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Therapy choice - Therapy possibility in PCOS infertility patients

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REVIEW

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ABSTRACT

Background
Polycystic ovarian syndrome (PCOS) constitutes the most common endocrinopathy of women of reproductive age. Infertility due to the PCOS is a complex and specific condition but the majority of the problem is the ovulatory dysfunction.

Aims
Evaluation of the therapy choice and reproductive therapy possibilities in PCOS infertility patients. Make it easier for clinicians.

Methods
Clinical experience based on review of the literature.

Results
The syndromes heterogeneity is reflected in the different response to the various ovulation inducting drugs. Management of anovulatory infertility associated with PCOS is based on the overall clinical picture. Lifestyle change programs, weight reduction diet and exercise, have been shown to be very effective in improving reproductive as well as metabolic characteristics of overweight and obese patients with PCOS. In women with anovulatory infertility, the first line of treatment for induction of ovulation is clomiphene citrate. Aromatase inhibitors have been suggested as an alternative treatment to clomiphene therapy. Gonadotropin treatment is effective, but there is a risk of ovarian hyperstimulation syndrome. Surgery, such as laparoscopic ovarian drilling should be considered in some patients. Reconsider a use of metformin and supplements.

Conclusion
Understanding specific features and metabolic implications of different PCOS patients, may guide us to treat individuals optimally, as well as to develop effective prevention strategies to reduce the risk of long term complications-consequences and improve reproductive outcomes. Individual treatment modalities in PCOS patients are imperative for successful therapy.

Key Words
PCOS, infertility, ovulation induction

What this review adds:

1. What is known about this subject?
Management of anovulatory infertility associated with polycystic ovarian syndrome PCOS is based on the overall clinical picture. The syndrome s heterogeneity is reflected in the different response to the various ovulation inducting drugs.

2. What new information is offered in this review?
This review explores differences in ovulation induction management in infertility PCOS patients, and suggests lifestyle change programs, weight reduction in overweight patients, different drug therapy with or without surgery.

3. What are the implications for research, policy, or practice?
Improvements in the clinical management of infertility PCOS patients via the use of simple clinical ovulation induction protocol.

Introduction

Polycystic ovarian syndrome (PCOS) constitutes the most common endocrinopathy of women of reproductive age. Infertility due to the PCOS is a complex condition but majority of the problem is the ovulatory dysfunction.

PCOS has been associated with genomic variants linked with increased oxidative stress, hyperandrogenemia, obesity, insulin resistance and/or type 2 diabetes mellitus. Each single feature of PCOS has specific genetic association and potential etiological mechanisms. Various susceptible genes are responsible for heterogeneity in PCOS pathophysiology. Management should be directed towards an individual's needs (cosmetic, reproductive or metabolic) and attention given to potential long term sequelae.[1-3]

A principal characteristic of PCOS is insulin resistance (IR). There is substantial evidence that insulin resistance is a cause of polycystic ovarian syndrome. PCOS is associated with major metabolic disorders, which are potentially due to the characteristic type of IR that accompanies the syndrome. There is no reliable way to diagnose insulin resistance. Some have used the glucose to insulin ratio or simply the insulin level to gauge the degree of insulin resistance. Insulin resistance can lead to glucose intolerance. Infertility patients with PCOS should have a fasting glucose or two-hour glucose tolerance test. This could be a cause of the chronic anovulation. Infertility in patients with PCOS is due to oligo or anovulation.[3-5]

Management of anovulatory infertility associated with PCOS is based on the overall clinical picture, which should include: age, duration of infertility, degree of the ovarian and adrenal androgen excess, overweight, insulin resistance problems.

Lifestyle change programs, which emphasize behaviour control and interventions of diet and exercise, have been shown to be very effective in improving reproductive as well as metabolic characteristics of overweight and obese patients.[6]

Weight reduction alone may result in spontaneous ovulation in overweight or obese women with PCOS, and it is recommended that diet and lifestyle changes (including increasing daily exercise) should be the first-choice treatment in overweight and obese women with PCOS.[6,7] The popularity of alternative medicine certainly also affects patients suffering from infertility. Practitioners and advocates of alternative medicine have used several strategies to defend their position. Effectiveness of their therapies should be proven in randomized trials, but there are very few well-designed papers on the effectiveness of alternative medicine.

