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Hyperinsulinemia and Polycystic Ovary Syndrome

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Summary

Hyperinsulinemia is central in the etiology of majority of PCOS. Hence the rational approach should be to improve the carbohydrate metabolism and thus reduce the endogenous production of excess of insulin by the pancreas. It has been well observed that metformin, the biguanide, is most effective in improving the glucose metabolism by multivarious approaches and thus revert the PCOS subject to normo-insulinemic status. Once the axis is down-regulated to normo-insulinemic status automatically the hyperandrogenemia is effectively controlled allowing for regular ovulation and conception.

This study presented here highlights the clinical application of metformin in infertile PCOS subjects. Remarkable improvement in conception rate, reduced pregnancy complications and higher incidence of take home baby rate are the unique features of this regime. Absence of ovarian hyperstimulation, "no need for cycle monitoring", simplicity of administration and cost effectiveness are other distinct benefits.

Anovulation is one of the common causes of infertility constituting 23.08% of the infertile couple investigated (Rajan, 1998). Anovulation is either due to abnormal hypothalamo-pituitary-ovarian axis and hence the subject could not ovulate; or due to normal but nonfunctioning axis and hence does not ovulate. Abnormal axis leading to anovulation is understandable, and examples are primary gonadal failure wherein the ovaries are devoid of primordial follicles and secondary gonadal failure wherein the hypothalamic or pituitary functions are deranged (commonest model being hyperprolactinemia).

A condition where the reproductive axis is normal but still nonfunctioning is usually designated as polycystic ovary syndrome (PCOS). This is a wide spectrum of androgenization ranging from the simple normoestrogenic anovulation to severe hyperandrogenic amenorrhoea (Nobels and Dewailly, 1992, Shoham et al, 1995). It is quite difficult to understand why a normal reproductive axis is nonfunctioning and results in anovulation. Trying to stimulate the axis in these situations to induce ovulation will be unphysiological and naturally least rewarding. More androgenic the subject is less attractive and more hazardous the results for induction of ovulation.

In such situations the prudent approach should be to search for defects in other endocrine systems, such as the metabolic hormones, which could interfere with the smooth functioning of the reproductive axis. Quite often insulin receptor gene mutation leading to hyperglycemia and hyperinsulinemia has been identified in majority of PCOS (Barbieri, 1990). Recognizing the extraneous influence of hyperglycemia and hyperinsulinemia on the reproductive axis and

rectifying the disorder by insulin sensitizing agents (metformin) should be the most logical science in achieving regular ovulation and successful pregnancies (Perloe, 1996, Nestler et al. 1998, and Weissman, 1998).

Statistical Data

Among the 1014 infertile couple investigated over a period of 6 years the incidence of anovulatory infertility has been 23.08% (Rajan, 1998) Of them 7% had primary gonadal failure, 11.74% had hyperprolactinemia and 2.50% had hypoituitarism and secondary gonadal failure. The remaining 79% of anovulatory subjects could be included in the wide spectrum of PCOS which included: (1) normoestrogenic and normoandrogenic anovulatory subjects (PCO) who formed 70% of the total PCOS subject; (2) hyperandrogenic obese subjects with typical PCOD ovaries and thecal hyperplasia; and (3) highly androgenized amenorrhoeic subjects with thecal hyperplasia or HAIR-AN syndrome. There were also 2 subjects with androblastoma of the ovary and 1 with virilizing adrenal tumor (Rajan, 1999).

Hyperinsulinemia

It has been estimated that 70% of the obese PCOS and 20% of the thin PCOS subjects have hyperinsulinemia (Glueck et al., 1998). These subjects have insulin resistance due to defect in the insulin receptor genes. Consequently they are rendered hyperglycemic. High circulating glucose stimulates increased secretion of pancreatic insulin, which leads to hyperinsulinemia. High insulin decreases the hepatic synthesis of IGF-1 binding protein, and thus unbound IGF-1 circuates freely leading to ovarian thecal stimulation of androgen production. It could also amplify the LH action on theca and increase androgen production. Dysregulation of cytochrome 450 17 α is another mechanism by which hyperinsulinemia causes hyperandrogenism.

The resultant hyperandrogenemia causes follicular atresia and stimulates the erratic LH secretion by the pituitary. This perpetuates more of the ovarian thecal androgen production. Thus it could be seen that hyperinsulinemia caused hyperandrogenism is the basic etiology of PCOS and high LH is only the consequence of this endocrine dysfunction.

Metformin

Metformin is insulin sensitizing agent, which declines the peripheral glucose level without interfering with pancreatic β cell function. Metformin is biguanide and it reduces the blood sugar level by the following mechanisms: (1) inhibiting hepatic gluconeogenesis; 2) increased insulin receptor affinity and thus enhances the sensitivity of peripheral tissues to insulin (3) reduces the intestinal absorption of glucose (4) reduces the appetite; (5) increasing muscle glyconeogenesis; (6) reducing plasma glucagon level. In effect metformin achieves euglycemic status without interfering with pancreas and causing hypoglycemia, and moreover effective weight reduction is achieved.

This has both reproductive and non reproductive benefits for the patient. Reversal to normoglycemic status leads to normoinsulinemia and culminates in normalization of ovarian steroidogenesis, regular menstrual cycles and ovulation resulting in pregnancy. The nonreproductive benefits achieved are reduction of obesity, hypertension and inhibition of PAI 1. Thus the cardiovascular risk factors are considerably reduced by metformin therapy, and the risk of chronic pancreatic stimulation leading to diabetes is also obviated or delayed.

