ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 November 26; 10(33): 12066-12461

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
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https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
November 26, 2022

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https://www.f6publishing.com

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World Journal of Clinical Cases

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World J Clin Cases 2022 November 26; 10(33): 12295-12304

DOI: 10.12998/wjcc.v10.i33.12295

ISSN 2307-8960 (online)

CASE REPORT

Surgical and nutritional interventions for endometrial receptivity: A case report and review of literature

Dinorah Hernández-Melchor, Cecilia Palafox-Gómez, Ivan Madrazo, Ginna Ortiz, America Padilla-Viveros, Esther López-Bayghen

Specialty type: Reproductive biology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Elfayoumy KN, Egypt; Shuang W, China

Received: June 20, 2022
Peer-review started: June 20, 2022
First decision: August 4, 2022
Revised: August 16, 2022
Accepted: October 17, 2022
Article in press: October 17, 2022
Published online: November 26, 2022

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Abstract

BACKGROUND

Polycystic ovary syndrome (PCOS) is an endocrine disease that combines metabolic, reproductive, and psychological dysfunctions. Ovulation disorders and impaired endometrial receptivity in PCOS can cause infertility. Insulin resistance (IR) is a pathological state of inadequate response to insulin that affects reproduction in PCOS, as damage caused by IR at the endometrial level becomes an obstacle for embryo implantation. Reversing IR resulted in spontaneous pregnancies in PCOS patients, indicating that metabolic corrections improve endometrial dysfunctions. Mesenchymal stem-cell treatment has also corrected endometrial quality and lead to pregnancies in patients with Asherman's syndrome. We propose a combination of nutritional intervention with the surgical placement of stem cells to improve endometrial quality to achieve pregnancy in a PCOS patient undergoing *in vitro* fertilization (IVF) treatment.

CASE SUMMARY

After two failed IVF cycles, a metabolic intervention, consisting of a ketogenic diet

with daily consumption of 50 g of carbohydrates (CH), was indicated until pregnancy. Metabolic Syndrome was assessed using the Harmonizing Definition (3 of 5 pathologies: Central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and dyslipidemia), and the Homeostatic Model Assessment of IR (HOMA-IR) was used to measure the level of IR. Once IR improved, endometrial quality improved. However, two day 5-thawed embryos (euploid, donated oocyte–partner's sperm) failed to implant, suggesting endometrial quality improvement was insufficient. Therefore, transmyometrial implantation of mesenchymal stem cells from the stromal vascular fraction of adipose tissue was performed to enrich the endometrial stem cell niche. Minimal endometrial mean thickness for embryo transfer (6.9 mm) was achieved three months after stem cell treatment and continuous dietary control of IR. Two euploid-day 5-thawed embryos (donated oocyte–partner's sperm) were transferred, and embryo implantation was confirmed on day 14 by β-hCG serum levels. Currently, a 37 wk baby girl is born.

CONCLUSION

In PCOS, endometrial quality can be improved by combining nutrient-based metabolic correction with endometrial stem cell niche enrichment.

Key Words: Polycystic ovarian syndrome; Insulin resistance; Nutritional intervention; Endometrial quality; Stem cell treatment; Case report

Core Tip: Polycystic ovary syndrome (PCOS) is an endocrine disease that causes infertility due to ovulation disorders and impaired endometrial receptivity related to a pathological state of insulin resistance (IR). To date, endometrial dysfunctions are the rate-limiting factor for pregnancy in PCOS patients using *in vitro* fertilization. Here, an overweight PCOS patient with euploid embryos available for transfer achieved pregnancy only after a continuous nutritional intervention to correct IR and metabolic parameters and the enrichment of endometrial stem cell niche with mesenchymal stem cells from adipose tissue. In this case, endometrial thickness and receptivity were improved with a combination of nutritional and surgical interventions to achieve pregnancy.

