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ASSESSMENT OF EFFICACY OF INSULIN SENSITIZER THERAPY IN WOMEN WITH PCOS TO REDUCE THE INFERTILITY RISK

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Abstract:

*Polycystic Ovary Syndrome (PCOS) is emerging endocrine disorder during Reproductive years. Ovulatory dysfunction in these women leads to increased risk of infertility and adverse obstetric outcomes. This study is intended to assess the efficacy of Insulin sensitizer to reduce infertility risk in PCOS patients. Study design is Prospective observational study, study site at Department of Gynaecology and Obstetrics, Government General Hospital, Guntur. Study period: 1st September 2018 to 28th February 2019. Present study shows results, out of total subjects 60% of subjects have stress and 45% of subjects have obesity as a promoting factor and only few as a family history of PCOS. Among 190 study sample, 101 subjects are taking different insulin sensitizer in that 66 subjects taking myocyst M (Myo-inositol and Metformin) as a insulin sensitizer and remaining 35 taking Metformin, about pregnancy status 146 are married and 44 are unmarried in that 146 married subjects 59 attained pregnancy during our study period, by correlating the pregnancy status with insulin sensitizer use out of 59 pregnant women 55 subjects were taken insulin sensitizer therapy and remaining 4 were not taken insulin sensitizer therapy, it clearly states that there is an association between insulin sensitizer usage and pregnancy outcome these can be stated by doing chi-square test which gives the significant value $p < 0.0001$****. Finally conclude that major risk factor for PCOD were stress and obesity. In that moderate stress subjects were more, most of the risk factors were modifiable. Women with PCOS suffered from infertility problem, by the use of insulin sensitizer infertility risk was reduced, mainly ≥6months duration use of myocyst M (Myo-inositol and Metformin) shows positive pregnancy outcome.*

Key Words: *promoting factors, Pregnancy outcome, insulin sensitizer therapy, Metformin, Myocyst-M*

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INTRODUCTION:

Polycystic ovary syndrome (PCOS) has recently been shown to affect a striking 1 in 5 females of India mostly who are in reproductive-age [1], it is a common endocrine disorder with a global prevalence of 5-10% and is an important cause of chronic anovulation in young women. It being a more common among those who are overweight or of Indigenous background. PCOS can be a frustrating experience for women, a complex syndrome for clinicians and a scientific challenge for researchers and is a major public health concern [2]. Polycystic ovary syndrome (PCOS), also known as the Stein-Leventhal syndrome, It is defined as a multifaced disorder characterized by ovulatory dysfunction, hyperandrogenism and gonadotropin abnormality with cystic changes in the ovary. Though the exact cause of PCOS is unknown but it is thought to be multifactorial. Mostly due to hormonal imbalances that is elevated luteinizing hormone (LH) and normal or suppression of follicle stimulating hormone (FSH) resulting in altered LH/FSH ratio. Also, the clinical features of hyperandrogenism are related hyperinsulinemia and insulin resistance. It not clears what are the factors that may predispose a woman for development of PCOS, however it was observed in some cases that PCOS is genetic in nature [3] and obesity was found to contribute for hyperinsulinemia there by predisposing individuals for PCOS. Anovulation (infertility) is the major risk for the PCOS in women with reproductive age. Motherhood is important for every woman's life. Anovulation is the cause of infertility in about a one-third of couples attending infertility clinics, and polycystic ovary syndrome accounts for 90% of such cases [4]. The current leading treatments for ovulation induction are clomiphene citrate (an antioestrogen agent) and letrozole. A recent Cochrane review showed improved live birth and pregnancy rates with the use of letrozole (an aromatase inhibitor) when compared to clomiphene citrate, although the quality of the evidence was low. Other treatments include insulin sensitizing drugs like Metformin and Inositol [5].

PCOD & INFERTILITY:

Women with PCOS experiencing fertility problems often have some degree of insulin resistance, which is defined as decreased insulin-mediated glucose utilisation by cells in the body, that results in raised blood sugar levels. It is thought that up to 50% of both obese and non obese women with PCOS have insulin resistance [6], whereas in the general population the prevalence is thought to be between 10% to 25%. The Burghen study first demonstrated the positive correlation between hyperandrogenism and hyperinsulinism in women with PCOS. There is a negative effect on having both PCOS and obesity on insulin action and the resulting hyperinsulinaemia contributes to reproductive problems in women with PCOS. The combination of obesity, metabolic, inflammatory and endocrine disorders may lead to problems in ovulatory function, oocyte quality and endometrial receptivity.

