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# Reproductive Outcomes in Patients with Infertility and Insulin Resistance

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**ABSTRACT**

Infertility defined as the inability of a couple to achieve conception after one year of sexual intercourse without contraceptive protection, or after 6 months in patients older than 35 years. According to the WHO, 10-15% of couples have some fertility problem and 25-50% of this is due to anovulatory female infertility, which could be due to insulin resistance, especially in overweight and obese patients, since 75% of obese patients suffer from IR, added to the fact that overweight and obesity have a high prevalence in the Mexican population, where a prevalence of up to 35% has been reported, it is important to consider it as a causal factor in patients with infertility. In 2021, 413 first-time patients with a diagnosis of infertility were received at the Gynecology-Obstetrics UMAE of CMNO IMSS; of these, 245 have a diagnosis of anovulation and about 40% are overweight or obese, however, there is no report on reproductive outcomes of these patients who undergo medical treatment, some cases achieve clinical pregnancy and of these some result in term births, preterm, miscarriage and / or death.

Infertility and obesity have a great impact on women's health, affecting the physical, psychological, family and social area, leading to a deterioration in the quality of life, in turn obesity is one of the main risk factors for numerous diseases, so they are of special interest to social level and in the health system, being important its study and treatment to achieve better results of fertility and health in general.

**KEYWORDS**: Infertility, HOMA-IR, hyperinsulinemia, Mexican population.

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## INTRODUCTION

Infertility is the inability of a couple to achieve conception after one year of sexual intercourse without contraceptive protection, or after 6 months in patients older than 35 years. According to the WHO, 10-15% of couples have some fertility problem and 25-50% of this is due to anovulatory female infertility, strongly related to endocrinological disorders such as insulin resistance, coupled with the fact that overweight and obesity have a high prevalence in the Mexican population, where a prevalence of up to 60% has been reported, it is important to consider it as a causal factor in patients with infertility. Insulin resistance is defined as a condition in which the tissue effects of insulin are diminished, generating an alteration of the metabolic state, in which higher levels of insulin are needed to achieve glycemic control, therefore pancreatic insulin secretion is increased, leading to a state of "hyperinsulinemia" to maintain glycemic control, these higher insulin levels increase androgen production (dehydroepiandrosterone sulfate and testosterone) interfering with follicular growth, contributing to follicular arrest and the relative decrease in FSH stimulation is not able to achieve follicular selection, ultimately resulting in anovulation. Among the diagnostic methods of insulin resistance are the euglycemic hyperinsulinemic clamp (gold standard), fasting plasma insulin, QUICKI index, Matsuda-DeFronzo index and the most widely used due to its simplicity, sensitivity and adequate correlation with the hyperinsulinemic euglycemic clamp, the Homeostasis Model Assessment of Insulin Resistance (HOMA), which is based on the measurement of two biochemical parameters, glycemia and basal insulinemia, by means of the following calculation:

HOMA-IR = fasting blood glucose (mg/dL) x basal insulinemia (uU/mL) / 405.

The cut-off values for HOMA to make a diagnosis of insulin resistance in the Mexican population being ≥ 2.5. The importance of diagnosing insulin resistance in women with infertility lies in the development of simple and accessible strategies for its treatment, which, in addition to reducing possible complications, would improve the chances of

achieving pregnancy in patients with infertility associated with insulin resistance.

