

Research Article

The Usage of Metformin in Women with Polycystic Ovary Syndrome and its Effect on *In vitro* Fertilization

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- *In vitro* fertilization
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Abstract

Objective: To show the beneficial impact of the use of metformin in women with polycystic ovary syndrome and its success in IVF at the Fertility Clinic of Baja California.

Material and methods: A randomized controlled clinical trial in women with polycystic ovary syndrome, who were subjected to IVF treatment, in a period during January 2015 to December 2015, in the Fertility Clinic of Baja California, at Santa Rosa de Lima Hospital. Overall, there were 17 female patients between aged 26 and 40 years, from who 8 patients were administered with Dabex (metformin) 500 mg oral during the dinner; starting with 500 mg weekly, the dose was gradually increased up to 1.5 gr. and Yasmin taken by oral via (3.0 mg drospirenone and 0.03 mg ethinylestradiol) 1 every 24 hours for a period of 3 weeks. The other 9 patients took oral Yasmin (drospirenone and 0.03 mg ethinylestradiol 3.00mg). SPSS 21 (Statistical Analysis Software Package) program was used for statistical analysis.

Results: There were no statistically significant differences in terms of the characteristics of the patients studied. The patients with polycystic ovary syndrome who took metformin obtained an implantation rate of 18.75% and a clinical pregnancy rate of 37.5%. Patients with polycystic ovary treated with contraceptive pills had an implantation rate of 3.4% and a clinical pregnancy rate of 22%, respectively.

Conclusion: The usage of metformin improved the success of IVF in women with polycystic ovary.

ABBREVIATIONS

IVF: *In vitro* Fertilization; IVFTE: Treatment for Fertilization *In vitro*; ICSI: Intracytoplasmic Sperm Injection; PAI-1: Plasminogen Activator Inhibitor 1; IGFBP-1: Insulin-like Growth Factor-Binding Protein 1

BACKGROUNDS

Metformin is a biguanide class drug, hypoglycemic oral drug that is the most commonly prescribed drug for diabetes type 2. In the last decade its clinical applications have increased, showing evidence mainly in metabolic syndrome patients with glucose intolerance, women seeking to get pregnant who have the polycystic ovary syndrome [1], cardiovascular disease, as well as cancer and aging. One of the mechanism of metformin is to reduce hyperinsulinemia even though the mechanism is not yet fully understood, it has been partly attributed to increased hepatic insulin sensitivity and the elevated uptake glucose in peripheral tissue [2], the ovarian diminish of excessive androgens production, the improvement in menstrual cycles and the probability of pregnancy, which is the reason that it has been

mentioned the main use of metformin as a coadjuvant treatment as a ovulation induction agent [3].

Some studies have evaluated the effectiveness and security of metformin as part of the treatment for IVFTE or ICSI, with the objective of accomplishment in a healthy pregnancy in women who suffer polycystic ovary syndrome [4]. For all those reasons already mentioned, it has been shown some benefits of use of metformin in patients with ovarian polycystic syndrome insulin-resistant [5]. The drug already mentioned, improves glucose tolerance, increases the insulin sensitization, normalizes the relationship LH/FSH, diminish PAI -1, restores menstrual cycles, and improves rates of pregnancy.

Endometrium

Along the pregnancy 20% of maternal blood goes through placenta, using the cellular invasion called trophoblast, that forms a cellular line dependent of the embryo. This cells secrete certain substances and digestive enzymes that initiate the processes of implantation [6] as the emergence of pinopods, the increment of glycodecin A, adhesion molecules, cytokines and

growth factors – epidermal growth factor, colony stimulating factor 1, leukemia inhibitory factor, interleukin 1, IGFBP-1, transforming growth factor beta – and HOXA genes, associated with adequate endometrial receptivity and the success of implantation [7,8]. Some of these markers already mentioned, had been studied in women with ovarian polycystic syndrome [9].

Both insulin and insulin-like growth receptor inhibit endometrial decidualization have been studied in patients with ovarian polycystic syndrome. These patients have endometrial changes which are reflected in alterations of the appearance pattern and the concentration of the hormonal steroids receptor [10].

Polycystic ovary syndrome

The polycystic ovary syndrome is an endocrine-metabolic disorder. This disorder has heterogeneous clinical presentation, it probably has a genetic origin, which is influenced by environmental factors such as nutrition and physical activity [11]. Worldwide statistics show that the polycystic ovary syndrome affects proximally 5-10% of women, while the prevalence in Mexico is reported in 6% [12]. Being the most common endocrinopathy in reproductive age women and the most frequent cause of infertility for an ovulation and premature loss of pregnancy [13].

