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PCOS and infertility. Metformin administration and ovulation induction in patients with reproductive failures. Preliminary data

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SUMMARY: **PCOS and infertility. Metformin administration and ovulation induction in patients with reproductive failures. Preliminary data.**

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The aim of this study is to investigate the effects of the metformin administration in patients with previous reproductive failures.

Inclusion criteria: 13 patients with chronic anovulation and PCOS, age < 38 years old, sterility not less than 2 years, C.C. resistance, conception failure in previous cycles with only r-FSH and negativity to the multiple miscarriages tests, absence of others infertility factors.

Metformin administration started 2 months before the ovulation induction.

Alternatively a spontaneous menstruation it was induced by progestin.

Ovulation was performed with r-FSH and patients were invited to have sexual intercourse during the 48h after the HCG trigger. Luteal support was administrated.

Results showed 100% of ovulatory cycles, 5 pregnancies and only 1 lost.

Few side effects.

RIASSUNTO: **PCOS e infertilità. Somministrazione di metformina e induzione dell'ovulazione in pazienti con insuccessi riproduttivi. Dati preliminari.**

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Lo scopo di questo studio è stato quello di osservare come la somministrazione della metformina potesse influire su pazienti con precedenti insuccessi riproduttivi.

Criteri d'inclusione*: 13 pazienti con anovulazione e PCOS, età inferiore a 38 anni, sterilità da non meno di 2 anni, C.C. resistenza, fallimento del concepimento nei precedenti cicli con solo r-FSH, negatività ai test della poliabortività, assenza di altri fattori d'infertilità.*

La somministrazione di metformina è iniziata due mesi prima dell'induzione dell'ovulazione.

Il ciclo mestruale, nei casi di assenza di uno spontaneo, indotto con progestinico.

L'ovulazione è stata indotta con r-FSH e pazienti sono state. invitate ad avere rapporti sessuali nelle 48h successive all'HCG trigger.

Somministrazione di un supporto luteale.

I risultati mostrarono il 100% di cicli ovulatori, 5 gravidanze ed 1 solo aborto.

Nessun effetto collaterale.

KEY WORDS: PCOS - Infertility - Metformin - Ovulation induction - Pregnancy.
PCOS - Infertilità - Metformina - Induzione dell'ovulazione - Gravidanza.

Introduction

Recently it has been given importance to the insulin levels role on the of polycystic ovary syndrome (PCOS) pathogenesis which can determine long-term development of important pathologies as endometrial cancer, type II diabetes, dyslipidemia, hypertension and cardiovascular problems.

Many studies have shown that the insulin reduction is possible both by the action on the pancreas both improving the peripheral insulin sensitivity that causes a plasma reduction of circulating androgens and an improvement in the ovulatory function (1-10).

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Table 1 - MAIN INCLUSION CRITERIA.

Research factors	Total patients (N= 13)	Pts without conception before treatment (N = 9)	Pts with previous miscarriages (N=4)
Age	29.5 ± 5.5 SD	29.6 ± 5.6 SD	29.3 ± 6.1 SD
Sterility period (ys)	4.5 ± 2.0 SD	4.3 ± + / -1.9 SD	5 ± 2.4 SD
Previous miscarriages			2.3 ± 0.5 SD
Previous cycles with O.I. by r - FSH	3.8 ± 0.8 SD	3.7 ± 0.7 SD	4.3 ± 0.96 SD
Medium time of O.I. during the previous cycles	18.5 (12 – 30 days)		
Medium numb. of r-FSH used in the previous cycles	1650 (1150 – 2225 I.U.)		

ys: years; SD: standard deviation; O.I.: ovulation induction; r-FSH: recombinant follicle stimulating hormone.

Materials and methods

Between March 2006 and June 2007 we followed at the Fertility and Sterility Unit (University of Palermo) 13 patients with chronic anovulation and PCOS.

Nine of those with primary infertility and four with previous multiple miscarriages.

Inclusion Criteria (IC): Age < 38ys, absence of others infertility factors that we checked by: vaginal ultrasound scan (u.s.), hysterosalpingography, hormonal assays, sperm and thyroid tests.

Sterility not less than 2 years, clomiphene citrate (CC) resistance, conception failure in previous ovulation induction cycles by recombinant follicle stimulating hormone (r-FSH) and negative multiple miscarriages exams (Table 1).

Metformin was administered with 500 mg as starting dose (to avoid the common side effects) and increasing doses up to 1500 mg.

All patients performed blood tests to exclude metformin contraindications.

Alternatively to a spontaneous menstruation was administered progestin for 7 days to induce it.

Ovulation induction was performed with r-FSH according to the *low - dose step- up* protocol (75 I.U./day) and keeping the same dose in case of a dominant follicle > 18mm and no more than two follicles > 16mm.

Human chorionic gonadotropin (HCG) was administered with an estradiol E_2 < 900 pg / ml inviting patients to have sexual intercourse in the next 48 hours.

Treatment was stopped in case of ovarian hyperstimulation syndrome (OHSS) risk.

