Review Article

Insulin Sensitising Agents and Infertility

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Abstract

Polycystic ovarian syndrome (PCOS) is a complex metabolic syndrome and the foremost ovarian factor that leads to infertility in the general population due to the increasing incidence of obesity and diabetes. Insulin resistance occurs in 25 – 70% of infertile patients with PCOS. Use of insulin sensitising agents is a recent therapeutic strategy in women with PCOS to reduce insulin resistance and induce regular menstrual cycles and fertility. Important drugs that are used as insulin-sensitising agents include metformin and thiazolidinediones (rosiglitazone and pioglitazone).

Key words: Polycystic ovary syndrome; metformin; thiazolidinediones; insulin resistance; obesity; diabetes mellitus

Introduction

Infertility is inability to conceive after 1 year of unprotected intercourse which can be due to ovarian factors (30-40%), pelvic factors (30-40%), cervical factors (5%), male factors (25-40%), and unexplained causes (10-15%).

Polycystic ovarian syndrome (PCOS) is a complex metabolic syndrome and the foremost ovarian factor leading to infertility in the general population due to rising incidence of obesity and diabetes [1].

Pathophysiology of Infertility caused by PCOS

Inability of women with PCOS to produce and release ovum is due to complex interplay of multiple hormonal imbalances. The hormones involved are insulin, androgens, estrogen, progesterone, luteinizing hormone, follicle stimulating hormone, adrenal androgens, thyroid hormone, prolactin and others. Women with PCOS are also at higher risk of insulin resistance, impaired glucose tolerance, metabolic syndrome, obesity, cardiovascular disease, etc. All the above conditions are complexly inter-related and forerunners of one another.

Insulin resistance and Infertility

Insulin resistance is defined as reduced insulin response to a given amount of insulin. It occurs in 25–70% of infertile patients with PCOS [2]. Insulin resistance can be due to reduced number of insulin receptors, altered insulin to receptor interaction or post receptor failure. In PCOS, it is mainly the post receptor defect which is due to increased serine phosphorylation of beta chain of insulin receptor and adrenal and ovarian cytochrome P450 enzyme. Increased phosphorylation causes increased 17-hydroxylase and 17-20 lyase action that leads to hyperandrogenemia. Also, there is increased conversion of androstenedione to estrone, yet ovarian estrogen production is sparse. Estrone level causes increased prolactin level in 30-40% patients.

Increased insulin levels reduce sex hormone binding globulin which in turn increases testosterone and estrogen level. Estrogen rise causes increased LH and decreased FSH level. Suboptimal FSH action leads to follicular stimulation but no maturation or ovulation; as a result numerous small follicles with hyperplastic and luteinized theca cells form. When these immature follicles undergo atresia, they lead to increase in stromal component which secretes androstenedione and testosterone and further prevents normal follicular growth and causes premature follicular atresia (Figure 1).

Role of 'insulin sensitising agents' in infertility due to PCOS

Use of insulin sensitising agents is a recent therapeutic strategy adopted for women with PCOS