## METHODS

This is an observational, cross-sectional, descriptive and retrospective study, which after review and authorization by the Local Health Research Committee (CLIS 1310) and by the Research Ethics Committee (CEI), the sample size previously calculated using the formula for estimating proportions was obtained, considering a confidence level of 95%, therefore, the electronic files of the 6595 consultations that were granted with the diagnosis of infertility during the period from January 01, 2018 to December 31, 2019 in the reproductive biology service of the High Specialty Medical Unit of the Centro Médico Nacional de Occidente were reviewed, from that review of clinical files a sample of 205 patient files that met the inclusion criteria was selected: records of women with a diagnosis of infertility ICD 10 N.97 from 18 to 34 years of age with insulin resistance identified by HOMA >2.5 and absence of pregnancy after 12 months of regular sexual activity without contraceptive protection and records of women with a diagnosis of infertility ICD 10 N.97 over 35 years of age with insulin resistance identified by HOMA >2.5 and absence of pregnancy after 6 months of regular sexual activity without contraceptive protection; not included were records of patients with a diagnosis of Diabetes Mellitus type 1 or 2, records of patients with drug addiction, alcoholism and smoking, as well as records of patients with added factors such as infertility due to male factor, uterine anomalies, tubal factor, as well as uncompensated endocrinological alterations in women. Files were reviewed to complete the variables to be evaluated, among these: general data (age, type of infertility, parity, schooling, occupation, marital status), aggregate clinical characteristics of each patient (weight, height, BMI, degree of obesity), in the case of weight and height these somatometric measurements were taken with a foot scale with a stadiometer, which were reported in the file at the time; Other variables such as follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, the treatment used, as well as their ovulation inducing doses such as gonadotropins, clomiphene citrate, letrozole and the number of cycles used were also collected, as well as the basal glucose and insulin results to calculate the HOMA index, which if found ≥ 2. 5 will be taken as positive for insulin resistance and will be included in the study protocol; they were classified into three groups 2.5-3.5, 3.5-4.5 and greater than 4.5 to correlate with the reproductive results of each patient; finally, information was collected from each record included about the reproductive results obtained in the patients, that is, whether it was a successful or unsuccessful clinical pregnancy, the evolution of the pregnancy (miscarriage or delivery) and whether it was a delivery to mention its term (preterm or term delivery). Subsequently, the data obtained from the files were processed in Excel and SPSS v.21 programs for statistical analysis and the results are expressed in descriptive statistics, for quantitative or numerical variables by means of mean, median and standard deviation and for qualitative or categorical variables by means of frequency and percentages.

## RESULTS

The present study included records of patients seen in consultation of the Reproductive Biology service of the UMAE CMNO during the period from January 01, 2018 to December 31, 2019 with a diagnosis of infertility and insulin resistance. At the end of the study we managed to include a total of 205 patients, where the mean age was 31 years with a standard deviation (SD) of 4.38 years. The most common educational level reported was high school in 36.1% of the cases (n=74), while the least frequent was women with a postgraduate degree, represented by 0.5% (n=1). The most frequent occupation was employed with 53.2% (n=109), followed by professional and housewife with 26.3% and 16.3% respectively. The most common marital status was married, reported in 75.1% of the cases (Table 1) (Table 1).

The clinical characteristics of the participants (Table 2), where it can be observed that more than half of the patients (56.1%) had never had a pregnancy (nulligestas), The average weight of the participants was 79.28 kg ± 15.3, in turn with an average height of 1.62 meters ± 6cm, which translates into an average BMI of 30. 15 ± 5.1 kg/m2, the above is represented by a nutritional status predominantly overweight with 34.6% of the total participants, approximately 49% of the patients had some degree of obesity, the most frequent degree was Obesity G1 with 31.2% of the total cases. With respect to infertility, 56.6% (n=116) presented primary infertility (Graph 1), and the average time of evolution with infertility was 45.5 months

**Table 1. General characteristics of the participants**

| Características / Factores | n | % |
|---|---|---|
| Age (years) | 30.82 ± 4.38 (p25 27, p50 30, p75 33) | |
| Escolaridad | | |
| - Primariy | 6 | 2.9 |
| - Secundary | 35 | 17.1 |
| - Preparatory | 74 | 36.1 |
| - Professional | 51 | 24.9 |
| - Undergraduate | 38 | 18.5 |
| - Postgraduate | 1 | 0.5 |
| Ocupation | | |
| - Employee | 109 | 53.2 |
| - Professional | 54 | 26.3 |
| - Housewife | 34 | 16.6 |
| - Student | 5 | 2.4 |
| - Laborer | 1 | 1 |
| - Other | 2 | 0.5 |
| Marital Status | | |
| - Married | 154 | 75.1 |
| - Free union | 31 | 15.1 |
| - Single | 19 | 9.3 |
| - Divorced | 1 | 0.5 |