INSULIN SENSITIZER TREATMENT FOR INFERTILITY:

INOSITOL THERAPY: Inositol is a chemical compound (a sugar alcohol) with nine forms. Two of these are myo-Inositol (MI) and D-chiro-inositol (DCI); both play an important biological role in mediating different actions of insulin and are known as insulin sensitizing agents. Inositol is found in fruits, nuts and beans, can be produced in the body from glucose, and can be taken as a dietary supplement. We consume approximately one gram a day in a regular diet, but the absorption of this free Inositol can be inhibited by glucose. Inositol also acts an antioxidant; a group of vitamins, minerals and fatty acids, that reduce oxidative damage stress by scavenging free radicals. Free radicals are released in the body as a result of oxidative stress and cause harmful reactions in the cells. Inositol is proposed as a therapy for many disorders including, diabetic nerve pain, high cholesterol, insomnia, depression and PCOS. Inositol is critical for many biological pathways: the concentration of Inositol is much higher in the reproductive organs than in the serum, perhaps indicating the importance of these substances in reproduction. The MI form is largely responsible for glucose up take, while DCI is responsible for glycogen synthesis. Inositol is available in tablet and powder form and has been given in a dose of 2 g/day to 4g/day, however the literature does not provide clarity on the appropriate therapeutic dose or any adverse effects. Inositol can also be given as Inofolic, a supplement that contains 2 g MI and 200 µg folic acid [7][9].

METFORMIN THERAPY: In women with PCOS, elevation of circulating insulin and insulin-like growth factor-I (IGF-I) levels results in overproduction of androgens in ovarian theca cells. Metformin inhibits production of androgens in the theca cells, in part through reducing pituitary secretion of LH, leading to ovulation and regular menstrual cycles. Clinically, Metformin is effective for ovulation induction, menstrual-cycle regulation and pregnancy in both obese and non obese patients with PCOS [10]. Previously, researchers demonstrated excellent efficacy of Metformin on induction of ovulation and pregnancy in Asian women with clomiphene citrate

(CC)-resistant PCOS. Although Metformin has been shown to be effective in the treatment of anovulation in women with PCOS, clomiphene citrate (CC) is still considered to be the drug of choice to induce ovulation in these patients. In addition, Metformin plus CC appears to be very effective for the achievement of pregnancy compared with CC alone. During pregnancy, Metformin therapy has been reported to be not teratogenic and safely associated with the reduction in spontaneous abortion and gestational diabetes in women with PCOS. The efficacy of Metformin used during pregnancy has encouraged the continued use of the drug after conception. Nevertheless, the use of Metformin during pregnancy should be performed with great caution because of the limited availability of clinical data [8] [11].

MATERIALS & METHODOLOGY:

Study design: Prospective observational study

Study site: Department of Obstetrics and Gynaecology, Government general hospital, Guntur.

Study period: 1st September, 2018 to 28th February, 2019 (6 months)

Sample size: Total of 190 subjects were included in our study based on study criteria.

Materials: Data collection form, prescriptions, case records, patient information leaf lets.

Inclusion criteria:

- Females with more than 14yrs of age and those who attained the age of menarche
- Females with PCOS.
- Married women are considered in order to assess the infertility rate.
- Patients who are concerned to participate in the study and willing to give informed consent.
- Those who can understand local language

Exclusion criteria:

- Women with other menstrual irregularities like fibroids, ovarian cysts, Abnormal Uterine Bleeding (AUB), Pelvic Inflammatory Diseases (PID)
- Women with other co-morbidities like thyroid, CVS problems, Hypertension (HTN), Diabetes Mellitus (DM) and any other respiratory problems.
- Those who are < 14 years of age.
- Those who cannot understand local language.
- Those who are not willing to participate in the study.