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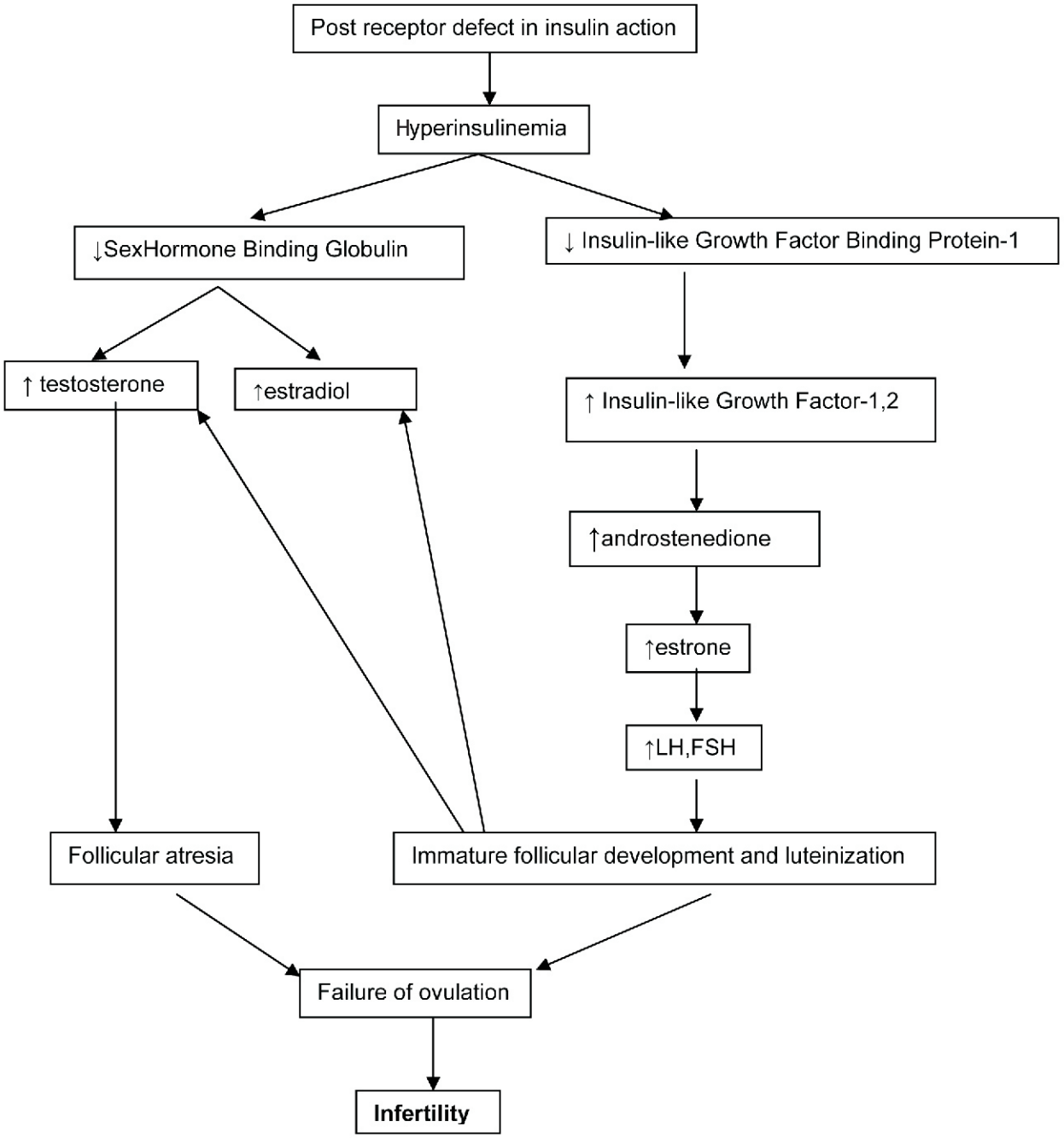

Figure 1- Mechanism of infertility in PCOS

to reduce insulin resistance and induce regular menstrual cycles and fertility. Candidate drugs that are used for the purpose include metformin and thiazolidinediones (rosiglitazone and pioglitazone).

Metformin

It is a biguanide, originally used as oral glucose lowering agent to treat type 2 diabetes mellitus. This drug acts by improving sensitivity of peripheral tissue and liver to insulin thus improving insulin resistance in type 2 diabetes. It also decreases basal hepatic glucose output thereby decreasing fasting glucose level [3]. Metformin also helps to increase insulin sensitivity of peripheral cells by increasing GLUT1 and GLUT4 receptor translocation [4]. Decrease in fatty acid oxidation by 10-20% also reduces glucose via glucose–fatty acid cycle. Metformin also has other beneficial actions viz. decreasing androgenemia, improving lipid profile, and increasing fibrinolytic action [5,6]. Metformin causes 3-4 kg of weight loss and 1-2 kg/m^2 decrease in BMI [7]. The effect on central adiposity is maximum at dose of 2500 mg/day [8].