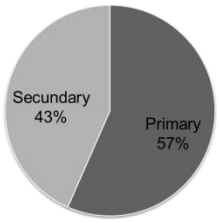
Source: data collection sheet. Statistics: Mean, SD, Percentiles. Frequency, Percentage

**Table 2. Clinical characteristics of the participants**

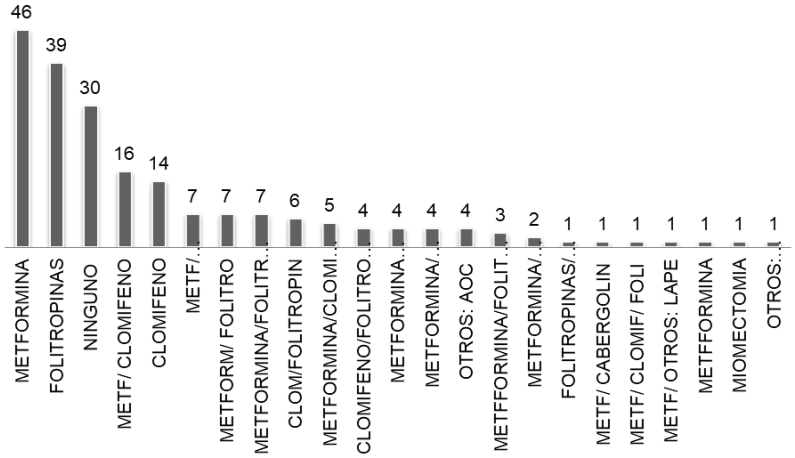
| Characteristics / Factors | n | % |
|---|---|---|
| Parity | | |
| - Nulligestation | 115 | 56.1 |
| - Primigesta | 36 | 17.6 |
| - Second stage | 22 | 10.7 |
| - Multigestation | 32 | 15.6 |
| Weight | 79.28±15.3 (p25 67, p50 79, p75 89) | |
| Height | 1.62±0.06 (p25 1.57, p50 1.62, p75 1.66) | |
| Body Mass Index (BMI) | 30.15±5.1 (p25 25.9, p50 29.8, p75 33.9) | |
| Nutritional status | | |
| - Normal | 34 | 16.6 |
| - Overweight | 71 | 34.6 |
| - Obesity G1 | 64 | 31.2 |
| - Obesity G2 | 26 | 12.7 |
| - Obesity G3 | 10 | 4.9 |
| Type of infertility | | |
| - Primary | 116 | 56.6 |
| - Secondary | 89 | 43.4 |
| Evolution | 45.5±30.97 (p25 24, p50 36, p75 60) | |

Source: data collection sheet. Statistics: Mean, SD, Percentiles. Frequency, Percentage

**Graphic 1. Type of infertility**




**Graphic 2. Type of management to infertility**




In the study, hormone levels showed significant variations. Follicle stimulating hormone (FSH) averaged 6.2 mIU/mL, with 18% of the participants outside the normal range. Luteinizing hormone (LH) averaged 6.8 mIU/mL, with 20% abnormal values. Estradiol averaged 44.7 pg/mL, with only 8.8% of abnormal cases. Prolactin showed alterations in 26% of patients, with an average of 16.7 ng/dL. Insulin was elevated in 58.5% of cases, with an average of 21.5 ng/mL. The average glucose was 92.5 mg/dL, resulting in an average HOMA index of 4.93, with 42.9% of the patients classified in stage 3. In addition, 45.9% of the participants had polycystic ovary. Regarding infertility treatment, 83.9% were receiving some pharmacological scheme, with an average of 1.4 cycles in those under treatment (Table 3).

