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Association between insulin hormone, homa index levels and vitamin D3 level in infertile women of Babylon provinces

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Abstract

A significant percentage of women seeking reproductive treatment suffer from secondary infertility. Homa index, insulin hormone, and vitamin D3 had all been linked to the fertility and reproductive health of women. Reproductive tissues have vitamin D receptors, and some research has linked a lack of these receptors to decreased fertility. One important indicator of ovarian reserve is insulin hormones. Nevertheless, little is known about the connection between vitamin D status and insulin levels and the Homa index (IR) in women who have secondary infertility. This research aims to examine if serum 25-hydroxyvitamin D3 levels, insulin, and Homa index values in women with secondary infertility are related. Between September 2024 to May 2025, a cross-sectional study was carried out at Tiba Infertility Center and Babylon Maternity and Pediatric Hospital. Two hundred eight women with secondary infertility, ages 18 to 40 years, made up the study cohort. Endometriosis, pelvic surgery, smoking, chemotherapy, radiation exposure, and recent hormone therapy were all considered exclusion factors. Homa index (IR), insulin, and 25-hydroxyvitamin D3 serum concentrations were measured by Chemiluminescence (CLIA) method (Maglomi X800). Vitamin D3 deficiency was observed in 63.5% of the study participants. A statistically significant positive correlation was identified between serum vitamin D3 and Insulin and Homa index levels ($r = 0.549$, $p = 0.000$). Insulin concentrations were highest in the vitamin D3 sufficient group (mean: 31.75 ± 2.42 ng/mL). Obesity was prevalent among the participants (48.1%), and the majority reported regular menstrual cycles (84.6%).

Conclusion: In women who report with secondary infertility, serum vitamin D3 levels show a positive correlation with insulin and Homa index levels, indicating a possible function in maintaining ovarian reserve. These results suggest that improving reproductive outcomes in this particular cohort may be impacted by treating vitamin D insufficiency.

Keywords: Secondary infertility, Vitamin D3 deficiency, Body Mass Index (BMI), Obesity, Menstrual cycle regularity

Introduction

Secondary infertility in women is defined as the inability to conceive or carry a pregnancy to term after having previously conceived and delivered a child. A considerable proportion of women seek gynecological care because of secondary infertility [1]. Various factors can play a role in secondary infertility, including age, lifestyle choices, stress levels, dietary habits, and diverse disorders affecting the reproductive system. Women beyond the age of 30 often have Diminished Ovarian Reserve (DOR), a physiological phenomenon that reduces both egg production and egg quality [2]. However, in some women, DOR occurs before age 30 and causes early infertility, a condition known as pathological DOR[3]

There are various reasons that may cause secondary infertility in women. Infections of the reproductive tract are especially damaging to women's fertility in developing countries [4]. These types of infections can cause a woman to have fallopian tube blockage with resulting adhesions that make the conception impossible. Other common causes are Defective Ovulation (28.9%), Tubal Adhesion or Obstruction (7.4%), and male factors (12.6%) [5]. Some uterine disorders like fibroids, as well as issues with the endometrial layer of the womb also causes secondary infertility [6]. As was noted the studies around andropause are quite limited and the results from some studies seem to be inconsistent regarding the ratio of primary infertility applications to secondary infertility applications. As some studies suggest, vitamin D has multifaceted role when it comes to women's fertility and its importance has been noted in the reproductive results for women with secondary infertility. The presence of vitamin D receptors in the male and female reproductive system and its deficiency brings additional matters pertaining to conception and increases the rate of miscarriage that is observed.[6]

Pregnancy rates among women undergoing

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reproductive therapy may be impacted by vitamin D levels, according to research. An adequate amount of vitamin D was found to be an independent predictor of chemical pregnancy in ovulation inducement in ovulatory women with infertility that could not be explained [7]. Additionally, women with appropriate serum vitamin D levels had considerably greater rates of positive chemical pregnancy tests than women with inadequate or deficient vitamin D levels. This proof is not entirely consistent, though. According to a number of MESTs, women with inadequate or deficient vitamin D levels do not have noticeably increased rates of positive chemical pregnancy tests. This evidence is not totally consistent, though. Vitamin D levels and pregnancy outcomes in women with infertility who are undergoing ovulation induction have not been found to be statistically significantly correlated in some studies [8]. Although causality has not yet been shown, this finding raises the possibility of a relationship between vitamin D levels and infertility. It is advised to evaluate vitamin D adequacy in women experiencing infertility, including secondary infertility, by measuring serum 25(OH) D levels and addressing any deficiencies to raise them beyond 30 ng/ml throughout the pregnancy preparation stage .[9]