Major side-effects of this drug are gastrointestinal

discomfort leading to nausea, abdominal pain, flatulence, abdominal bloating, vitamin B12 deficiency, etc. [9]. The gastrointestinal side-effects can be minimized by gradually increasing the dosage and by taking the drug after meals. A major side effect is lactic acidosis and hence this drug is contraindicated in hepatic and renal failure; however, phenformin and not metformin has been the culprit on most occasions.

Contraindications for metformin include renal dysfunction (a serum creatinine level >1.4 mg/dL), hepatic dysfunction, severe congestive heart failure, or a history of alcohol abuse.

Standard dosage of metformin is 500-1000 mg/day as a starting dose. It is advisable to increase the dose by 500 mg every week till the required dose. If side-effects appear, dose should be reduced or stopped for next 2-3 weeks. US guidelines suggest maximum of 2500 mg/day, others use maximum of 3 gm/day.

Ovulation induction and metformin

Metformin is the most commonly used insulin sensitising agent for ovulation induction. The indications for starting metformin therapy are [10]-

1) fasting insulin level >25 IU/L
2) post prandial insulin levels >100 IU/L
3) PCOS women with raised androgens
4) failure of ovulation induction after clomiphene with BMI >25 kg/m^2.
5) patient has Metabolic Syndrome
6) genetic predisposition to type 2 diabetes or cardiovascular diseases

Metformin is initiated in the follicular phase as 500 mg/day for 5 – 7 days. Dosage is increased weekly by 500 mg till 1500-2000 mg/day and is continued for 2-3 months to show results [11]. If after 3 months of therapy, serum insulin is still high then one can add other drugs like rosiglitazone or pioglitazone, etc.

Optimum results of the therapy noticed are regularization of menstrual cycle in 60-95% of patients within 4 to 6 months of treatment and improved ovulation by decreased hyper-androgenemia and insulin resistance.

Better results are seen when metformin therapy is combined with clomiphene; ovulation rates with clomiphene alone are lower (76% vs 46%) [12]. Similar results are seen when rosiglitazone is combined with clomiphene.

Also, effect of metformin to improve FSH-induced ovulation in women with clomiphene resistant PCOS is still investigational. Yet, it decreases intraovarian androgens which leads to reduced estradiol and causes orderly follicular growth in response to exogenous gonadotropins [13]. It is also notable that combined treatment with rosiglitazone and metformin improved the number of ovulatory cycles in non-obese patients with PCOS although definitive trials are still awaited [14-18].

Reduced hyperandrogenemia and insulin resistance in PCOS women by insulin sensitising agents facilitates FSH stimulation; and therefore parallel administration of metformin before and during IVF cycle decreases the requirement of FSH and increases pregnancy rates. In a trial, both the fertilization (64% vs 43%) and pregnancy rate (70% vs 30%) were increased in metformin and FSH treated cycles as compared to only FSH treated cycles. Nevertheless, role of metformin is still investigational as regards use with FSH and in IVF cycle and further studies are awaited [19-21].

Rosiglitazone

It is a thiazolidinedione derivative. It mainly activates nuclear peroxisome proliferator activated receptor gamma (PPAR-γ) and sequesters lipids in adipocytes, thereby decreasing lipid accumulation in muscle and increasing insulin sensitivity [22]. It also decreases LH, testosterone, androstenedione, DHEAS, and leptin level. It increases ovulation rate by 50% [23]. It is taken as 4-8 mg/day [24].

Pioglitazone

Pioglitazone belongs to the same thiazolidinedione family. Only difference is that it activates PPAR-γ leading to regulated glucose and lipid metabolism by amplifying post-receptor action of insulin in liver and peripheral tissue. Standard dosage is 30-45 mg/day.