| Table 3. Clinical and biochemical assessment of participants | | |
|---|---|---|
| Characteristics / Factors | n | % |
| FSH level | 6.2±5.7 (p25 4.4, p50 5.7, p75 6.8) | |
| FSH anormal | 37 | 18 |
| LH level | 6.8±9.8 (p25 2.6, p50 4.7, p75 7.9) | |
| LH anormal | 41 | 20 |
| Estradiol level | 44.7±29.7 (p25 26.7, p50 37, p75 53.8) | |
| Estradiol anormal | 18 | 8.8 |
| Prolactina level | 16.7±8.76 (p25 11, p50 15.5, p75 20.5) | |
| Prolactina anormal | 53 | 25.9 |
| Insulina level | 21.5±10.36 (p25 15, p50 18.4, p75 25) | |
| Insulina anormal | 120 | 58.5 |
| Glucosa level | 92.5±10.9 (p25 85.9, p50 92, p75 97) | |
| HOMA | 4.93±2.58 (p25 3.25, p50 4.18, p75 5.77) | |
| Estado HOMA | | |
| - 1 | 61 | 29.8 |
| - 2 | 56 | 27.3 |
| - 3 | 88 | 42.9 |
| Ovario poliquístico | | |
| - With polycystic ovarian syndrome | 94 | 45.9 |
| - Without polycystic ovarian syndrome | 111 | 54.1 |
| In treatment for infertility | 172 | 83.9 |
| Number of cycles | 1.44±1.6(p25 0, p50 1, p75 3) | |
| Source: data collection sheet. Statistics: Mean, SD, Percentiles. Frequency, Percentage | | |

The distribution of the treatment schemes used can be seen in graph 2, where it is highlighted that metformin was the most used, followed by follitropins and the combination of metformin with clomiphene.

| Table 4. Infertility treatment results | | |
|---|---|---|
| Characteristics / Factors | n | % |
| Pregnancy | | |
| - Achieved | 54 | 26.3 |
| - Not achieved | 151 | 73.7 |
| Reproductive Results | | |
| - Not achieved | 151 | 73.7 |
| - Term live birth | 37 | 18.1 |
| - Preterm live birth | 5 | 2.4 |
| - Orbito | 1 | 0.5 |
| - Abortion | 8 | 3.9 |
| - Ectopic pregnancy | 3 | 1.5 |
| Source: data collection sheet. Statistics: Mean, SD, Percentiles. Frequency, Percentage | | |

As a result of the treatment, only 26.3% (n=54) of the patients achieved pregnancy at the end of the treatment. The most common results were that 73.7% did not achieve pregnancy, 18.1% (n=37) achieved a live term newborn, followed by 3.9% who, although they achieved pregnancy, it ended in miscarriage (Table 4).

Comparative analysis of the factors that influenced the achievement of pregnancy revealed similarities between the groups. The mean age differed by less than one year, and the percentage of polycystic ovary was slightly higher in those who achieved pregnancy (48% vs 45%). HOMA levels and prevalence of stage 3 were similar in both groups. Primary infertility was more common in those who did not achieve pregnancy, although the majority of both groups received treatment. Overweight was prevalent in both groups. None of these differences reached statistical significance ($p>0.05$) (Table 5).

Graph 3 highlights that treatment schedules that included metformin, either alone or in combination, were associated

with a higher percentage of pregnancies (p=0.016), indicating a statistically significant difference.

Although no statistically significant differences were found between the clinical characteristics of the patients and the reproductive outcome, it should be noted that patients with grade 3 obesity had a higher percentage of unsuccessful pregnancies or preterm newborns. Ectopic pregnancy was more frequent in women with primary infertility, while miscarriages, abortions and preterm products were more frequent in those with secondary infertility (see Table 6).