RESULTS AND DISCUSSION:

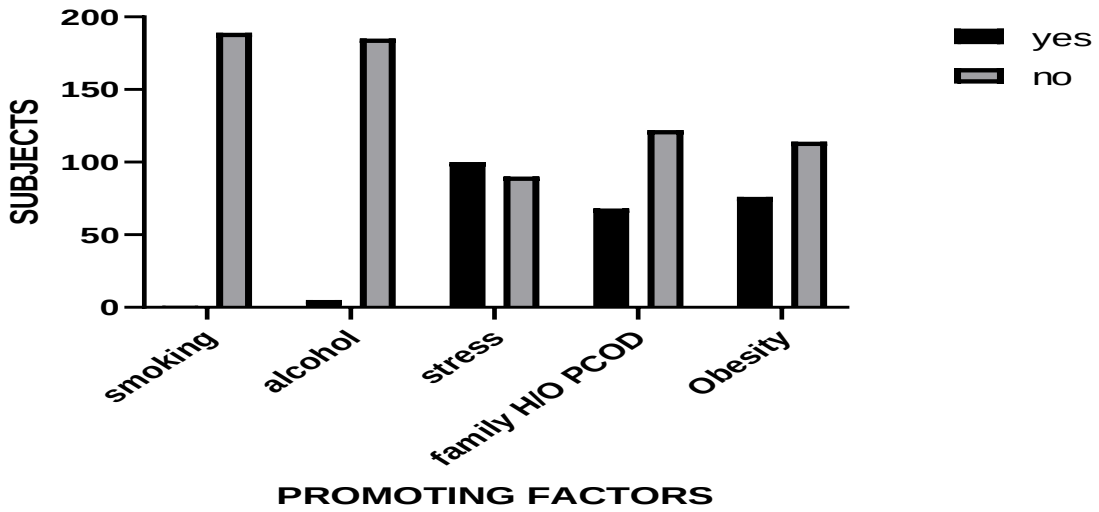

Fig 1: Distribution of subjects according to their promoting factors

From the above figure it is infer that **stress shows the positive association with PCOD** when compared to other factors like smoking and alcohol, after that **obesity and family history show** positive association.

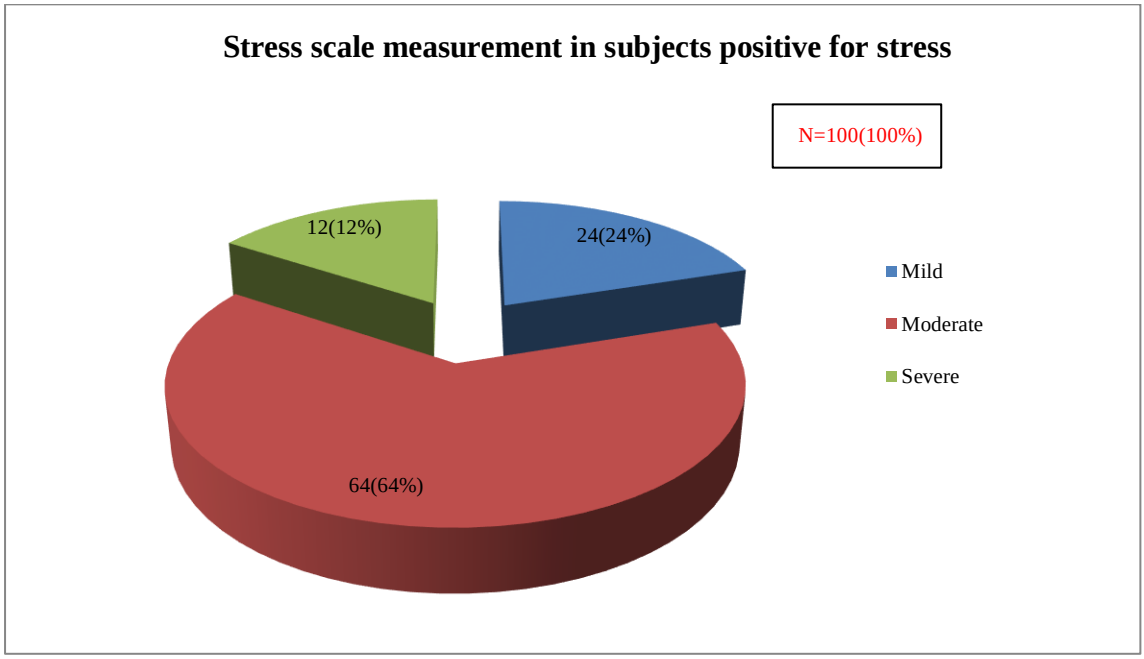

Fig 2: Stress scale measurement in subjects positive for stress

These measured by using perceived stress scale, which shows most of them were fell under moderate stress scale measurement.