Newer Drugs

D-chiroinositol- It increases phosphoglycan that mediates insulin action. It takes 6- 8 weeks to show its effect. According to some studies it has 86% ovulation rate [25].

Acarbose

It is alfa-glucosidase inhibitor which slows down carbohydrate digestion and absorption in the body. Its role in ovulation is still investigational.

Somatostatin analogue

It is an endogenous hypothalamic peptide that besides blunting LH response to gonadotropin releasing hormone and decreasing GH, it inhibits pancreatic insulin release. According to studies, 7-day administration of octreotide, a synthetic somatostatin, decreases fasting and glucose stimulated insulin [26]. It also improves pulsatile gonadotropin pattern, reduces LH, androgen, increases spontaneous and stimulated ovulation [27-29]. To overcome its short half life, octreotide-LAR has been devised, although its role is still investigational.

Needless to stress is the importance **of diet, exercise and life style measures**. It has been reported that 10% weight loss improves hormonal profile, menstrual irregularity, ovulation and pregnancy rates [30].

Dietary management with modification of sedentary lifestyle is recommended initially; pharmacological and other interventions should be reserved for use when weight loss regimens and life style measures have proved unsuccessful. A subgroup of PCOS women (10-13%) are lean in whom weight loss is not effective, thereby arising need for other therapeutic strategies [15]. Use of insulin-sensitising agents is a recent therapeutic strategy and a lot of work is being done in this field, but definitely, it opens up new vistas for management of the infertile PCOS patient.

Key Points

- PCOS is multi-system disorder hence approach to treatment should be multi-dimensional.
- Lifestyle measures with weight loss, diet and exercise are recommended as primary therapeutic measures.
- Treatment with insulin sensitising agents should not be started indiscriminately to all PCOS women. Insulin sensitising agents have been found to be effective in PCOS patients who harbour insulin resistance and/or obesity.
- Metformin is the drug of choice. Thiazolidinediones (rosiglitazone and pioglitazone) still have to establish their places and need to be considered when metformin is contraindicated.
- Combination of clomiphene and metformin is associated with significantly better outcome in terms of ovulation and pregnancy rates than clomiphene alone.
- There is no substantial evidence to show usefulness of metformin and FSH use over FSH use alone in ovulation induction cycles. Similarly, in IVF cycles, role of metformin is being evaluated.