**Graphic 3. Pregnancy achievement by type of treatment**

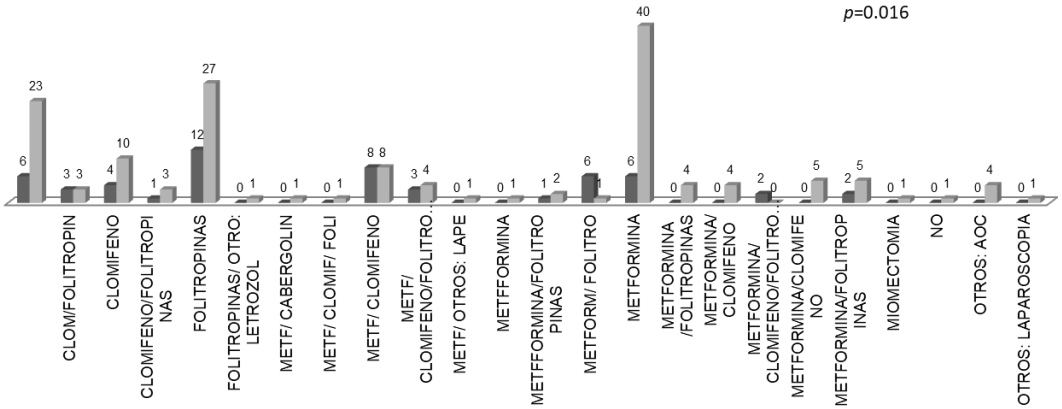



**Table 5. Factors associated with pregnancy achievement**

| Characteristics / Factors | Achieved | Not achieved | p |
|---|---|---|---|
| Age (Media, DE) | 31.2 ± 4.5 | 30.7 ± 4.3 | 0.864 |
| Polycystic Ovarian Syndrome (n. %) | 26, 48.14% | 68, 45.03% | 0.693 |
| HOMA level (Media, DE) | 5.02 ± 2.7 | 4.9 ± 2.5 | 0.244 |
| HOMA (n. %) | | | |
| - 1 | 17, 31.5% | 44, 29.1% | 0.821 |
| - 2 | 13, 24.1% | 43, 28.5% | |
| - 3 | 24, 44.4% | 64, 42.4% | |
| Type of infertility (n. %) | | | |
| - Primary | 26, 48.15% | 90, 59.6% | 0.145 |
| - Secondary | 28, 51.85% | 61, 40.4% | |
| Management to infertility (n. %) | | | |
| - Yes | 47, 87.03% | 125, 82.8% | 0.680 |
| - No | 7, 12.97% | 25, 17.2% | |
| Nutritional state (n. %) | | | |
| - Normal | 11, 20.4% | 23, 15.2% | 0.536 |
| - Overweight | 21, 38.9% | 50, 33.1% | |
| - Obesity G1 | 16, 29.6% | 48, 31.8% | |
| - Obesity G2 | 5, 9.3% | 21, 13.9% | |
| - Obesity G3 | 1, 1.9% | 9, 5.9% | |

Source: data collection sheet. Statistics: Mean, SD, Percentiles. Frequency, Percentage

**DISCUSSION**

Obesity and insulin resistance (IR) are prevalent medical conditions today, and their impact on female fertility is a topic of growing interest in medical research. Although obesity is frequently associated with IR, its relationship with reproductive outcomes in infertile women remains a matter of debate. The present study sought to evaluate the association between obesity and IR in infertile women, as well as its impact on fertility treatment outcomes.

The results of the present study show that only 45.9% of the patients had polycystic ovary (PO), which differs from what is reported in the literature, where it is mentioned that 73% of IR is related to polycystic ovary syndrome (26).

It was observed that 83.9% of the patients were receiving some type of pharmacological treatment for infertility, with metformin being the most commonly used treatment. This coincides with what is reported in the literature, where it is suggested that the ideal treatment for patients with insulin resistance is weight reduction, insulin sensitizers and insulin correction to achieve a better reproductive outcome (26).

Santillana Espinosa and Avila Esquivel, 2009 have reported that patients treated with metformin, weight reduction and ovulation induction had a favorable response to treatment,

achieving full-term pregnancies (26). In our study, it was observed that the treatment schemes that included metformin, either alone or in combination, were associated with a higher percentage of pregnancies (p=0.016), a result that coincides with that reported by Barbieri in 2000 (58).

The research identified that 26.3% of the patients achieved a pregnancy at the end of treatment. The most common results were that 73.7% did not achieve pregnancy, 18.1% (n=37) achieved a live newborn at term, followed by 3.9% who, although they achieved a pregnancy, it ended in miscarriage. This differs from that reported by Santillana Espinosa and Avila Esquivel (2009), where they report that pregnancy was achieved in 46% of patients (26).