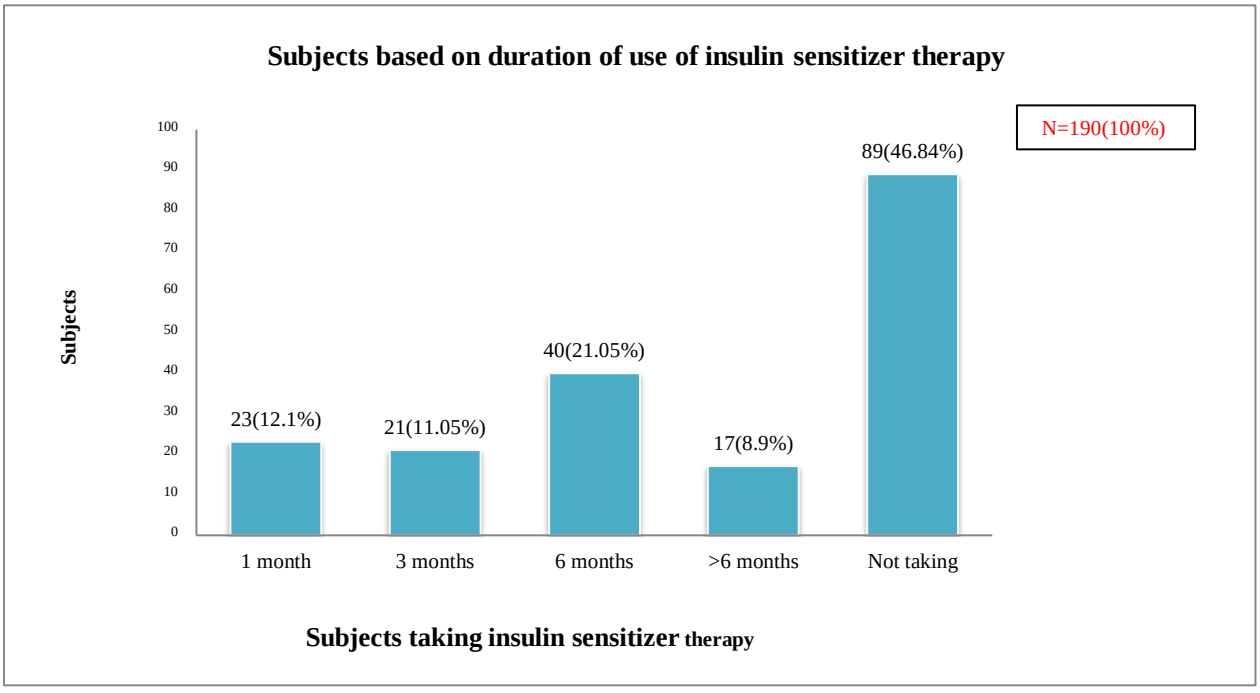

Fig 3: Subjects based on duration of use of insulin sensitizer therapy

Above figure shows the duration of use of insulin sensitizer therapy of subjects out of 101 subjects who are taking insulin sensitizers, majority of subjects which is 40 were taking 6months of duration.