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References

1. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223–36.
2. Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv 2004;59:141–54.
3. Boyd K, Rogers C, Boreham C, Andrews WJ, Hadden DR. Insulin, glibenclamide or metformin treatment for non insulin dependent diabetes: heterogenous responses of standard measures of insulin action and insulin secretion before and after differing hypoglycaemic therapy. Diabetes Res 1992;19;69–76.
4. Hundal HS, Ramlal T, Reyes R, Leiter LA, Klip A. Cellular mechanism of metformin action involves glucose transporter translocation from an intracellular pool to the plasma membrane in L6 muscle cells. Endocrinology 1992;131:1165–73.
5. Landin K, Tengborn L, Smith U. Treating insulin resistance in hypertension with metformin reduces both blood pressure and metabolic risk factors. J Intern Med 1991;229:181–7.
6. Velazquez EM, Mendoza SG, Wang P, Glueck CJ. Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein (a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. Metabolism 1997;46:454–7.
7. Radosh L. Drug treatments for polycystic ovary syndrome. Am Fam Physician 2009;70:671-6.
8. Diamanti-Kandarakis E, Christakou CD, Kandaaki E, Economou FN. 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.
9. Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Saf 1994;11:223–41.
10. Baillargeon JP, Farid NR. Medical treatment. In: Farid NR, Kandarakis ED (ed). Diagnosis and management of polycystic ovary syndrome 1st edn, 2009, Springer (India) Pvt Ltd New Delhi: pp 209-32.
11. Lord JM, Flight IH, Norman RJ. Insulin sensitising drugs (metfromin, troglitazone, rosiglitazone, pioglitazone, D-chiroinositol) for polycystic ovary syndrome. Cochrane Data Base Syst Rev 2003;3:CD003053.
12. Harborne L, Fleming R, Lyall H, Norman J, Sattar N. Descriptive review of the evidence for use of metformin in polycystic ovary syndrome. Lancet 2003:361:1894-901.
13. Yarali H, Yildiz B. Metformin and FSH for induction of ovulation in women with polycystic ovary syndrome. Hum Reprod 2002;17:3007–8.
14. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004;82:893–902.
15. Checa MA Requena A, Salvador C, Tur R, Callejo J, Espinos JJ, et al. Insulin-sensitising agents: use in pregnancy and as therapy in polycystic ovary syndrome. Reproductive Endocrinology Interest Group of the Spanish Society of Fertility. Human Reproduction Update 2005;11:375–90.
16. De Leo V, la Marca A, Petraglia F. Insulin lowering agents in the management of the polycystic ovary syndrome. Endocr Rev 2003;24:633–67.
17. Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligoamenorrhea treated with metformin in a randomized double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2002; 87:569–74.
18. Romualdi D, Guido M, Ciampelli M, Giuliani M, Leoni F, Perri C, et al. Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. Hum Reprod 2003;18:1210-8.
19. Fedorcsak P, Dale PO, Storeng R, Abyholm T, Tanbo T. The effect of metformin on ovarian stimulation and in vitro fertilization in insulin-resistant women with polycystic ovary syndrome: an open-label randomized cross-over trial. Gynecol Endocrinol 2003:17:207–14.
20. Kjotrod SB, von During V, Carlsen SM. Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study. Hum Reprod 2004:19:1315–22.
21. Stadtmauer LA, Toma SK, Riehl RM,Talbert LM. Impact of metformin therapy on ovarian stimulation and outcome in 'coasted' patients with polycystic ovary syndrome undergoing in vitro fertilization. Reprod Biomedicine Online 2002;5:112–6.
22. Ye JM, Doyle PJ, Iglesias MA, Watson DG, Cooney GJ, Kraegen EW. Peroxisome proliferator-activated receptor (PPAR)-alpha activation lowers muscle lipids and improves insulin sensitivity in high fat-fed rats: comparison with PPAR-gamma activation. Diabetes 2001;50:411–7.
23. Zheng Z, Li M, Lin Y, Ma Y Effect of rosiglitazone on insulin resistance and hyperandrogenism in polycystic ovary syndrome. Zhonghua Fu Chan Ke Za Zhi 2002; 37:271–3.
24. Stout DL, Fugate SE. Thiazolidinediones for treatment of polycystic ovary syndrome. Pharmacotherapy 2005;25:244-52.
25. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovarian syndrome. N Engl J Med 1999;340:1314-20.
26. Prelevic GM, Wurzburger MI, Balint-Peric L, Hardiman P, Okolo S, Maletic D, et al. Effects of the somatostatin analogue, octreotide, in polycystic ovary syndrome. Metabolism 1992;41:76–9.
27. Prelevic GM, Wurzburger MI, Balint-Peric L, Nesic JS. Inhibitory effect of sandostatin on secretion of luteinizing hormone and ovarian steroids in polycystic ovary syndrome. Lancet 1990;336:900–3.
28. Morris RS, Carmina E, Vijod MA, Stanczyk FZ, Lobo RA. Alterations in the sensitivity of serum insulin-like growth factor 1 and insulin-like growth factor binding protein-3 to octreotide in polycystic ovary syndrome. Fertil Steril 1995;63:742–6.
29. Wenzl R, Lehner R, Schurz B, Karas H, Huber JC. Successful ovulation induction by sandostatin-therapy of polycystic ovarian disease. Acta Obstet Gynecol Scand1996;75:298–9.
30. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 1995;10:2705–12.