Citation: Hernández-Melchor D, Palafox-Gómez C, Madrazo I, Ortiz G, Padilla-Viveros A, López-Bayghen E. Surgical and nutritional interventions for endometrial receptivity: A case report and review of literature. *World J Clin Cases* 2022; 10(33): 12295-12304

URL: https://www.wjgnet.com/2307-8960/full/v10/i33/12295.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i33.12295

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complicated endocrine disease that combines metabolic, reproductive, and psychological dysfunctions. Ovulation disorders are causes of PCOS-related infertility[1]. In addition, alterations in the ability of the endometrium to accept an implanting embryo and a blastocyst's entry (endometrial receptivity) are critical factors of PCOS-related infertility[2,3]. Numerous studies have proved that hormonal disturbances and metabolic changes in PCOS patients could influence endometrial receptivity[4,5]. Insulin resistance (IR) refers to the complicated pathological state of inadequate insulin action. During *in vitro* fertilization (IVF) with oocytes from IR-PCOS patients, embryo development and quality were not affected after *in vitro* culture; however, the pregnancy rate for these patients was significantly reduced, suggesting that one of influences of decreased success is caused by compromised endometrium function due to IR-associated damage[6,7]. Some treatments to correct ovulatory issues in PCOS, which resulted in reversing IR, lead to a surge of spontaneous pregnancies[8]; however, these treatments are not well explored in combination with IVF. Moreover, little attention has been paid to the exact changes in the endometrium after metabolic correction, even though the PCOS-endometrium effect may need more robust approaches to achieve implantation and pregnancy[9].

Stem cells are a powerful tool to respond to the needs of modern medicine, given their high potential in therapeutic applications[10]. Adipose tissue has become a convenient source for stem cell extraction after lipo-aspiration under local anesthesia, yielding significant quantities with a minimum invasive technique, low risk of morbidity, minimal discomfort, and almost zero chance for other possible complications[11]. Adipose-derived mesenchymal stem cells (ADMSC) have prolonged self-renewal

ability and the capability to differentiate into various mature somatic lineages[12]. In addition, ADMSC possesses neovascularization, immune-modulating, and anti-inflammatory properties[13]. The Stromal Vascular Fraction (SVF) is the minimum manipulated heterogeneous cell population isolated from the adipose tissue with comparable regenerative potential as cultured ADMSC. SVF contains ADMSC, endothelial precursors, T-regulatory and smooth muscle cells, macrophages, pericytes, and preadipocytes[14]. Endometrial mesenchymal stem cells (EnMSCs) are adult stem cells, similar to those found in other tissue. This endometrial niche can be colonized by autologous stem cells derived from different tissues[15]. In addition, stem cell transplantation can activate endogenous endometrial stem/progenitor cells inside the uterine cavity at the sub-endometrial zone in the junction between myometrium and endometrium. In patients with Asherman's syndrome, endometrial regeneration occurs as the EnMSCs can replace the functional layer[16], correcting the endometrium to achieve a clinical pregnancy[16,17]. Therefore, we propose a combination of a continuous nutritional intervention consisting of a well-designed ketogenic diet with daily consumption of 50 g of carbohydrates (CHO) to improve IR and the surgical placement of stem cells from SVF to improve endometrial quality and achieve pregnancy in a PCOS patient.

CASE PRESENTATION

Chief complaints

A 37-year-old woman attended the Ingenes institute in México city for secondary infertility with one previous abortion in 2008 at 11 wk of gestation.

History of present illness

The patient and her current partner had been trying to conceive a pregnancy for two years, with 1 previous attempt in which the embryo implanted but resulted in an early abortion. Her periods are normal, and she does not remember any problems with her cycle. The patient was diagnosed with PCOS according to Rotterdam criteria, presenting signs of clinical hyperandrogenism (acne and hirsutism) and the polycystic ovary phenotype, which was confirmed with ultrasound (30-40 follicles in each ovary). She was counseled for IVF.

History of past illness

There is no relevant history of past illness.

Personal and family history

The patient has had a previously failed pregnancy, which resulted in an early abortion, in 2008. Moreover, the patient had uterine synechiae in 2019, which was resolved by hysteroscopic adhesiolysis. She has no other medical history associated with reproduction and no history of alcohol or drug abuse. There was no significant history reported by the partner. Lastly, there was no relevant family history of reproductive complications.

Physical examination

Upon physical examination, the patient did not present any concerning symptoms. The patient's initial body-mass index (BMI) was 29.24 kg/m^2. The anthropometric parameters are shown in Table 1. Due to the patient's weight and BMI, it was postulated that the patient has Metabolic Syndrome (MetS). Her waist circumference was elevated (> 80 cm for female Latinas) [18]. She was overweight and had at least one criteria of Metabolic Syndrome, according to the harmonizing definition.