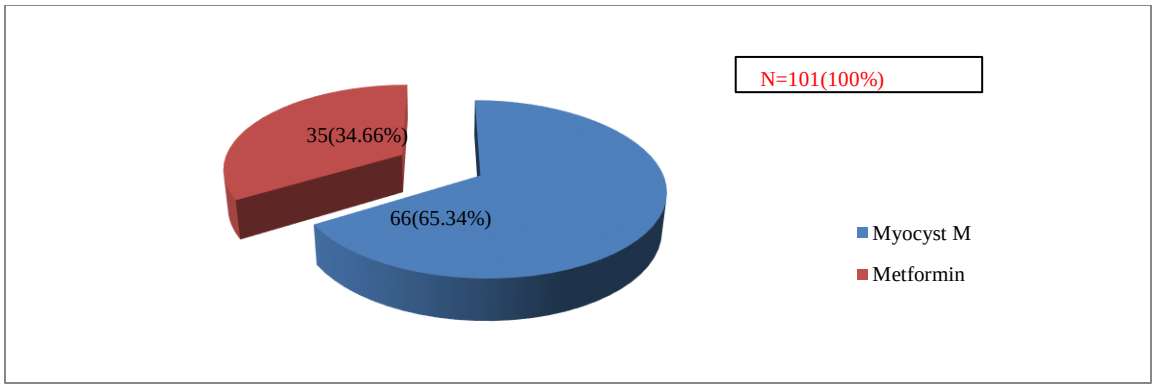

Fig 4: Subjects according to use of different insulin sensitizer therapy

It shows that out of 101 subjects, 66 subjects taking insulin sensitizer myocyst M and remaining 35 taking Metformin, **Finally majority of the subjects taking myocyst M.**

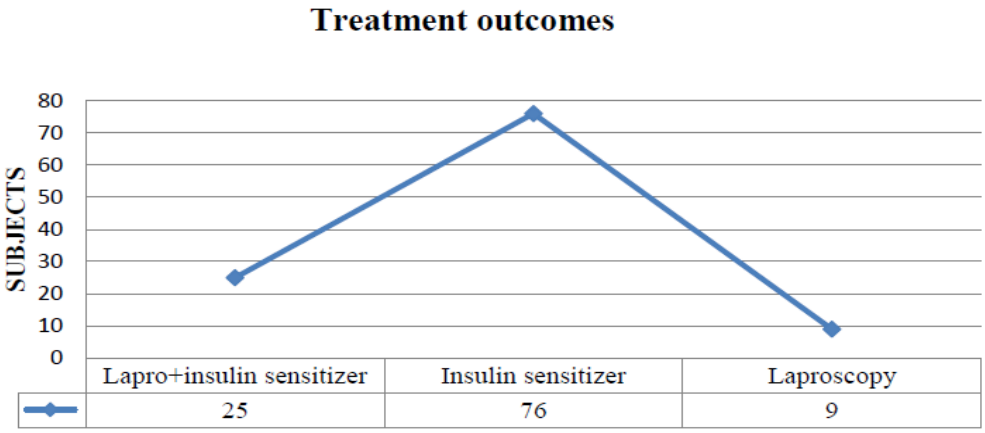

Fig 5: Subjects according to different treatment outcomes

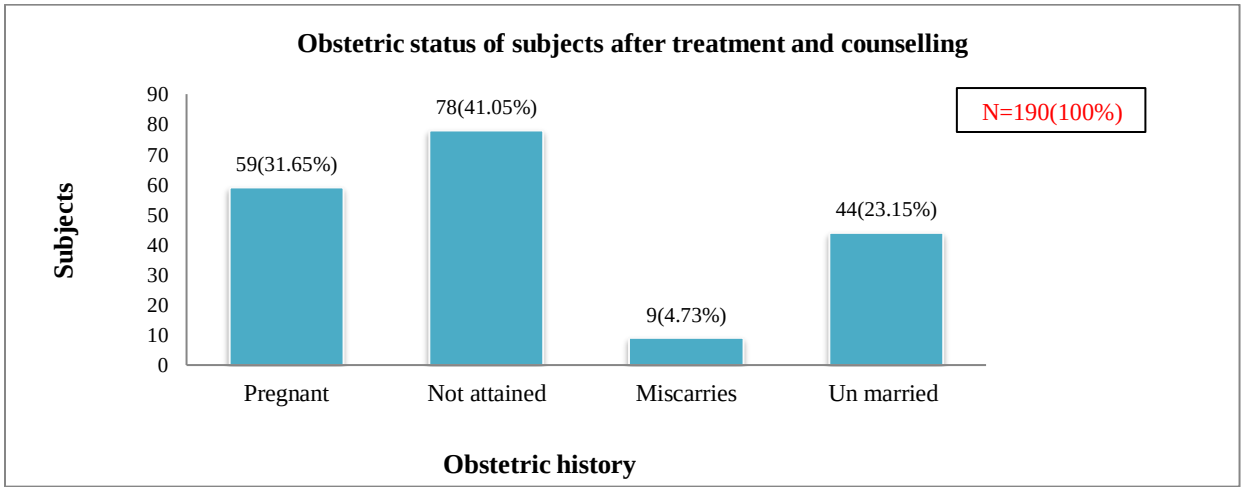

Fig 6: Obstetric status of subjects after treatment and counselling

Above figure shows that out of 146 married subjects 59 attained pregnancy, 78 not attained and 9 subjects attained but unfortunately they miscarried and remaining 44 were unmarried, **it conclude that 59 subjects were attained pregnancy is due to the treatment with insulin sensitizer**