Induction of ovulation may include medical medicamentosus therapy or/and surgical procedures.

Among all approaches to ovulation induction, drug therapy remain the most common.[8]

The syndromes heterogeneity is reflected in the different response to the various ovulation inducting drugs. In women with anovulatory infertility, the first line of treatment for induction of ovulation is an antiestrogen, most commonly clomiphene citrate (CC) which was first introduced over 50 years ago.[9,10] Clomiphene citrate is a triphenylethylene derivate that is related to tamoxifen which has also been used but less frequently. He exists in two isomeric form zuclomiphen and enclomiphen citrate.

Treatment cost is low, adverse effects are relatively few and mild. Clomiphene citrate is weak oestrogen agonist and binds to hypothalamic oestrogen receptors. Clomiphene administration results in the state of pseudohypoestrogenism which change the frequency of GnRH pulses and results in the elevation of LH secretion. Although 70–80 per cent of PCOS women can ovulate by the treatment with CC, only 22 per cent become pregnant.[11,12] CC has a half-life of five days and can be detected in the blood up to six to eight weeks after administration. Despite the long half life of clomiphene citrate there are no reported increases in congenital anomalies that can be attributed to the use of this medication. Side effects are: vasomotor symptoms, abdominal discomfort breast discomfortnause, vomiting, visual symptoms and headaches. CC is given orally from 50 mg up to150mg/day for five days, starting on day one or two or three after the onset of spontaneous or progestin induced menses (typically 100mg between cycle days three to seven). FIGIt appears that efficiency of CC therapy is decreased in the presence of obesity, hyperandrogenemia, elevated testosterone concentrations and severe insulin resistance. Women who do not ovulate with increasing doses of CC are described as CC-resistance and remain a major challenge in gynaecologic endocrinology.[1,13,14]

Clinical data showed a higher incidence of miscarriage in conception cycles due to antiestrogenic mechanism, which involves long lasting oestrogen receptor (ER) depletion. Clomiphene citrate may have negative effect on the quality and quantity of the cervical mucus, on endometrial development and on other undetermined infertility factors.

Therapeutic interventions in the form of metformin and other insulin sensitizing drugs appear to be potentially effective tools in ameliorating insulin resistance with improvement in clinical and hormonal parameters, and possible reduction in cardiovascular risk.

Metformin increases the peripheral action of insulin on glucose uptake, possibly by acting at a post receptor level. Mefromin improves insulin sensitivity at muscular tissue, reduces the basal hepatic production of glucose. Metfromin reduces lipolysis at the adipose tissue. Metfromin improves insulin sensitivity at the muscular tissue. Metformin also increase ovulation and pregnancy rate in patients with PCO disease who are CC resistant. Spontaneous ovulation can occur within three months after the initiation of treatment with metformin. Results of the initial clinical trials suggested that addition of metformin improves the efficacy of CC treatment but subsequent data from large, prospective; double-blind, randomized control trials have shown no benefit of metformin alone or in combination with CC in terms of live birth rates. It has been reported that monotherapy with metformin is less effective than clomiphene citrate in the induction of ovulation and pregnancy in patients with PCOS.[14-17]

Reconsider a use of metformin and supplements such as L-arginine, inositol selenium, N-acetyl cysteine, Vitamin E, glycyrrhizin, diosgenin and omega 3-fatty acid. There are some data which support a positive influence on fertility in PCOS patients.[18,19]

Aromatase inhibitors have been suggested as an alternative treatment to CC. Letrozole is a nonsteroidal competitive inhibitor of aromatase enzyme that selectively inhibits gonadal steroidogensis. It also has no effect on mineral corticoids and glucocorticoids synthesis in adrenal. Letrosole administration in the early part of the menstrual cycle would release the pituitary/hypothalamic axis from estrogenic negative feedback, but without oestrogen receptors down regulation and adverse cervical mucus and endometrial effects.[20,21] The major advantages of letrozole, and possibly other aromatase inhibitors, include absence of persistent antiestrogenic effect owing to the short half/life and lack of oestrogen receptor depletion. This ensures a higher physiological oestrogen concentration around ovulation, with preservation of the hypothalamo-pitutary-ovarian axis leading to mono follicular ovulation. The standard dose is 2.5mg tablets and it is taken once a day, and can be increased up to 7.5mg a day for five days. Typically 2×1 a 2.5mg administered between cycle days three and seven. Side effects are: nausea, dizziness, hot flashes and headache. Risk includes twins 5–10 per cent, triplets or more are rare but OHSS is theoretically possible. The patient needs to be advised of the potential increased risk of malformations. All patients prior to take this medication should have a serum pregnancy test. The favourable response of letrozole was not demonstrated in all patients with PCOS.[22,23]