Laboratory examinations

Laboratory examinations were performed to assess the patient's metabolic status with respect to the MetS harmonized definition[18]. On initial evaluation, the patient's fasting plasma glucose suggests that she is at risk for prediabetes. Two of five criteria were abnormal for MetS (waist circumference and fasting plasma glucose); systolic and diastolic blood pressure, tryglycerides, and high-density lipoprotein cholesterol (HDL-C) levels were normal. Values are presented as Biochemical parameters in Table 1.

Imaging examinations

Due to the patient's previous abortion and uterine synechiae, a sonohysterography was performed. There were no uterine synechiae or other issues associated with the uterus. However, more than 30 follicles on each ovary were detected by ultrasound (PCOS criteria).

Table 1 Cycles and interventions for the case

Categories	First cycle	Second cycle	Third cycle	Fourth cycle
Nutritional intervention	None	Caloric restriction[a]	Ketogenic diet[b]	Ketogenic diet[c]
Stem cell treatment	None	None	None	Live cells trans-myometrial injection
Anthropometric parameters (at the cycle starting point)				
Age (years)	37 (2019)	38 (2020)	39 (2021)	40 (2021)
Weight (kg)	73	69	59	59
Waist circumference (cm)	81	73	65	65
BMI (kg/m^2)	29.24	27.64	23.63	23.63
Blood pressure (mmHg)	120/80	120/78	119/80	111/74
Biochemical parameters				
Fasting glucose (mg/dL)	104	102	86	78
Urine ketones (mg/dL)	-	Negative	40-80	50
Insulin (U/mL)	-	13.89	3.20	2.4
HOMA-IR	-	2.95	0.67	0.46
Insulin resistance	-	Yes	Corrected	Corrected
Triglycerides (mg/dL)	-	89	92	82
HDL-Cholesterol (mg/dL)	-	58	62	71
IVF parameters				
Ova source	Patient	Patient	Donor	Donor
Ova collected	26	15	Not applicable	Not applicable
Own embryos frozen (day), quality	7 (day 5), BC	1 (day 5), BC	---	---
		1 (day 6), BC		
Endometrial intervention/treatment	None	Hysteroscopic evaluation and mild reactivation	Pentoxifylline	Pentoxifylline
			E-Vitamin	E-Vitamin
			L-Arginine	L-Arginine
				Stem cells
Endometrial thickness final size (mm)	3.6	4.3	5.9	6.9
Transferred thawed embryos and PGTA result	*n* = 2	*n* = 2	*n* = 2	*n* = 2
	Quality: BC	Quality: BC	Quality: AC and BC	Quality: AC and BC
	Day 5: Euploid	Day 5 and 6: Euploid	Day 5: Euploid	Day 5: Euploid
Transfer result	Failed	Failed	Failed	Success
β-hCG serum levels on day 14	Negative	Negative	Negative	Positive, 90.89 mUI/mL
Clinical pregnancy	-	-	-	One sac, 158 bpm week 18
Pregnancy outcome	-	-	-	Healthy baby girl, 37 wk, 2690 g; 47 cm; Apgar 9

[a]Standard 1800 calorie-diet with 55% carbohydrate content.
[b]Nutritional intervention inducing ketosis with a maximal consumption of 50 g of carbohydrates/day (15% on an 1800 calorie diet).
[c]NI controlling fasting glucose and urine ketones; carbohydrates/d: 50 g before the transfer, 100 g after embryo transfer, and 150 g during pregnancy.

MULTIDISCIPLINARY EXPERT CONSULTATION

There is no multidisciplinary expert consultation.

FINAL DIAGNOSIS

At the initial consultation, infertility associated with PCOS was diagnosed with IR.