In the study, no association was found between body mass index (BMI) and reproductive outcomes, which differs from what is reported in the literature, where they describe that BMI has a negative impact on female fertility, since obese women are more likely to present ovulatory dysfunction due to dysregulation of the hypothalamus-pituitary-ovary axis (59).

Comparative analysis of the factors that influenced the achievement of pregnancy revealed similarities between the groups. The mean age differed by less than one year, and the percentage of polycystic ovary was slightly higher in those who achieved pregnancy (48% vs 45%). HOMA levels and prevalence of stage 3 were similar in both groups. Primary infertility was more common in those who did not achieve pregnancy, although the majority of both groups received treatment. Overweight was prevalent in both groups. None of these differences reached statistical significance (p>0.05). This is in agreement with that reported by Cai et al. (2022), who did not find that hyperinsulinemia and insulin resistance affected reproductive outcomes, including pregnancy, live birth and miscarriage in women without polycystic ovary undergoing assisted reproduction (50).

Although no statistically significant differences were found between the clinical characteristics of the patients and the reproductive outcome, it should be noted that patients with grade 3 obesity had a higher percentage of unsuccessful pregnancies or preterm newborns. Ectopic pregnancy was more frequent in women with primary infertility, while miscarriages, abortions and preterm products were observed more frequently in those with secondary infertility. This differs from that reported by Cai et al. (2022) (50), who found no association between obesity and reproductive outcomes. However, it coincides with that reported by Ahmad et al. (2022) (23), who mention that increased BMI in women is related to a higher incidence of miscarriages and complications during pregnancy.

The differences found between the results of the present study and what is reported in the literature may be due to the fact that this study only included patients with a diagnosis of infertility and insulin resistance, whereas the studies by Santillana Espinosa and Avila Esquivel (2009) and Cai et al. (2022) included patients with a diagnosis of infertility without considering whether or not they suffered from insulin resistance. On the other hand, the study by Broughton and Moley (2017) was performed in obese women with and without infertility (23, 26, 59). Additionally, Sakumoto et al. (2010) (4) found that hyperinsulinemia can negatively affect endometrial functions and environment, and lead to implantation disorders and/or early pregnancy loss. This could explain the higher miscarriage rate in the present study compared to that reported by Santillana Espinosa and Avila Esquivel (2009) (26).

One of the limitations of this study is that it does not include a control group of women without insulin resistance, which limits the ability to establish causal relationships between insulin resistance and the results of infertility treatment. In addition, other factors that could influence infertility treatment outcomes, such as lifestyle, diet and general health status of the patients, were not taken into account, which would be of great support because these factors could interact with insulin sensitivity and affect treatment outcomes. However, the present project can serve as a precursor for further research where future studies on obesity and female infertility should employ rigorous methodological designs to establish causal relationships, evaluate the efficacy of interventions, and understand the underlying molecular mechanisms with designs such as prospective cohorts or clinical trials to evaluate the efficacy of different interventions. In addition, it is essential to consider the heterogeneity of the population of infertile women and to use different diagnostic criteria to obtain more accurate and generalizable results.

## CONCLUSIONS

The success rate was 26.3% in achieving pregnancies, with most of these culminating in live births at term, but with a considerable percentage of miscarriages. Notably, treatments that included metformin were associated with higher pregnancy rates, supporting its use in the management of infertility in this population. Thus, the study underscores the importance of metformin and suggests a possible influence of obesity on reproductive outcomes, although further research is needed to confirm these findings.

The study provides valuable information on reproductive outcomes in patients with infertility and insulin resistance, highlighting the importance of metformin treatment and suggesting a possible influence of the degree of obesity on outcomes. Further studies are needed to confirm these findings and explore other variables that may affect reproductive outcomes in this population.

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## COMPLIANCE WITH ETHICAL STANDARDS

**Conflict of interest.** The authors declare that they have no conflict of interest.

**Author contributions**

- **Conceptualization:** Flores-Acosta Mariana, Altamirano-Briseño Gustavo
- **Research:** Flores-Acosta Mariana
- **Visualization:** Flores-Acosta Mariana, Altamirano-Briseño Gustavo, Moreno-Vargas Julieta.

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