The first line treatment for those patients with polycystic ovary syndrome that do not desire pregnancy is combined oral contraceptives, can be used for periods longer than 6 months. The most recommended are the low dose containing ethinylestradiol 20 ug [14].

Knowing the relationship between insulin resistance and the physiopathology of the polycystic ovary syndrome, studies have emerged that refer that metformin is capable of decrease ovary hyperandrogenism, improving the metabolic, endocrine and reproductive parameters of patients. In the next study it will check the main findings of the metformin effects and the success of assisted reproduction techniques of high complexity in women with polycystic ovary syndrome.

In the following research we wanted to determine whether metformin has beneficial outcomes in the pregnancy and implantation rates in patients with polycystic ovary syndrome and promote the use of metformin as adjuvant treatment for infertility.

MATERIAL AND METHODS

This randomized controlled clinical trial was performed in women with polycystic ovary syndrome, they were submitted to IVF treatment, in the period from January to December 2015. We included 17 female patients aged between 26-40 years diagnosed with polycystic ovary syndrome through medical history and pelvic ultrasound according to the Rotterdam criteria. In all the cases, the results of thyroid function tests were normal. Three patients presented amenorrhea and the rest oligomenorrhea during fertile life.

After signing an informed consent of all the patients, treatment was initiated, the first group included 8 patients

treated with Dabex (metformin) 500 mg oral during the dinner; starting with 500 mg weekly; the dose was gradually increased up to 1.5 gr., and Yasmin (Drospirenone 3 mg/ ethinylestradiol 0.03 mg) 1 tablet every 24 hours for a period of 3 weeks. The other group of 9 patients were controlled with contraceptives Yasmin (Drospirenone 3 mg/ethinylestradiol 0.03 mg) oral 1 tablet every 24 hours for 3 weeks; after 10 days of stimulation with follitropin alpha 75 UI subcutaneous per day, when the follicles measure between 18 to 20 mm; is performed ovular capture, a puncture is done through the follicles with endovaginal transducer of 5 MHz brand Aloka SSD-1400. Subsequently the oocytes are aspirated using the aspiration follicular bomb brand Gen X with a medical Cook needle caliber 17G, and they are transferred to the laboratory. The oocyte maturation was observed by an optical microscope, by locating cells with polar body outside the cytoplasm of the oocyte. Already identified, they are prepared for the technique of ICSI. On the other hand for the IVF technique the oocytes were wash out along with the granulosa cells, subsequent they are moved to a second plate were the cumulus – oocyte complex is trimmed, once they were clean, they were classified morphologically and deposited in a culture medium, they were later taken to the incubator at 37 degrees Celsius and 6% of carbon dioxide. On the morrow, the confirmation of the fertilization is made by the observation of 2 pro-cell nuclei and 2 polar bodies, the cell culture is carried out until day 3 of *in vitro* development and the embryonic transfer is performed using a transabdominal transducer of 3.5 Mhz, brand Aloka SSD-1400. The development phase was observed with Frydman catheter of 18 cm the 2nd day with 2-4 cells and the 3rd day with 6-8 cells. Fourteen days after the transfer, is performed the blood measurement of BhGc. Patients with BhGc positive, continue metformin dose throughout pregnancy.

The implantation rate was defined as the number of gestational sacs with active embryo among the number of embryos transfer and the clinical pregnancy rate was the number of patients with active gestation among the number of patients with embryonic transfer.

The obtained data were captured in a data base for their further analysis in the package of de Statistics analysis program SPSS21, it was used descriptive statistics for the variables, using for the quantitative variables measures of central tendency and dispersion, for the qualitative variables percentages and frequencies.

RESULTS

In this study, the mean age of the participants was 33.1 years old (range 26 to 41 years) and mean body mass index was 28 (range 23 to 40).

According to the statistical analysis of both groups, it was found that there were no statistically significant differences in terms of the characteristics of the studied patients such as age, count of antral follicles, oocytes aspirated number, and oocytes fertilized number, endometrial thickness, and total dose of gonadotropins, culture hours and number of embryos transferred (Table 1).

In the group of patients with polycystic ovary syndrome

who was administered metformin acquired an implantation rate of 18.75%, and a clinical pregnancy rate of 37.5%. The other group of patients with polycystic ovary syndrome who took contraceptives pills presented an implantation rate of 3.4% and a clinical pregnancy rate of 22%, respectively (Table 2). Additionally, this patient presented an average of endometrial thickness of 19.22% with respect of the average of 11.89% in patients who was administrated metformin, although this was not statistically significant.