TREATMENT

First IVF attempt

In 2019, the patient underwent standard controlled ovarian stimulation (Gonal 150 UI and Merapur 150 UI). The stimulus was prolonged until the diameter of the leading follicles was > 18 mm. Afterward, recombinant human chorionic gonadotropin was administered. After 36 h, the oocytes were retrieved with ultrasound guidance. All 14-18 mm follicles were aspirated. Ova was collected, fertilized by intracytoplasmatic sperm injection with the partner's sperm, and then cultured. The yields and quality of embryos are depicted in Table 1. Embryos were cryopreserved using the vitrification technique, thawed, and transferred after standard endometrial preparation. Two embryos were transferred. The endometrial mean thickness (EMT) was sub-optimal, and a thin endometrium was diagnosed (EMT = 3.6 mm). On day 14, there was no detectable amount of β-hCG.

Second IVF attempt

As the patient was overweight and following an unbalanced standard American 2000 calories diet with 45% CHO, 47% fat, and 7% protein content (direct food intake questionnaire), a caloric restriction diet (averaging a total of approximately 1800 calories) was advised with macronutrients adjustment to 55% CHO, 25% protein and 25% fat. This resulted in a 4-kg weight loss but not a BMI reduction to normal weight status. The standard controlled ovarian stimulation protocol was repeated as before. Hysteroscopy was performed because of the thin endometrium diagnosis (EMT=3.6 mm). Again, we ruled out synechiae and found a normal cervical channel, normal uterine cavity, and a visible and permeable ostium; no other abnormalities were found. Gentle endometrial reactivation was performed. Endometrial preparation was carried out using primogyn (estradiol valerate) with incremental dosing for 12 d (2 mg/d for four days, 4 mg/d for four days, and 6 mg/d for four days)[19]. Luteal phase support was carried out with utrogestan (300 mg/vaginal, three times a day). Two cryopreserved embryos were thawed and transferred. On day 14, there was no detectable amount of β-hCG.

Third attempt at IVF

Because the patient's initial BMI was 29.24 kg/m^2 and PCOS diagnosis, metabolic parameters were assessed (Table 1). Triglycerides and HDL-C were within the normal range. Fasting glucose was above the normal range, suggesting the patient was prediabetic. In addition, IR was calculated using HOMA-IR (Table 1). The patient had significant IR. A nutritional intervention was started to correct for IR, with a secondary goal to increase endometrium and ova quality. The patient was instructed to follow a ketogenic diet, which typical consists of 1800 calories/day, daily consumption of ≤ 50 g of total CHO (15% or less), 1.5 g of protein per kilogram of body weight (25% maximum), with the remainder being fat (approximately 60%). The patient auto-registered all food consumption in the MyFitnessPal app, and the dietician confirmed the macros every week, correcting them when needed. In addition, the patient received nutritional education (video) that focused on controlling the glucose load. The purpose was to teach food choices and avoid ultra-processed food, starches, juices, bread, sweets, sugared beverages, and CHO-rich food (rice, beans, tortilla, legumes). The patient was followed *via* electronic messaging every two to three days, inquiring about any doubts, symptoms, changes in weight, fasting glucose, ketone detection in urine, and counseling about the general guidelines. Before the start and during all nutritional interventions, the patient auto-monitored their urinary ketone levels using the Ketone Test Strips (acetoacetate), measuring at least twice a week with MUNDO-Keto reactive strips. Once, laboratory tests confirmation of improve IR and with the patient's approval, the physician and the specialist in Reproductive Medicine moved to ova donation. Donated oocytes were fertilized by ICSI with the partner's sperm, which produced four embryos (two day 5 and two day 6 embryos). Before all embryos were vitrified, Preimplantation Genetic Testing for Aneuploidies (PGT-A) was performed following a standardized protocol[20]. Endometrial preparation consisted of Primogyn (same as described before) while adding 400 mg of Pentoxifylline twice a day, 1 g of L-Arginine (vasodilator), and 1 g of Vitamin E daily (vascular and antioxidant effects), which improved the EMT (Table 1). Embryo transfer was performed with one embryo AC and one embryo BC. Both embryos failed to implant.