Due to the hypersecretion of LH in some patients with PCOS, gonadotrophin preparations containing only FSH activity were considered to have theoretical advantages over human menopausal gonadotrophin (hMG) preparations which contain both FSH and LH activity. However, the existing data do not support these theoretical concerns, and there have been no studies powered to detect differences in clinical outcome. The available individual studies and meta-analyses have not been able to document significant differences in ongoing pregnancy and live birth rates between preparations containing only FSH activity and hMG preparations. Within each protocol, there were no clinically relevant differences between the two gonadotropin-treatment groups in the high AMH category regarding demographics, fertility history and markers of ovarian reserve.[24,25]

The recommended starting dose in the gonadotropin treatment protocols is 37.5 /50 IU FSH per day. The starting period of 14 days, at least during the first cycle. The two low dose gonadotropin regimens that are most frequently used are step/up and step/down FSH regimens.[26]

The popularity of alternative medicine certainly also affects patients suffering from PCOS infertility. Practitioners and advocates of alternative medicine have used several strategies to defend their position. Effectiveness of their therapies should be proven in randomized trials, but there are very few well-designed papers on the effectiveness of alternative medicine.

L - Arginine is an amino acid, an endogenous precursor of nitric oxide (NO), which participates in the physiological process of vasodilatation. L-Arginine has been show to increase ovarian response, endometrial receptivity, and pregnancy rates in patients who were supplemented with L-arginine. L -Arginine stimulates growth hormone secretion by suppressing endogenous somatisation secretion.

Plasma ADMA (ADMA is an endogenous competitive inhibitor of NOS (nitric oxide synthase)) levels is higher and nitric oxide is lower in PCOS patients which could indicate presence of endothelial dysfunction in PCOS patients. L -

Arginine supplementation could improves the ratio of ADMA/L - Arginine and affect endothelial dysfunction increasing the permeability of follicular epithelium to plasma proteins and exerting a positive effect on pregnancy outcomes in PCOS patients.[27-29] The association of 25(OH)D levels with metabolic and endocrine parameters in PCOS women as well as the promising results from intervention studies in PCOS women might lead to a recommendation for measuring 25(OH)D and for vitamin D supplementation to improve fertility as well as metabolic disturbances.[30]

Laparoscopic ovarian surgery (LOS) applies diathermy or laser for ovarian drilling aiming at restoring ovulation and achieving pregnancy. The main indication for LOS is PCOS patients' resistance to clomiphene citrate. This method is alternative option to gonadotropin administration in ovulatory patients with PCOS who are resistant to CC.LOS should be performed by adequately trained physicians and should not be applied for other indication except infertility. Data from an randomized control trail suggest that laparoscopic ovarian diathermy may be as effective as low dose FSH in inducting ovulation, but adjunctive therapy with CC and/or FSH was also require after surgery in about two-thirds of cases. The most important benefit of surgical LOD treatment is the fact that surgery gives a long lasting effect, although the effect appears later than when pharmacological therapy is used.[1,31,32] Understanding specific features and metabolic implications of different PCOS and PCOM patients, may guide us to treat individuals optimally, as well as to develop effective prevention strategies to reduce the risk of long term complications-consequences and improve reproductive outcomes. Individual treatment modalities in PCOS patients are imperative for successful therapy.