Therapeutic approach and results

Subjects who belong to the obese hyperandrogenic group, who evidence thecal hyperplasia and polycystic ovaries at USG, have been recruited for metformin therapy. The PCO subjects who fail to respond to low dose CC and those PCOD subject who are refractory to ovarian follicular puncture are the other subjects recruited. Many patients had family history of diabetes, and routine estimation of insulin or glucose levels have not been contemplated in this study. Insulin estimation and GTT could be considered before initiating therapy, but many a time these biochemical estimations will not be diagnostic.

Metformin has been administered after food in a dose of 500 mgs tid, or qid, depending on the acceptance. The dose has been titrated up beginning with 500 mg/day. The drug is well tolerated, and even euglycemic subjects accept the drug without developing hypoglycemia. Hence the fear of hypoglycemia or other ill effects are unwarranted (Glueck et al. 1998, Nestler et al., 1998).

From January, 1998 to May, 1999 33 subject have been recruited, treated and followed on metformin therapy. Many of these subjects had laparoscopic ovarian follicular puncture and CC (50 mg for 5 days) for 3 courses.

The duration of therapy ranged from 3 to 6 months in this series. The following were the

Table I

Regime	No.	pregnant	%age	Perg. Wast.%	Take-home %
Clomiphene	90	61	67.78	46.43	36.04
Diathermy	90	29	32.33	31.03	24.40
Fol. Puncture	85	27	31.76	7.40	29.41
Gonadotropin	23	8	34.78	50.00	17.39
Metformin	33	13	39.39	7.69	36.36

observations: weight reduction was observed in 67% of subjects, ranging from 2 to 6 kg. Menstrual cycles reverted to near normal in 70% of subjects. There is no toxicity for this drug and could be safely administered. Mild intestinal complaints disappeared after a few days of treatment. Those who felt tired and could not tolerate the dose (only 10%) could be managed on a lower dosage of 1000 mg/day.

Among the 33 subjects followed 13 had achieved a conception, giving a pregnancy rate of 39.39% (Table I). Of the 13 subjects there was one ectopic gestation (7.69%), and there were no abortions or multiple gestations. There have been no risk of ovarian hyperstimulation, hypoglycemia or other ill effects.

Conception occurs within 1 to 3 months in 80% of subjects and the remaining achieve a pregnancy within 6 months. Usually the drug has been stopped after diagnosing pregnancy, even though metformin has been considered to be nonteratogenic and reduces the risk of abortion (by its effect on lowering the PAI-1) (Nestler et al. 1996, Glueck, et al 1999).

Clomiphene citrate appears the best agent for nonobese, normoestrogenic anovulatory PCO subjects. Those who fail to respond to lose dose CC (50 mg for 5 days for 3 to 6 cycles), and the obese hyperandrogenic PCOD subjects with thecal hyperplasia are best down regulated employing metformin. They may ovulate and conceive spontaneously or may do so with the help of ovarian follicular puncture or CC. However, it is better to avoid ovarian diathermy for reasons it causes high incidence of ectopic gestation (Rajan, 1998). Ovaian follicular puncture employing sharp needle (Veres needle) could achieve the same results with lesser incidence of ectopic gestation (Rajan, 1999).

Conclusion

Administration of insulin sensitizing agent (metformin) appears to be a logical approach to management of PCOS, particularly the hyperandrogenic obese subjects majority of whom are hyperinsulinemic. Metformin down regulates the hyperstimulated reproductive axis and allows for reversal to normoestrogenic and normoandrogenic state.

Quite possibly the patients could spontaneously ovulate, or will do so with the help of other ovulogens such as CC or gonadotropins.

Apart from the fact metformin therapy is the most logical approach to management of PCOS there are certain special advantages for this treatment:

1. Simple oral administration and is very cost effective
2. No need for any cycle monitoring or frequent follow up
3. Nontoxic and safe, and has minimal and acceptable side effects
4. No risk of ovarian hyperstimulation and superovulation
5. Higher pregnancy rate and lower rate of pregnancy wastage
6. Nonreproductive benefits on CVS, BP, coagulation and diabetes

References

1. Barbieri, R.L.: Clin. Obst. Gynec. 33:640, 1990
2. Glueck, T Tracy, P Wang, I. Sieve-Smith, R. N. Fontaine, A Gupta.: J. Investigative Med 46:208A 1998
3. Glueck CJ, Tracy T, Wang P, Sieve-Smith I, Fontaine R, Gupta A.: Metabolism 48:511, 1999
4. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. New Eng J. Med 335:617:1996
5. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R.: New Eng J. Med 338:1876-1880, 1998
6. Nobels, F., and Dewailly, D.: Fertil. Steril. 58:655, 1992.
7. Perloe, M.: ASRM Meeting 1996
8. Rajan, R.: "Couple friendly" approach to management of infertility and the "Take-home baby rate". Science Technology.: Indian Academy of Human Reproduction, 6: 11, 1998
9. Rajan, R.: FOGSI Guidelines on Management of Infertility: J. Obst. Gyn. India., (FOGSI Guidelines) 48:28 1998.
10. Rajan, R.: Hyperinsulinemia and PCOS: Lecture: 2 meeting of the Bangalore Obstetric and Gynecological Society: 9th May, 1999
11. Rajan, R.: "Hyperinsulinemia and polycystic ovarian syndrome". Infertility, Gynecology and Obstetrics. 1 Rajan, R.: IAHR publication: 1 Trend. P. 14 1999
12. Rajan, R.: Evoluation in the management of polycystic ovary syndrome and anovulation. Science and Technology, IAHR, 7: 1, 1999.
13. Shoham, Schachtger, and Insler, V.: Fertil. Steril 64:237 1995.
14. Weissman, A.: Science Technology, Indian Academy of Human Reproduction; 6: 1, 1998.