Fourth IVF attempt

Autologous mesenchymal stem cells in the SVF of adipose tissue were placed in the patient's uterine cavity to improve endometrial quality. Micro liposuction was performed to obtain 20 mL of abdominal fat. Adipose tissue was washed, mechanically disaggregated, and treated with collagenase type I to isolate SVF. A total of 6.27 × 10^7 live cells were isolated and transmyometrial injected. Changes in the

EMT were monitored for three months until an EMT of 6.9 mm was reached. Two Day 5, euploid-thawed embryos (from oocyte donor and partner's sperm) were transferred. The uterine transfers occurred during a controlled endometrial development cycle for frozen embryos, free of gonadotropin stimulation, but with the addition of Pentoxifylline, L-Arginine, and E-Vitamin (same as described before). The ketogenic intervention was sustained until pregnancy was achieved. Embryo implantation was determined on day 14 by serum β-hCG concentrations (>10 mUI/mL) and by the presence of a fetal heartbeat using ultrasound at six weeks (Table 1).

OUTCOME AND FOLLOW-UP

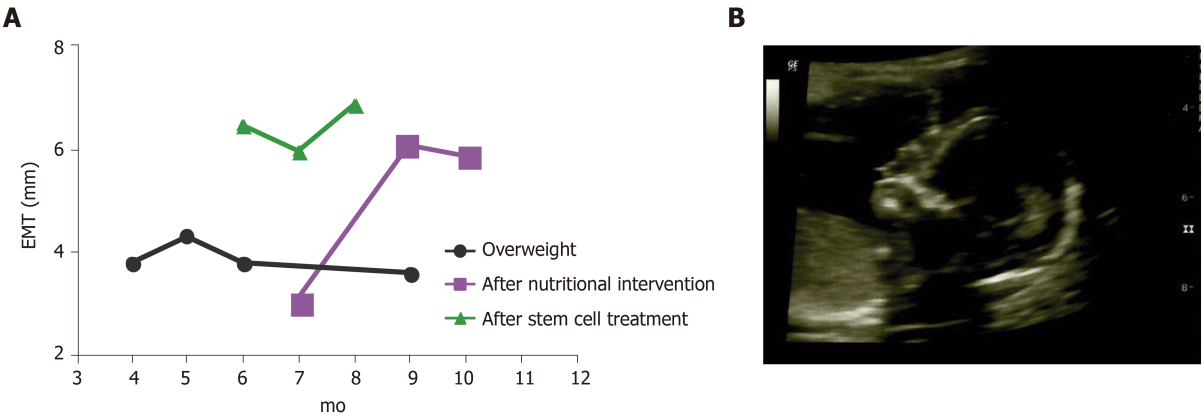
Table 1 depicts all results and details of the interventions during the four IVF cycles. After induction and maintenance of nutritional ketosis, IR was corrected. As a result, BMI decreased to 23.63 kg/m^2 and the final fasting glucose was 78 mg/dL. Figure 1A shows the changes in the EMT after the two major interventions: nutritional ketosis and endometrial regeneration. Pregnancy was finally achieved after a continuous dietary intervention, which resulted in metabolic normalization when complemented with endometrial reparation using mesenchymal stem cells and the transfer of euploid embryos from donated ova. One gestational sac with a fetal heartbeat was detected *via* the ultrasound at week 6. The gestational sac presented with 158 beats per minute, normal amniotic liquid, and the absence of ultrasound markers for chromosomopathies. No apparent structural alterations were detected at week 18 (Figure 1B). Metabolic control continued to avoid the risk of gestational diabetes with the proper caloric increase by trimester and 100 g - 150 g of CHO for daily consumption. Pregnancy resulted in the born of a healthy baby girl at 37 wk (2690 g; 47 cm; Apgar 9).

DISCUSSION

In a PCOS-related infertility case, a patient achieved pregnancy after combining interventions, specifically implementing a ketogenic diet, and improving the endometrium receptivity with mesenchymal stem cells. The most concerning problem with PCOS is infertility at the reproductive age, as this degenerative disease predisposes women to reproductive complications and possible infertility. Lower pregnancy rates are observed in obese PCOS compared to non-obese PCOS patients[21,22], demonstrating a crucial metabolic component for PCOS women concerning fertility. IR-PCOS patients develop sub-optimal oocytes, with fewer MII oocytes[23]. Moreover, IR-PCOS patients have lower pregnancy rates after IVF, even if oocyte development, embryo quality[7], or risk for embryonic aneuploidy was not affected[24], suggesting that the effects of IR on endometrial function and embryo implantation underlie the decreased pregnancy rates[7].