References

1. Conway G, Dewailly D, Diamanti-Kandarakis E, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol. 2014;171:P1–P29.
2. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98:4565–4592.
3. Cussons AJ, Stuckey BG, Walsh JP, et al. Polycystic ovarian syndrome: marked differences between endocrinologists and gynaecologists in diagnosis and management. Clin Endocrinol (Oxf). 2005;62:289–295.
4. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33:981–1030.
5. Moran LJ, Misso ML, Wild RA, et al. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16:347–363.
6. Welt CK, Carmina E. Lifecycle of polycystic ovary syndrome (PCOS): from in utero to menopause. J Clin Endocrinol Metab. 2013;98:4629–4638.
7. Moran LJ, Pasquali R, Teede HJ, et al. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril. 2009;92:1966–1982.
8. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod. 2008;23:462–477.
9. Kousta E, White DM, Franks S. Modern use of clomiphene citrate in induction of ovulation. Human Reproduction Update. 1997;3:359–365.
10. Polson DW, Kiddy DS, Mason HD, et al. Induction of ovulation with clomiphene citrate in women with polycystic ovary syndrome: the difference between responders and nonresponders. Fertil Steril. 1989;51:30–34.
11. Brown J, Farquhar C, Beck J, et al. Clomiphene and antioestrogens for ovulation induction in PCOS. Cochrane Database Syst Rev. 2009.
12. Abu Hashim H. Clomiphene citrate alternatives for the initial management of polycystic ovary syndrome: an evidence-based approach. Arch Gynecol Obstet. 2012;285:1737–45.
13. Abu Hashim H, Foda O, Ghayaty E. Combined metformin-clomiphene in clomiphene-resistant polycystic ovary syndrome: a systematic review and metaanalysis of randomized controlled trials. Acta Obstet Gynec Scand. 2015;94:921–930.
14. Diamanti-Kandarakis E, Christakou CD, Kandaraki E, et al. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. Eur J Endocrinol. 2010;162:193–212.
15. Costello M, Shrestha B, Eden J, et al. Insulinsensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. Cochrane Database Syst Rev. 2007.
16. Abu Hashim H, Wafa A, El Rakhawy M. Combined metformin and clomiphene citrate versus highly purified FSH for ovulation induction in clomiphene-resistant

PCOS women: a randomized controlled trial. Gynecol Endocrinol. 2011;27:190–6.
17. Diamanti-Kandarakis E, Spritzer PM, Sir-Petermann T, et al. Insulin resistance and polycystic ovary syndrome through life. Curr Pharm Des. 2012;18:5569–76.
18. . Abu Hashim H, Anwar K, El-Fatah RA. N-acetyl cysteine plus clomiphene citrate versus metformin and clomiphene citrate in treatment of clomiphene-resistant polycystic ovary syndrome: a randomized controlled trial. J Womens Health (Larchmt). 2010;19:2043–8.
19. Tang T, Lord JM, Norman RJ, et al. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2012;(5):CD003053.
20. Abu Hashim H, Shokeir T, Badawy A. Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Fertil Steril. 2010;94:1405–9.
21. Casper RF, Mitwally MF. Review: aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab. 2006;91:760–71.
22. Legro RS, Brzyski RG, Diamond MP, et al.; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014;371:119–29.
23. Tulandi T, Martin J, Al-Fadhli R, et al. Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril. 2006;85:1761–5.
24. Palomba S, Falbo A, La Sala GB. Metformin and gonadotro pins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2014;12(1):3.
25. White DM, Polson DW, Kiddy D, et al. Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women. J Clin Endocrinol Metab. 1996;81:3821–3824.
26. Fauser BC. Prediction of the individual follicle-stimulating hormone threshold for gonadotropin induction of ovulation in normogonadotropic anovulatory infertility: an approach to increase safety and efficiency. Fertil Steril. 2002;77:83–90.
27. Battaglia C, Salvatori M, Maxia N, et al. Adjuvant L-arginine treatment for in-vitro fertilization in poor responder patients. Hum Reprod. 1999;14(7):1690–1697.
28. Fenkci SM, Fenkci V, Oztekin O, Rota S, Karagenc N. Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome. Hum Reprod. 2008;23(7):1602.
29. Ismail AM, Hamed AH, Saso S, et al. Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. Eur J Obstet Gynecol Reprod Biol. 2014;180:148–52.
30. Farquhar C, Brown J, Marjoribanks J. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev. 2012;(6):CD001122.
31. Lerchbaum E, Obermayer-Pietsch B. Mechanisms in endocrinology: Vitamin D and fertility: a systematic review. Eur J Endocrinol. 2012 May 1;166(5):765–78.
32. Palomba S, Falbo A, Battista L, et al. Laparoscopic ovarian diathermy vs. clomiphene citrate plus metformin as second-line strategy for infertile anovulatory patients with polycystic ovary syndrome: a randomized controlled trial. Am J Obstet Gynecol. 2010;202:577.e1–8.

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CONFLICTS OF INTEREST

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