higher BMI the results were not statistically significant [31].

Role of Electroacupuncture

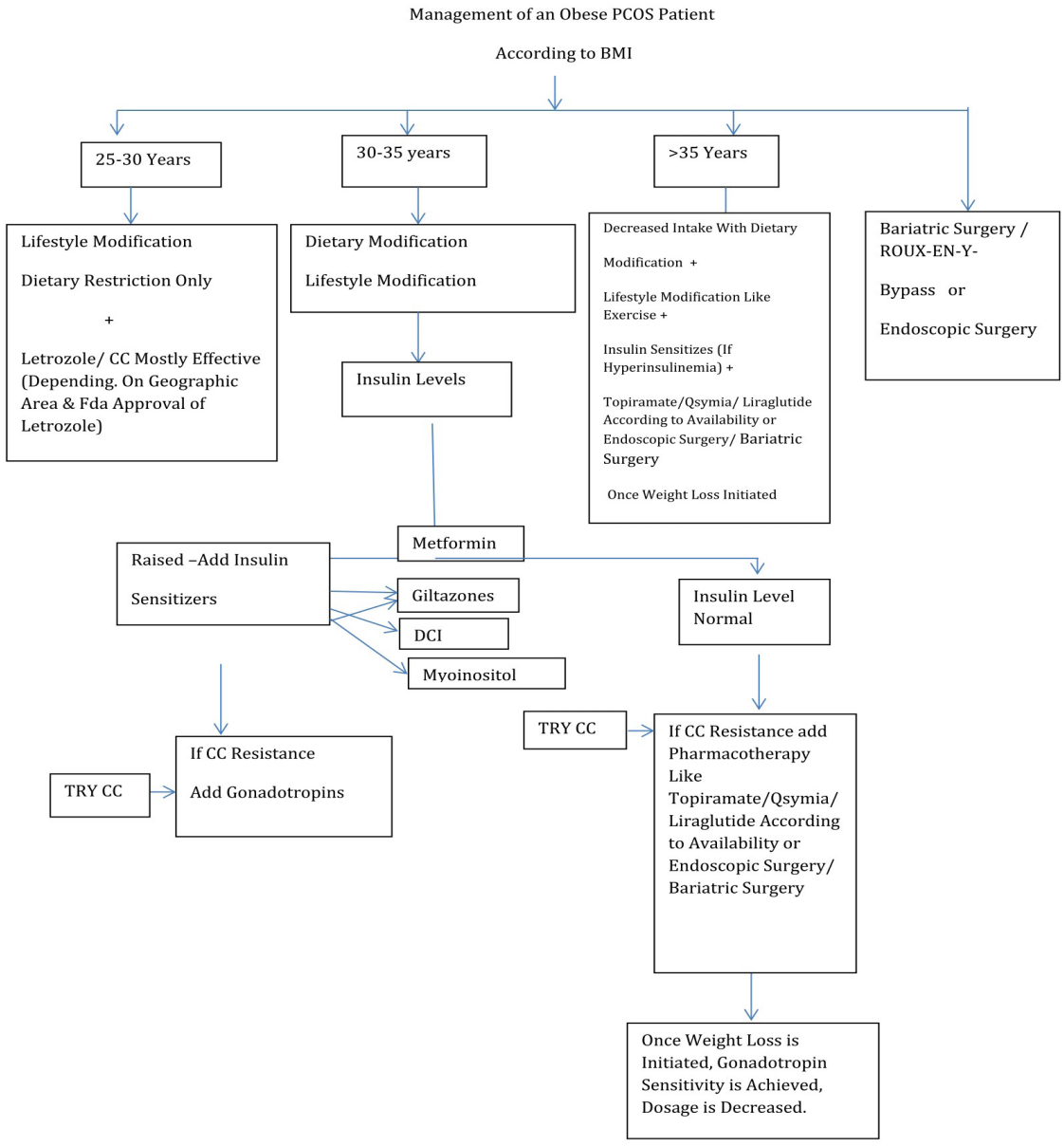
In a total of 200 PCOS patients undergoing IVF-ET the grp that received EA along with COH the grp showed higher quality embryos, serum and follicular fluid stem cell factor in EA grp than the medicine grp. While the dosage and administration duration was significantly lower in EA grp as compared to medication grp, no differences were found in the number of the oocytes retrieved, fertilization rate, cleavage rate, OHSS rate and the serum hormones in the 2 groups. Hence EA can improve pregnancy by improving high quality embryos associated with higher stem cell factor [32].

Since in general obesity is associated with poor reproductive outcomes, Machlinger., *et al*. studied the cytoskeletal and chromosomal organizations of failed fertilized oocytes from severely obese (BMI > 35 kg/m^2) altered as compared to that in patients with normal BMI (8 - 24.9 kg/m2). They found significantly more oocytes from the severely obese grp exhibited 2 spindles compared to those of the normal BMI grp (58.9 vs 35.1%) and among oocytes with single spindle, severely obese patients showed a significantly higher prevalence of disarranged spindles with non-aligned chromosomes compared with those from normal BMI patients (28.6 vs 8.6%) [33].

Role of Anti-obesity Drugs

In severely obese cases topiramate and exenatide are some drugs which can be considered in morbid obesity. The FDA Report 2013 highlights previous findings that women who received topiramate during pregnancy (for its existing epilepsy indication)were more likely to have infants born with an orofacial cleft. In the phentermine/topiramate obesity trials 34 pregnancies were reported and the drug was discontinued soon after pregnancy became known; 19 pregnancies were carried to term; 15 births had exposure to topiramate and there were no fetal adverse outcomes. Despite that, to reduce the risk of teratogenicity, women should have a negative pregnancy test prior to starting phentermine/topiramate combination [34]. Although not many trials with liraglutide are there recent reports of safety in pregnancy have started coming [35].

Lastly occasionally one comes across case with multiple df's where it may be physically impossible to get a few DF'S recruited and such few difficult case were successful OI was done and pregnancy was obtained in over 100 df's is discussed [36]. Table 2 summarizes a plan for different ages and geographical areas and most appropriate therapies according to BMI.



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