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RESEARCH ARTICLE

COMPARISON OF SPIRONOLACTONE PLUS METFORMIN VERSUS ORAL CONTRACEPTIVES IN PCOS

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Abstract

Background: Androgen excess is a major mechanism leading to polycystic ovary syndrome (PCOS); yet, insulin resistance and obesity are frequently found in these women explaining the association of this syndrome with diabetes and increased cardiovascular risk factors. Accordingly, current strategies for the treatment of PCOS include amelioration of androgen excess using combined oral contraceptives (COC) and/or antiandrogens and insulin sensitizers such as metformin.
Objectives: To see the effect of combined therapy with low-dose spironolactone plus metformin versus oral contraceptives in Polycystic Ovary Syndrome (PCOS) patients.
Methods: All subjects included had menstrual disturbances and Hirsutism after ruling out disorders such as Cushing's syndrome, nonclassical adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, and androgen-secreting tumors.Blood samples were collected from the patients after an overnight fast for the estimation of T4, TSH, LH, FSH, prolactin (PRL), blood counts, electrolytes, lipids, liver, and kidney functions. Blood samples for hormonal investigations were collected from d 3-7 (early follicular phase) in subjects with spontaneous menstrual cycles.
Results: Menstrual cycle frequency improved significantly (**P** = 0.01) in all the three groups at 6 months. The hirsutism was significantly decreased in group II and menstrual cycle frequency improved significantly (**P** = 0.005) in group III at 6 months. There was significant decrease in Testosterone levels in group III, with no significant effect on LH, FSH, LH/FSH, PRL, TSH and Fasting insulin levels.
Conclusion: Combination therapy is more effective than metformin alone for symptoms of polycystic ovarian syndrome.

Introduction:-

Polycystic Ovary Syndrome (PCOS) is recognized as the most common endocrine disorder of reproductive-aged women around the world.[1]PCOS has been defined using various criteria, including menstrual irregularity, hyperandrogenism, and polycystic ovary morphology (PCOM).

The existing Rotterdam guidelines suggest that PCOM is indicated by the presence of at least 12 follicles measuring 2 to 9 mm in the whole ovary or by the finding of increased ovarian size (>10 mL).[2] These criteria were based on a

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completely different ultrasound technology however, and the unjustified increase in diagnoses of PCOS that has arisen from their use in conjunction with new ultrasound technology indicates that they are no longer appropriate in the clinic New AES guidelines, which are based upon a review of the data published using new ultrasound technology, have increased the threshold count of small ovarian follicles to 25. When using the new ultrasound machines, therefore, diagnosis of PCOM is possible in patients having at least 25 small follicles (2 to 9 mm) in the whole ovary. Ovarian size threshold has not been influenced by new technologies, and 10 Ml remains the threshold between normal and increased ovary size. In certain populations and during adolescence or in aging, however, a different threshold for ovarian size may be needed.[3]

The mainstay of first-line therapy for all dermatologic symptoms of hyperandrogenism is OCP therapy. OCPs contain estrogen (almost exclusively ethinyl estradiol) and a progestin. A daily dose of 20 to 35 μg of ethinyl estradiol effectively suppresses pituitary-ovarian communication, thereby decreasing ovarian androgen production. Newer progestins have been developed with an emphasis on greater progestogenic and less androgenic effects.[4]Although the ideal progestins to use in PCOS are those with the lowest androgenic profile, such as chlormadinone and drospirenone, these may induce a higher number of venous thrombosis events and may be contraindicated in patients with severe obesity.[5]

The association of insulin resistance in the pathophysiology of PCOS has given rise to the use of insulinsensitizing drugs in its treatment. Studies of metformin in both obese and lean PCOS women have documented a significant decrease in fasting insulin and androgen levels, as well as a restoration of menstrual cyclicity. Moreover, metformin may indirectly induce ovulation by reducing the concentration of circulating insulin, leading to normalization of the pulsatile production of GnRH and gonadotropins.[6] Metformin has also been shown to improve hyperandrogenemia, even in non-obese women with PCOS who appear to have normal metabolic insulin sensitivity. Whether it is the correction of abnormal insulin action per se or the reduction of plasma insulin levels that is responsible for these beneficial effects of insulin sensitizers is currently unclear.[7] In a small group of normal-weight PCOS women with normal insulin sensitivity established by OGTT and insulin area under the curve analysis, up to 75% of the metformin-treated PCOS women experienced a restoration of menstrual cyclicity in the absence of any significant modification in BMI, WHR, or gluco-insulinemic and lipid profiles.

Objectives:-

To see the effect of combined therapy with low-dose spironolactone plus metformin versus oral contraceptives in Polycystic Ovary Syndrome (PCOS) patients.

Material And Methods:-

Women aged 16–45 years, referred to the outpatient clinic of Endocrinology Division of Internal Medicine and fulfilling 2006 Androgen Excess Society Criteria for PCOS were taken for study. The study was done over a period of one year in the Department of General Medicine, Government Medical College, Srinagar. All subjects included had menstrual disturbances and Hirsutism after ruling out disorders such as Cushing's syndrome, nonclassical adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, and androgen-secreting tumors.