Hyperandrogenemia and Insulin Resistance (IR) constitute the cardinal hormonal defects encountered in the vast majority of patients, irrespective of race and ethnicity. The central role of IR in the pathophysiology of PCOS was elucidated from the elegant work by Dunaif and coworkers in the 1990s [10]. IR has been linked to oxidative stress, subclinical inflammation, and endothelial dysfunction, usually encountered in patients with Polycystic Ovary Syndrome (PCOS). IR constitutes a prerequisite for diabetes mellitus (DM) and/or metabolic syndrome development, and consequently the increased incidence of these two morbidities in women with PCOS, compared with their BMI-matched peers, is expected [11]. During aging in normal subjects of either sex, a gradual increase in body weight is observed, which is associated with an unfavorable impact on metabolic profile and IR has been considered the main pathophysiological link between obesity and metabolic derangements.[12]

HOMAIR, which is widely regarded as a suitable instrument for assessing IR and the development of DM in population studies, was used as an index of IR [13].It was demonstrated that HOMAIR was considerably greater in women with PCOS, whether they were lean or obese, in a sample of PCOS participants older than 30 [14].According to NIH standards, PCOS is the most frequent endocrinopathy in women, with an estimated prevalence of 4% to 10% of women in their reproductive years according to published reports. PCOS patients frequently have insulin resistance, and obesity adds to this condition in obese PCOS patients [15]. The presence of Acanthus nigricans was used to subjectively diagnose clinical insulin resistance. In our lab, hormonal testing was performed using commercial kits following an overnight fast. Prolactin, thyroid stimulating hormone, and serum fasting insulin (FI) were all included of the hormonal profile.[16]

Materials & Methods

Study design & setting: A cross-sectional study will be conducted in (Babylon maternity and Pediatric Hospital and Tiba Infertility Center) from (1/9/2024) to (1/5/2025). Inclusion criteria: Any woman with secondary infertility (women who failed to conceive after 1 year of unprotected intercourse with a history of one previous conception [16]) aged 18-40 years will be included in the study.

Exclusion criteria: Patients with endometriosis, pelvic surgery, smoking, prior chemotherapy, or pelvic radiation. Patients received hormonal treatment within the preceding six months .

Participants selection: All the woman with secondary infertility who is consulted the infertility center during the period will be included in the study

Variables: Variables such as age, employment, education, smoking status and body mass index will be collected analysis of the Insulin and Homa index (IR), and 25 hydroxyvitamin D3 level will be investigated by using, CLIA (Chemiluminescence Immunoassay) principle involves combining the sensitivity of chemiluminescence with the specificity of an immunoassay to detect and quantify analytes in a sample

Ethical approval and consent

All subjects involved in this work will be informed, and agreement will be obtained verbally from each subject before the collection of samples. This study is approved by the committee on publication ethics at college of medicine, University of Babylon, Iraq, under the reference No. BMS/0255/016. Data collection and processing: Data will be collected using a form prepared by the investigator. The investigator interviewed each participant to obtain their consent and obtain their information.

Statistical analysis

The data were analyzed using SPSS version 26. The data will be shown in tables and figures, and the effect size will show Pearson correlation for continuous variables, Chi-square test, or one-way ANOVA test for categorical variables. Statistical significance was set at $p < 0.05$.

Results

This study enrolled 208 women with secondary infertility who met the inclusion criteria to enter the study. The mean weight for the study group was 77.13 Kg, ±16.57 SD. The mean height of the patients was 160 cm ± 5.4 SD. The mean body mass index for the study group 30.1 Kg/m2, ± 6.2 SD. Table (1) shows the basic and clinical variables of the study groups. The most prevalent age group among participants was 25-23 years (n=54, 51.9%). Nearly half of the study population was classified as obese (n=50, 48.1%) and the majority were unemployed (n=66, 63.5%). Infertility was most commonly reported at duration (1-2) years, followed by (3-4) years (34.6% and 32.7%, respectively). Additionally, most women had regular menstrual cycles (n=88, 84.6%).