Evidence in adult women indicated that treatment of IR, either by lifestyle changes or pharmacological support, improves reproductive and metabolic abnormalities[25]. Thus, it was expected that the nutritional intervention would improve the reproduction potential of our PCOS patients. IR is mainly caused due to a constant glucose overload, leading to continuous hyperinsulinemia; therefore, restricting glucose exposure *via* dietary modifications should improve IR and reproductive outcomes for PCOS women[26]. Therefore, it is crucial to determine a subject's IR status before considering any intervention containing a diet. However, not all diet modifications are optimal for PCOS. Here, a low caloric diet with standard macro nutrients distribution improved weight but did not correct IR (Table 1). Diets with lower carbohydrate content are more likely to improve IR in PCOS women with severe IR[19,27,28]. In this case, a diet modification with CHO limitation to a maximal daily consumption of 50 g successfully corrected IR and improved pregnancy chances. Even when Metformin is widely used for IR as an important insulin sensitizer, a recent meta-analysis shows that Metformin does not improve insulin sensitivity over hypocaloric diets in women with polycystic ovary syndrome[19]. When pre- and post-intervention values for fasting plasma glucose, fasting plasma insulin, and IR indices (HOMA-IR, ISI, and QUICKI) were compared, any benefit of using Metformin was already achieved when a diet intervention was implemented. This means that adding Metformin to hypocaloric diets did not improve serum glucose or insulin concentrations, or IR in PCOS women, but controlling the CHO intake does.

In PCOS patients, endometrial tissue function is altered due to abnormal glucose homeostasis and insulin action[29], presumably due to GLUT4 alterations. GLUT4 is the main glucose transporter in charge of glucose uptake at the cellular level, regulated by insulin through protein synthesis and translocation. Hyperinsulinemia and PCOS are conditions associated with decreased GLUT4 expression at the endometrial level[30]. Lifestyle modification (physical exercise and low CHO/high protein diet) improves glucose homeostasis in PCOS patients. Consequently, the endometrial function is restored due to GLUT4 down-regulation, resulting from the up-regulation of endometrial IRS1 and GLUT1[31]. In support of this, we show that a continuous and closely supervised nutritional intervention resulted in total correction in IR, complete normalization of metabolic parameters, and improved endometrial growth. Improving endometrial function may be a necessary approach for PCOS-related infertility[9], as for improving metabolic health was not enough to resolve the patient's reproductive issues. The uterine



DOI: 10.12998/wjcc.v10.i33.12295

Figure 1 The endometrial mean thickness along with the two major interventions. A: Endometrial quality was assessed by determining the endometrial mean thickness, the physician performed measurements under ultrasonographic guidance; B: Current ultrasound at the time of submission of the single gestational sac due to treating the ketogenic diet with endometrium preparation with mesenchymal stem cells, the sonogram is at 16 wk after embryo transfer.

lining in our patient improved after the nutritional intervention (Figure 1), with the EMT consistently increasing above 6 mm. Nevertheless, considering past failed embryo transfers and lack of abnormalities in the uterine cavity, additional support for endometrial development and embryo implantation was explored. Generally, an endometrial thickness of 7 mm is the cut-off point for a "good endometrium, adequate for embryo transfer", and a value below 6 mm may result in unfavorable IVF outcomes[32]. The endometrium is an exceptional tissue that monthly undergoes cyclic proliferation, differentiation, disintegration, shedding, and repair under hormonal command, going through approximately 450 regeneration cycles over women's reproductive lifetime[33]. Endometrium's regenerative ability is attributed to stem/progenitor cells residing in the basalis layer of the tissue[34]. EnMSCs exhibit immunomodulatory and anti-inflammatory functions[35]. It has been proposed that the endometrial niche can be colonized by autologous stem cells derived from other tissues when there is a lack of EnMSCs[15]. Colonizing improved endometrial quality in dysfunctional conditions in Asherman's syndrome[16,17] and refractory endometrium[11]. Sub-endometrial application of autologous ADMSC led to an endometrial thickness increase in 80% of patients, a pregnancy rate of 52%, and a live birth rate of 36%[11].