All subjects underwent Anthropometric assessment including measurement of body weight (kg), height (cm), BMI (kg/m^2), and WHR. Waist circumference was measured at the umbilical level and hip circumference at the trochanter region. Blood samples were collected from the patients after an overnight fast for the estimation of T4, TSH, LH, FSH, prolactin (PRL), blood counts, electrolytes, lipids, liver, and kidney functions. Blood samples for hormonal investigations were collected from d 3-7 (early follicular phase) in subjects with spontaneous menstrual cycles. For insulin estimation, samples were collected in ice and plasma was separated immediately in cold centrifuge and stored at −20 C until the assay.A single observer did transabdominal ultrasonography to demonstrate any suggestion of polycystic ovarian morphology, i.e. presence of 10 or more peripheral follicles each measuring 2–8 mm in size with echogenic ovarian stroma and/or increased ovarian volume.

Three groups received eithermetformin (1000mg) or metformin plus spironolactone (50mg) or oral contraceptive Ethinyl Estradiol (35 g) + Cyproterone acetate (2mg) with the objective to compare the efficacy and safety of these drugs in the management of women with PCOS. All patients were reassessed after 6 months with respect to clinical, horomonal and radiological features of PCOS.

Statistical Methods:-

Data was entered in a Microsoft Excel spreadsheet. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as percentages. Independence between two categorical variables were tested using chi-square test. Difference between two independent samples means was tested using unpaired 't' test. Difference between two paired samples means was tested using paired 't' test. Two sided p values were reported and p values < 0.05 were considered statistically significant. Data was analyzed using Statistical Package for Social Sciences (SPSS Ver. 20.0).

Results:-

In a period of two years, we enrolled 100 clinically confirmed cases of PCOS. Out of these, 2 cases had elevated blood glucose (>120mg/dl) and were excluded from the present study. The mean age of presentation was 22.53+3.28 and the age of menarche was 13.23+1.07. Twenty out of 98 patients had grade III acne, 9 had grade II acne and 5 had grade I acne.Ninety eight out of 100 (98%) cases were divided into three groups based on drug(s) given to them. Group I (n=30) was given metformin, group II (n=32) was given combination of metformin and aldactone, group III (n=36) was given oral contraceptives (OCPs).Menstrual cycle frequency improved significantly (**P** = 0.01) with metformin, from 10.47+1.61 to 11.21+0.32 cycles/y at 6 months (Table 1). There was a significant decrease in BMI (P=0.005) with metformin, from 24.57+6.65 to 20.32+4.51 at 6 months. There was no significant effect on WHR, systolic and diastolic blood pressure, FG Score with 6 months of metformin therapy. Menstrual cycle frequency improved significantly (**P** = .001) with metformin and Aldactone therapy, from 7.13+2.95 to 9.69+1.61 cycles per year at 6 months. The hirsutism score decreased (**P**= 0.001) gradually from 12.78+4.83 at baseline to 9.34+3.38 at 6 months of therapy. Systolic blood pressure showed a significant decrease with metformin and Aldactone therapy, from 115.53+9.5 to 109.13+9.40 at 6 months (P=.003)and Diastolic blood pressure (P=0.03) from 71.94+9.65 to 69.06+8.54. There was no significant effect on WHR and on BMI.Menstrual cycle frequency improved significantly (**P** = .005) with OCPs, from 8.42+4.80 to 11.11+1.80 cycles per year at 6 months. The hirsutism score decreased (**P**= .001) gradually from 14.17+4.63 at baseline to 13.53+4.02 at 6 months of therapy. There was no significant effect on WHR, systolic and diastolic blood pressure and BMI with 6 months of OCPs therapy.

There is statistically significant decrease in fasting blood glucose with metformin, from baseline 103.10+27.95 to 88.17+8.72 (P=0.007) at 6 months. There was significant increase in bilirubin levels from baseline 0.58+0.13 to 0.93+0.45 (P=<0.001) at 6 months of metformin therapy. There was significant increase in LDL levels from baseline 106.53+0.16 to 108.60+0.12 (P=<0.001) at 6 months of metformin therapy. Also there was significant decrease in total cholesterol levels from baseline 160.80+45.88 to 125.00+45.88 (P=0.003) at 6 months of metformin therapy. There was no significant effect on TP, ALB, ALP, SGOT, SGPT, TG and HDL with 6 months of metformin therapy. There was no significant effect on BGF, BILIRUBIN, TP, ALB, ALP, SGOT, SGPT, Total cholesterol, TG, LDL and HDL with 6 months of metformin and Aldactone therapy.There was significant increase in TG levels from baseline 117.67+38.71 to 160.66+37.42 (P=<0.001) at 6 months of OCPs therapy. There was no significant effect on BGF, Bilirubin, TP, ALB, ALP, SGOT, SGPT, Total cholesterol, TG, LDL and HDL with 6 months of OCPs therapy.