Table-1: Comparison of pregnancy status between insulin taking and non taking groups

Pregnancy status	Insulin sensitizer taking group(101)		Insulin sensitizer not taking group(89)	
	Married (82)	Unmarried (19)	Married (64)	Unmarried (25)
Pregnant	55	--	4	--
Non-Pregnant	27	--	60	--

It shows that out of 59 pregnant women, 55 subjects were taken insulin sensitizer therapy and remaining 4 were not taken insulin sensitizer therapy, **finally it clearly states that there is an association between insulin sensitizer usage and pregnancy outcome these can be stated by doing chi-square test which gives the significant value p<0.0001**** (Chi-square done by using graph pad prism software).**

Comparison of pregnancy status and insulin sensitizer use:

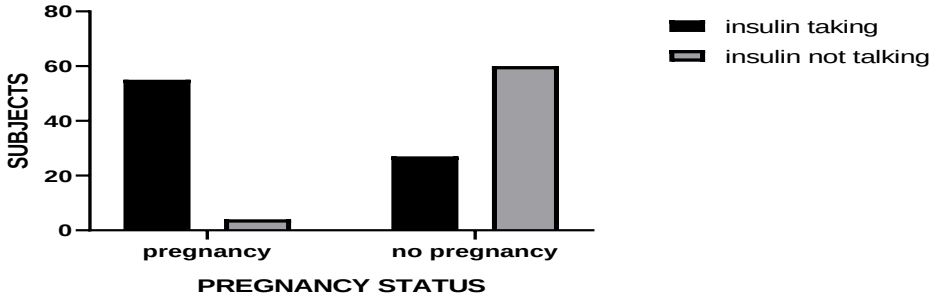

Fig 7: Comparison of pregnancy status and insulin sensitizer use

Above figure states that there is **positive association between pregnancy out come and insulin sensitizer usage** (figure from graph pad prism)

Table-2: Pregnancy outcome (married population) those who are taking different treatment options

Pregnancy status	Insulin sensitizer taking	Insulin sensitizer + laproscopy	Only laproscopy	Not taking any treatment
Pregnant	38	17	2	2
Non- pregnant	16	10	9	51

It shows that out of 82 married subjects who are taking different treatments (insulin sensitizer, laproscopy) in that 38 subjects were pregnant due to usage of insulin sensitizer alone, 17 subjects were pregnant due to use of both insulin sensitizer and laproscopy and only 2 subjects were pregnant due to laproscopy, **it conclude that majority of subjects were pregnant due to insulin sensitizer usage.**

Table-3: Distribution of subjects based on duration of use of different insulin sensitizer and pregnancy outcome

	Metformin duration in months				Myocyst M (Myoinositol+ Metformin) duration in months			
	1 mon	3 mon	6 mon	>6 mon	1 mon	3 mon	6 mon	>6 mon
Pregnant	0	0	8	4	1	3	18	5
Laproscopy+ pregnant	0	0	1	2	1	3	7	3
No pregnancy	2	1	1	0	4	7	0	0
Laproscopy + no pregnancy	0	0	1	4	4	0	3	1

Above table it shows that most of the subjects get pregnancy by use ≥ 6 months duration of myocyst M when compared to Metformin, only few were pregnant by using at the duration of 3 months and 1 month, **finally it shows that minimum of 6 months usage of Myocyst M shows the positive pregnancy outcome.**

CONCLUSION:

Based on the findings of our prospective observational study we finally conclude that major risk factor for PCOD were stress, family history and obesity. In that moderate stress subjects were more, most of the risk factors were modifiable; by proper counselling we can reduce the risk of PCOS. Women with PCOS suffered from infertility problem, by the use of insulin sensitizer infertility risk was reduced, mainly ≥6months duration use of myocyst M (Myo-inositol and Metformin) shows positive pregnancy outcome.

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