Table 1 Basic & clinical factors of the study group

Basic & clinical factors	(total n= 208)	Frequency (n=)	Percentage (%)
Age	< 25 years	48	23.1
	25 - 35 years	108	51.9
	> 35 years	52	25
BMI*	Slim <18	3	1.4
	Normal 18-25	45	21.6
	Overweight >25-30	60	28.8
	Obese >30	100	48.1
Job	Unemployed	132	63.5
	Employee	76	36.5
Smoking status	Non-smoker	188	90.4
	Smoker	12	5.8
	Ex-smoker	8	3.8
Duration of infertility from the last baby	1-2 years	72	34.6
	3-4 years	68	32.7
	5-6 years	40	19.2
	> 6 years	28	13.5
Menstrual cycle	Regular cycle	176	84.6
	Oligomenorrhoea	20	9.6
	Menorrhagia	4	1.9
	Amenorrhea	8	3.8
Total		208	100

(*: BMI: Body mass index)

Table (2) shows the vitamin status of the study sample; most participants were deficient in vitamin D3 [n= 132 (63.5%)]. In addition, this table shows the central tendency and dispersion of fasting insulin hormone level in each subgroup of vitamin D3 level; the vitamin D3 sufficient group had a higher Insulin level [mean 31.75 (±2.42 SD), than insufficient groups (27.33 (±1.93 SD) in comparison with normal insulin level in sufficient group. A one-way ANOVA test revealed a statistically significant difference in Insulin levels between at least two groups of Vitamin

D3 levels (F (2, 205) = 29.2, p = .000).

Table 2 The vitamin status at Insulin hormone level of the study sample

Vitamin D3 level subgroups	n=	Percentage (%)	F. Insulin H. Mean (± SD)	95% CI for the Mean
Deficient <20 ng/ml	132	63.5	31.75 (2.42)	1.57-1.93
Insufficient 20-30 ng/ml	52	25	27.33 (1.93)	1.93-2.73
Sufficient >30-100 ng/mL	24	11.5	21.82 (1.64)	3.07-4.57
Total	208	100%	22.13 (1.76)	1.94-2.32

(F; Fasting , H. Hormones , CI : Confidence interval)

As like as table (2), the table (3) shows the vitamin status of the study sample; most participants were deficient in vitamin D3 [n= 132 (63.5%)]. Have higher homa index or insulin resistance, the vitamin D_3 sufficient group had a higher Homa index level [mean 4.84 (±1.02 SD) in comparison with other subgroups of vitamin D3 , although the Homa index have more than normal level at all subgroups , this result might be due to high BMI or increased of body weight . A one-way ANOVA test revealed a statistically significant difference in Insulin levels between at least two groups of Vitamin D_3 levels (F (2, 205) = 29.2, p = .000).

Table 3 The vitamin status at Homa index of the study sample

Vitamin D3 level subgroups	n=	Percentage (%)	Homa index Mean (± SD)	95% CI for the Mean
Deficient <20 ng/ml	132	63.5	4.84 (1.02)	1.37-1.89
Insufficient 20-30 ng/ml	52	25	3.79 (1.43)	1.93-2.68
Sufficient >30-100 ng/mL	24	11.5	3.18 (1.78)	3.07-4.57
Total	208	100%	3.43 (1.39)	1.94-2.32

The table (4) show the correlation between studied parameters, the results were show that highly correlation of Insulin, Homa IR index level with vitamin D3 as well as BMI of infertile women, the negative correlation might be refer to that vitamin D3 deficiency lead to increased insulin resistance as Homa index and insulin hormone level.

Table (4) Pearson Correlation of Vitamin D3 with Insulin and Homa index in infertile women.

Correlations		BMI	Vit.D3	Insulin	Prolactin	Homa Index
BMI	Pearson Correlation	1				
	Sig. (2-tailed)					
Vit. D3	Pearson Correlation	-.456-**	1			
	Sig. (2-tailed)	0				
Insulin	Pearson Correlation	-.037-	-.465-**	1		
	Sig. (2-tailed)	0.711	0			
Homa index	Pearson Correlation	-.007-	-.496-**	.994**	0.04	1
	Sig. (2-tailed)	0.941	0	0	0.696	
**. Correlation is significant at the 0.01 level (2-tailed). The mark (-) before the value refer to negative correlation or indirect relationship.						
*. Correlation is significant at the 0.05 level (2-tailed).						