Three mechanisms of action have been proposed for stem cell therapy to improve endometrial quality in the injured uterus of murine models: (1) Stem cell engraftment followed by trans-differentiation; (2) Environment modulation through trophic factors; and (3) Angiogenesis promotion. First, mesenchymal stem cells are highly proliferative cells that can transdifferentiate into various non-hematopoietic cell types. This differentiation potential in transplanted bone marrow-derived stem cells allows stem cell engraftment in the uterus, then differentiation into an endometrial phenotype expressing vimentin and lacking CD45 expression[36]. Second, LIF and integrins are regulators of endometrial function, markers for endometrial receptivity, and essential proteins for embryo implantation. Expression of cytokeratin, vimentin, integrin αγβ3, and LIF significantly increased after bone marrow-derived stem cells were transplanted, mimicking levels found in normal conditions, suggesting that stem cell treatments improve endometrial thickness but also contribute to endometrial receptivity[37]. Last, human endometrial mesenchymal stem cells derived from menstrual blood (MenSCs) have been demonstrated to promote angiogenesis in treating an endometrial injury. Newly formed blood vessels were observed after MenSCs were transplanted *in vivo* under the control of the AKT and ERK signaling pathways, suggesting that revascularization and angiogenesis can improve the injured endometrium. Furthermore, this revascularization process allows paracrine signaling (cytokines and growth factors) to repair injured tissues[38]. SVF is a minimum manipulated heterogeneous cell pool containing ADMSC and is efficiently obtained *via* minimal liposuction. Its use has been extended and represents a convenient source for stem cells[39]. Considering its therapeutic potential, comparable to cultured ADSC[14], we propose a surgical intervention to implant SVF-containing stem cells into the patient's uterus to achieve minimal EMT for embryo transfer. Three months after stem cell treatment, endometrial thickness improved up to 6.9 mm, allowing successful embryo implantation and pregnancy. We assume that more than one of the proposed mechanisms for stem cell therapy helped in our case. The endometrium thickness was improved, and receptivity and paracrine signaling were boosted, allowing successful embryo implantation.

Our study has two significant limitations. First, the patient's advanced maternal age. The effect age has on the result presented here still needs to be investigated. Nevertheless, we demonstrate that for certain circumstances, the use of a ketogenic diet and stem cell treatment maybe required for even the transfer euploid embryos. Lastly, the quality of the SVF was not specifically measured, with respect to

the other components of the fluid. It is possible other components, such as endothelial precursors, macrophages, pericytes, and preadipocytes as well as the concentration of cytokine and adipokine, could improve or inhibit the effect present here.

CONCLUSION

We show that a continuous nutritional intervention resulted in correction of IR, normalization of metabolic parameters, and improved endometrial growth. Furthermore, stem cell treatment improved endometrial quality concerning endometrial thickness and receptivity. We conclude that correcting IR in PCOS patients may improve reproductive outcomes and stem cell treatment, using SVF, could become a handy intervention to improve endometrial receptivity.

ACKNOWLEDGEMENTS

We want to express our gratitude to this study's participant and the IVF and medical staff at Ingenes SC and Regenera SC. In addition, we would like to thank Dr. Leonardo M P for his critical reading of the manuscript.

FOOTNOTES

Author contributions: Hernández-Melchor D, Palafox-Gómez C, and López-Bayghen E conceived the project. Ortiz G and Madrazo I performed the surgical procedures; Hernández-Melchor D and Palafox-Gómez C performed clinical data acquisition while Ortiz G and Madrazo I handled the case as the clinicians, collecting information regarding the parental history and *in vitro* fertilization data. López-Bayghen E, Hernández-Melchor D, and Palafox-Gómez C analyzed the data. López-Bayghen E and Hernández-Melchor D drafted the article. America Padilla critically revised the manuscript; all authors have approved the final version of the manuscript.

Supported by the National Council of Science and Technology of Mexico (CONACYT), No. 790971 (to Hernández-Melchor D), and No. 781208 to (to Palafox-Gómez C).

Informed consent statement: The patient and her partner provided written informed consent to participate in this study under the Declaration of Helsinki. Written informed consent was obtained from them for their anonymized information published in this article.

Conflict-of-interest statement: The authors have no relevant financial or non-financial interests to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Mexico

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S-Editor: Xing YX
L-Editor: A
P-Editor: Xing YX

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