Metformin Group

There was significant Improvement in HOMA-IR from baseline 1.42+0.91 to 0.78+0.52 (P=<0.001) at 6 months of metformin therapy. There was no significant effect on LH, FSH, LH/FSH, Testosterone, PRL, TSH and Fasting levels with 6 months of metformin therapy. There was no significant effect on LH, FSH, LH/FSH, Testosterone, PRL, TSH and Fasting insulin levels with 6 months of metformin and Aldactone therapy. No significant improvement in HOMA-IR has been seen with metformin and aldactone combination therapy.There was significant decrease in Testosterone levels from baseline 0.34+0.12 to 0.14+0.35 (P=0.001) at 6 months of OCPs therapy. There was no significant effect on LH, FSH, LH/FSH, PRL, TSH and Fasting insulin levels with 6 months of OCPs therapy. No significant improvement in HOMA-IR has been seen with OCPs therapy.

Discussion:-

Metformin, a known insulin sensitizer, is now considered the first-line drug in the management of women with PCOS. Administration of metformin (1g/d) to women with PCOS in the present study increased menstrual cyclicity and improved insulin sensitivity at 6 months of therapy. In our study, we found that menstrual cycle frequency improved significantly (**P** = 0.01) with metformin, from 10.47+1.61 to 11.21+0.32 cycles per year at 6 months

which was similar to study by Ganie MA et al[8]. However no significant effect was observed on WHR, systolic and diastolic blood pressure, FG Score with 6 months of metformin therapy.Also metformin showed a significant decrease in BMI (P=0.03) with metformin, from 28.57+6.65 to 25.32+4.51 at 6 months consistent with study done byHaas DA et al[9].

In our study it was observed that there was a significant decrease in LDL levels from baseline 108.60 ± 0.12 to 106.53± 0.16 (P=<0.001) at 6 months of metformin therapy. Also there was also a significant decrease in total cholesterol levels from baseline 160.80 ± 45.88 to 125.00 ± 45.88 (P=0.003) at 6 months of metformin therapy. These findings are similar to that observed by Mehandiratta R et al[10]. However the decrease in TG and increase in HDL was not statistically significant with 6 months of metformin therapy. No significant effect was observed on LH, FSH, LH/FSH, PRL, T, TSH and fasting insulin levels. There was significant Improvement in HOMA-IR from baseline 1.42 ± 0.91 to 0.78 ± 0.52 (P = <0.001) at 6 months of metformin therapy consistent with study done by Tan S et al[11]. Spironolactone, an antiandrogen administered at a dose of 50mg/d in our study. In our study patients on combined therapy of spironalactone with metformin were observed over a period of 6 months.

Menstrual cycle frequency improved significantly (**P** = .001) with metforminandAldactone therapy, from 7.13+2.95 to 9.69 ± 1.61 cycles per year at 6 months (Table 1). The hirsutism score decreased (**P**= 0.001) gradually from 12.78 ± 4.83 at baseline to 9.34 ± 3.38 at 6 months of therapy. Systolic blood pressure showed a significant decrease with metforminandAldactone therapy, from 115.53+9.5 to 109.13+9.40 at 6 months (P=.003) and Diastolic blood pressure (P=0.03) from 71.94+9.65 to 69.06+8.54. These findings are similar to that observed in the study done by Ganie MA et al[12]. Similar findings were observed in another study Kulshreshtha B et al[13]. There was no significant effect of combination therapy on WHR and on BMI. There was no significant effect on BGF, Total cholesterol, TG, LDL and HDL with 6 months of metformin and spironalactone therapy. No significant improvement in HOMA-IR has been seen with metformin and spironalactone combination therapy.

In our study, 36 out of 98 patients were on OCPs, we observed that menstrual cycle frequency improved significantly (**P** = .005) with OCPs, from 8.42+4.80 to 11.11 ± 1.80 cycles/y at 6 months (Table 1). The hirsutism score decreased (**P**= .001) gradually from 14.17 ± 4.63 at baseline to 13.53 ± 4.02 at 6 months of therapy. Similar findings were reported byYang YM et al[14], Morin-Papunen LC et al[15]. Another study done by Costello MF et al[16] showed similar results. There was no significant effect on WHR, systolic and diastolic blood pressure and BMI with 6 months of OCPs therapy.There was significant increase in TG levels from baseline 117.67± 38.71 to 160.66 ± 37.42 (P=<0.001) at 6 months of OCPs therapy. Similar findings have been seen by Costello MF et al[17]. There was significant decrease in Testosterone levels from baseline 0.34±0.12 to 0.14 ± 0.35 (P=0.001) at 6 months of OCPs therapy.Similar findings were reported by Al-Zubeidi Het al[18]. There was no significant effect on BGF, Total cholesterol, LDL and HDL, LH, FSH, LH/FSH, PRL, TSH with 6 months of OCPs therapy.

We also studied liver function tests in three groups and found that the results were comparable in three groups except for bilirubinwhich showed a significant increase in metformin group. It may be because of non-alcoholic fatty liver disease studied similarly byMira Aubuchonet al[19].

Conclusion:-

It is concluded that, compared to OCPs, the overall benefit and treatment outcome was seen with combination therapy of low dose spironolactone with metformin.

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