All patients were invited to intake a 100 mg luteal support (vaginal progesterone) for 14 days and to continue oral metformin during the first trimester in case of positive β-HCG test.

All the patients performed a β-HCG blood test the 14^{th} day after the induction.

Results

We obtained 100% of ovulatory cycles with the treatment and three patients with more than one follicular size between 16 and 18 mm on the HCG day.

The average FSH dose (1650 I.U. *vs* 1700 I.U.) and

TABLE 2 - RESULTS OBTAINED BY USE OF R-FSH PLUS METFORMIN.

	Total pts:13	Pts without pregnancy before treatment	Pts with miscarriages before treatment
N° of ovulatory cycles / N° of cycles with treatment	13 / 13 (100%)	9	4
Medium dose of r-FSH (I.U)	1700 + / -758.7 SD		
N.° cycles with more 1 follicle on the HCG day	3 / 13 (23.1%)		
N° of pregnancy	5 / 13 (38.5%)	3 (23.1 %)	2 (15.4 %)
N° of miscarriages	1 / 5 (20%)	0	1/2 (50 %)
Stopped cycles to avoid OHSS	1 (7.7%)		
N° of cycles without follicles	0		
N° of OHSS post HCG	0		

pts.: patients; r-FSH: recombinant follicle stimulating hormone; SD: standard deviation; HCG: human chorionic gonadotropin; OHSS: ovarian hyperstimulation syndrome.

the average number of stimulation days (19.7 *vs*18.5 days) were similar before and after metformin.

Five patients with amenorrhea started to have a menstrual cycle after only 2 months of treatment, that to confirm a restoring rhythmicity role.

Five pregnancies obtained and only one was lost in a patient who had 3 biochemical pregnancies during the previous cycles without metformin.

None stopped cycle after the HCG trigger for OHSS risk.

Few side effects but not such as to stop the therapy.

About the other four pregnancies, three in the group without previous pregnancies and one conception in a woman with two previous miscarriages had good neonatal outcomes (Table 2).

Discussion

Many studies showed as insulin plays a key role in the endocrine and paracrine ovarian control and that more than 70% of patients with PCOS have insulin resistance.

Has been shown that insulin has an active role in the amplification of androgens production LH - stimulated especially in correspondence of theca cells (Figure 1).

This would explain the hyperandrogenic symptoms prevalence in obese PCOS patients.

It is also an important factor in the ovarian androgen synthesis to confirm its hyperandrogenic responsibility in these patients.

Metformin effects in PCOS patients includes:

- Total and free testosterone plasma levels reduction
- Increasing of sex hormone binding protein (SHBG) and FSH synthesis levels
- Improvement of insulin sensitivity
- Ovarian function restoring.

It was demonstrated how the spontaneous and induced ovulations frequency can be increased by lowering insulin levels performed by metformin.

It plays a role on the cycle regularization especially reducing luteinizing hormone (LH), free-testosterone,

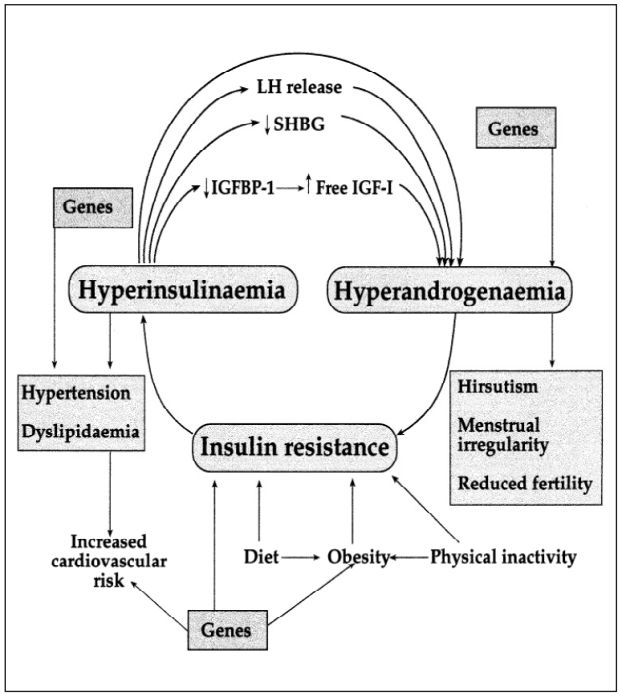

Figure 1 - Correlation hyperinsulinaemia - hyperandrogenaemia.

androstenedione and hormones levels as the LH/FSH ratio (11-15).

Furthermore many studies have confirmed the absence of teratogenicity and its action to reduce the incidence of miscarriage during the first trimester of pregnancy due the action on the plasminogen activator inhibitor (PAI).

This metabolic metformin role can reduce the hyperstimulation risk, improves the FSH exogenous response and the oocytes quality.

Our results in addition to other randomized and controlled studies may help to evaluate the metformin effects on the multiple miscarriages and gestational diabetes prevention considering the long term tolerability to the treatment and the fetus safety in patients with reproductive failures.

Disclosure

Limitations. Reason for causion: further RCT studies are needed to confirm our results.

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Competing interest(s). None.

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