Discussion

From the result of present study, might be mentioned that, most participants were deficient in vitamin D3 , Have higher homa index or insulin resistance , as well as BMI were have positive correlation with fasting insulin and Homa IR levels. This results in which that relatively consistent with other studies done at different area and populations .

The related study in which stated that, Detection of insulin resistance among women with PCOS is highly method-dependent with more severe cases being detected with HOMA-IR.[15]

Sarantis et al., (2020) they stated that : In stepwise multivariate regression analysis with HOMA-IR as a dependent variable and age, BMI, and hormones (TSH , LH , Insulin and androgen hormone) as independent variables, HOMA-IR was found to be independently associated with age.[16]

Jayashree et al., (2019) in which stated that: HOMA-IR and fasting insulin values showed a significant positive correlation with BMI. Both obese and lean women with PCOS are vulnerable to the problems of insulin resistance irrespective of BMI and insulin resistance shows a positive correlation with BMI.

The BMI of the participants in this study (30.1 Kg/m2, ± 6.2 SD) was consistent with the results of Momtaz et al., who reported BMI (29.90 Kg/m2 ± 4.58 SD) , and slightly higher than that reported by Ramy et al. (2023) (27.8Kg/m2, ± 2.9 SD).[17]

This study's high obesity prevalence (48.1%) emphasizes how obesity is a controllable risk factor for secondary infertility. Obesity increases oxidative stress, which may affect endometrial function and oocyte quality, and aggravates postpartum problems, such as pelvic inflammatory disease and adhesions due to cesarean sections [18]. Similar demographic trends were observed in Ghana, where 63% of women with secondary infertility were overweight or obese. Furthermore, hyperinsulinemia and hyperandrogenism linked to obesity interfere with folliculogenesis and embryo implantation, which lowers the likelihood of conception even further.[19]

In line with the findings of Momtaz et al. [20], the age group of 2535 years old accounted for 51.9% of the study participants. In line with the findings of Momtaz et al. (2011), who discovered that the percentage of housewives in the case group was 58.6%, over half of the study group (n=132, 63.5%) was unemployed. A similar proportion of housewives (68.5%) was reported by Eraky and El-Nasr (2016 (.[21]

The majority (84.6%) of participants had regular cycles, implying that ovulatory dysfunction may not be the primary driver of secondary infertility in this study. This aligns with research indicating that secondary infertility is often linked to structural or acquired factors, such as tubal obstruction (e.g., post-pelvic inflammatory disease) or uterine adhesions from prior surgeries (e.g., cesarean sections) [20] For example, about 11% of female infertility worldwide is caused by tubal damage, which is frequently brought on by infections like Chlamydia trachomatis [22].Furthermore, postpartum infections and other complications from previous pregnancies are known to contribute to secondary infertility, which lends credence to the idea that ovulatory problems may be overshadowed by anatomical or iatrogenic factors in this population .[23]

In addition to impairing bone mineralization, a vitamin D deficiency has been linked to a number of chronic illnesses in humans. Women with polycystic ovarian syndrome (PCOS) frequently have vitamin D deficiency; blood concentrations of 25hydroxy vitamin D (25OHD) are less than 20 ng/ml in 67–85% of PCOS patients [23].With observational studies demonstrating that lower 25OHD levels were linked to insulin resistance, ovulatory and menstrual irregularities, a lower pregnancy success rate, hirsutism, hyperandrogenism, obesity, and elevated cardiovascular disease risk factors, vitamin D deficiency may exacerbate PCOS symptoms. Menstrual dysfunction and insulin resistance in women with PCOS may benefit from vitamin D supplementation, according to some, albeit scant, data [24]. PCOS may be exacerbated by vitamin D deficiency, and vitamin D supplementation may be useful in managing this syndrome. However, the available data is weak, and more randomized controlled trials are needed to confirm the possible advantages of vitamin D supplementation in this population .[25]

In Conclusion, the Serum vitamin D3 levels demonstrate a positive association with Insulin, Homa index levels in women presenting with secondary infertility, suggesting a potential role in the preservation of ovarian reserve. These findings indicate that addressing vitamin D deficiency may have implications for enhancing fertility outcomes in this specific population. Obesity was prevalent among the participants, underscoring its role as a modifiable risk factor for secondary infertility.

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Data availability: All relevant data are within the paper and its supporting information files.

Conflict of interest: The authors declare that they have no competing interests.

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