DISCUSSION

In this study, throughout the pregnancy we continue to administrated metformin 1 -1.5 gr daily, however, none of the products presented anomalies or fetal risk; monitoring the first 24 hours after delivery, none of the patients presented hyper or hypoglycemia . Despite that, some authors referred that the use of metformin on pregnancy and his use as a coadjuvant treatment on assisted reproduction is not yet complete standardized, it has been proved that can be classified on B category, which means that studies have been directed on animals and their toxicity or fetal risk in women has not been demonstrated [15]. Other researchers have also reported that metformin have a protective mechanism by decreasing the levels of constitutive phosphorylation of H2AX on Ser139 and constitutive activation of ATM [16].

FedorcsaÈk et al., found that treatment with metformin did not modify the amount of gonadotropins used, but did provoke an increased in the average number of recollected oocytes in the capture procedure (8.6 versus 4.6). The same study reported an increased rate of pregnancy through IVF on the patients with ovarian polycystic syndrome and normal weight [17].

Stadtmauer et al., published that the usage of metformin prior to IVF in patients with polycystic ovarysyndrome, achieved a smaller number of follicles, a lower maximum level of estradiol and a higher number of mature oocytes. This group of patients had a 70% clinical pregnancy rate, meantime in the group who didn't used metformin this rate was a 30% [18].

Moreover, early gestational loss is one of the complications related to polycystic ovary syndrome. Some studies have evaluated the effectiveness of metformin by decreasing rates of early gestational loss compared with the clomiphene administration or fertility treatment with ovarian perforation by laparoscopy [19].

As discussed previously, polycystic ovary syndrome is frequently related with infertility. A pilot study carried out in 2001, elucidated the causes of abortions in the first trimester; there was observed an important elevation of the PAI-1 independently. In three outcomes of different pregnancies, was associated catastrophic results in each one with the presence of PAI -1. The PAI - 1 promote the abortions through thrombotic induction and placental insufficiency. As previously mentioned, the metformin foster the regulation of menstrual cycles in 91% of women with polycystic ovary syndrome that previously were infertile and with oligomenorrhea. It was shown that metformin reduced the PAI-1 activity by decreasing insulin concentration and resistance. Therefore, the administration of metformin (1.5-2.5 g/day) reduced the abortion rate from 73% to 10% and metformin was given throughout the pregnancy without producing teratogenicity [20].

In the present study we found significant differences in implantation rates, being 18.75% in women with polycystic ovary syndrome who use metformin and 3.4% in contraceptive users. The clinical pregnancy rate reached in the group of metformin users and in the group treated with contraceptives only respectively was 37.5% and 22%. The use of metformin in women with polycystic ovary syndrome improve insulin resistance by decreasing the enzyme cytochrome P450 17^a activity. This leads consequently to lower levels of androgens, allowing the improvement of the intrafollicular microenvironment [21].

Earlier studies have shown that hyperinsulinemia is the primary cause of the biochemical alterations produced; metformin is the antihyperglycemic drug more used and studied in the market, its impact on the pathophysiology of the disease is overwhelming, enhanced the pathological biosynthesis of androgens and hence improve ovary function [22].

CONCLUSION

Despite the size of the sample, the findings in the use of metformin as a coadjuvant therapy were promising. The improvement shown in the pregnancy and implantation rate were encouraging, and without any side effects in the products

Table 1: Characteristics of the patients.

	Patient with metformin and contraceptive	Patient with contraceptives	Value
	Media	Media	P
Age (years)	38,78	37,56	0,868
Antral follicle count	11,11	8,11	6,59
Aspired oocytes	7,00	7,22	9,74
Fertilized oocytes	5,63	5,67	0,91
Endometrial thickness	11,89	19,22	0,65
Total of GnRH	1138,89	1269,44	0,595
Hours of cultivation	67,00	61,67	0,414
Transferred embryos	3,44	3,67	0,215

Table 2: Implantation rate, biochemical pregnancy and clinical pregnancy.

	Patient with metformin and contraceptives	Patient with contraceptives
Transference	8	9
Transferred embryos	32	58
Positive B-hCG	6	2
Women with gestational sac	3	2
Active embryo	6	2
Number of gestational sac with active embryo	6	2
Implantation	6/32=18.75%	2/58=3.4%
Clinical Pregnancy	3/8=37.5%	2/9=22%

of gestation. The use of metformin improves the success of pregnancy in IVF and diminish symptoms in polycystic ovary syndrome.

The knowledge in the administration of metformin in the field of reproductive medicine it is yet uncertain, opening the door for further investigations.

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