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Case Report

First live births after adipose-derived stem cells and platelet-rich plasma intraovarian administration

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Abstract: This report describes two women aged 45 and older who achieved live births following intraovarian administration of a novel combination of mechanically processed adipose nanofat rich in adipose-derived stem cells (ADSCs) and autologous platelet-rich plasma (PRP). Both patients had a history of prolonged infertility and multiple failed assisted reproductive technology cycles with in vitro fertilization (IVF). Case 1, a 46-year-old with diminished ovarian reserve and prior miscarriage, underwent adipose-PRP treatment after unsuccessful minimal stimulation IVF. Six months later, she conceived naturally and delivered a healthy infant at age 47. Case 2, a 45-year-old with endometriosis and multiple failed IVF attempts, conceived via frozen embryo transfer of her only euploid embryo produced three months after adipose-PRP treatment, resulting in the birth of a healthy infant. The combination approach was developed to comply with U.S. FDA minimal manipulation guidelines, avoiding enzymatic processing of adipose tissue. This report is, to our knowledge, the first to document natural conception in women with age over 45 following combined adipose nanofat ADSCs and PRP intraovarian injection, and among the few to describe live births at this age using autologous oocytes after such therapy. These findings suggest that adipose-PRP treatment may offer a promising regenerative option for women with extremely diminished ovarian reserve who desire genetically related offspring, though controlled studies are required to confirm long term safety, efficacy, and appropriate patient selection.

Keywords: Adipose, stem cell, Platelet-Rich Plasma (PRP), in vitro fertilization (IVF), pregnancy, live birth

Introduction

Societal changes have led to a noticeable trend of motherhood at a delayed age. Recent data indicate that the age at which women have their first child has shifted into older ages, in particular late 30's and early 40's [1]. This shift is accompanied by age-related reproductive decline, including lower ovarian function and fertility potential, and ultimately menopause. Despite these physiological limitations, many women retain a desire to conceive even in their late 40's.

While the use of donor oocytes remains a usual recommendation for women over 43 due to its high success rates and cost-effectiveness, it could be a problem for those who have the desire for a genetically related child. Therefore, some women explore alternative reproductive options. With the limitations of the conventional fertility treatments, researchers have explored new regenerative therapies to "boost" reproductive potential in older women or women in early menopause, like intraovarian autologous platelet-rich plasma (PRP) known to be rich in biologically active molecules including cytokines and growth factors that play roles in cellular repair and regeneration [2, 3]. The active components present in PRP such as Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF) Transforming Growth Factor-Beta (TGF-β), Basic Fibroblast Growth Factor (bFGF), Insulin-Like Growth Factor 1 (IGF-1), and Insulin-Like Growth Factor 2 (IGF-2) have been shown to support angiogenesis and follicular development [2, 3]. Emerging

evidence, including basic science studies and preliminary clinical studies, suggests that intraovarian PRP administration may support ovarian function in women with diminished ovarian reserve or premature ovarian insufficiency (POI) [2, 3]. Women who had previously declined the use of donor oocytes for conception but underwent PRP treatment have demonstrated potential for natural conception and progression to viable pregnancy [4]. Even though intraovarian PRP administration has shown hope for those who desire a genetically related child, it has several limited efficacies. Thus, there is need to explore other potential venues, one of which is autologous adipose mesenchymal stem cells (ADSCs) whose safety has been studied in humans and animals [5-8].

In humans, a non-randomized, phase I clinical trial evaluated the safety and efficacy of intraovarian administration of autologous ADSCs over 12 month period and demonstrated that the procedure was safe, feasible, and effective in restoring menstruation in some women with POI [5]. Most studies [5] on ADSCs have involved enzymatic digestion (e.g., collagenase) and cell culture prior to intraovarian injection [9]. However, in compliance with U.S. FDA regulations that discourage manipulation of these cells [10], the purpose of this study was to employ a novel approach combining mechanically processed, untreated adipose tissue that is naturally rich in ADSCs with autologous PRP. This combination has been shown to be potentially more superior over component alone in the ovaries of animal models [11]. This report describes two patients older than 45 who conceived and delivered healthy infants following intraovarian administration of adipose and PRP, after many years of unsuccessful assisted reproductive technology with in vitro fertilization (IVF).

Cases presentation

Case 1

A 46-year-old woman presented after being declined treatment by multiple fertility clinics due to her advanced maternal age. She reported regular menstrual cycles, a 1 cm intramural fibroid, and a history of a miscarriage one year prior to her presentation, that was managed by dilation and curettage procedure. Her medical history included well-controlled Lyme disease and subclinical hypothyroidism managed with levothyroxine. Her baseline ovarian reserve testing showed an AMH of 0.29 ng/mL and an antral follicle count (AFC) of 2. Following counseling, she underwent intraovarian PRP administration. Six weeks later, minimal stimulation IVF (gonadotropins 150 IU/day and clomiphene citrate 100 mg/day) was initiated, yielding to only one dominant follicle. Oocyte retrieval after human chorionic gonadotropin (hCG) trigger produced no oocytes. She subsequently consented to a novel adipose-PRP intraovarian procedure, performed on December 18, 2023.

Case 2

A 45-year-old woman with a history of endometriosis, cutaneous mastocytosis, and prior spontaneous abortion at 6 weeks in 2017 presented with a 6-year history of infertility. She reported regular menstrual cycles and had previously undergone one intrauterine insemination (IUI) and five conventional IVF cycles elsewhere, all resulting in poor-quality blastocysts without pregnancy.

At our center, she received intraovarian PRP injections, followed 4 weeks later by a minimal ovarian stimulation IVF cycle with oral pills only (clomiphene citrate 50 mg/day and letrozole 2.5 mg/day). After ovarian stimulation and trigger with hCG, 3 oocytes were retrieved, inseminated by intracytoplasmic sperm injection (ICSI), yielding 1 blastocyst. Preimplantation genetic testing for aneuploidy (PGT-A) revealed aneuploid embryo containing monosomy on chromosome 15 and trisomies on chromosomes 8 and 15. A second minimal stimulation IVF cycle yielded 3 mature oocytes, but no blastocysts were formed. She subsequently consented to a novel adipose-PRP intraovarian procedure, performed on December 11, 2023.

Adipose microfat preparation by miniliposuction

Microfat is composed of condensed adipose tissue containing growth factors, bioactive cytokines, tissue stromal vascular fraction and ADSCs. On the other hand, nanofat, or filtered lipids, are made by the mechanical emulsification of microfat. The goal was to collect microfat first then emulsify it to nanofat that was added to the PRP (**Figure 1**); the combination of which to be injected into the ovaries. One mL of

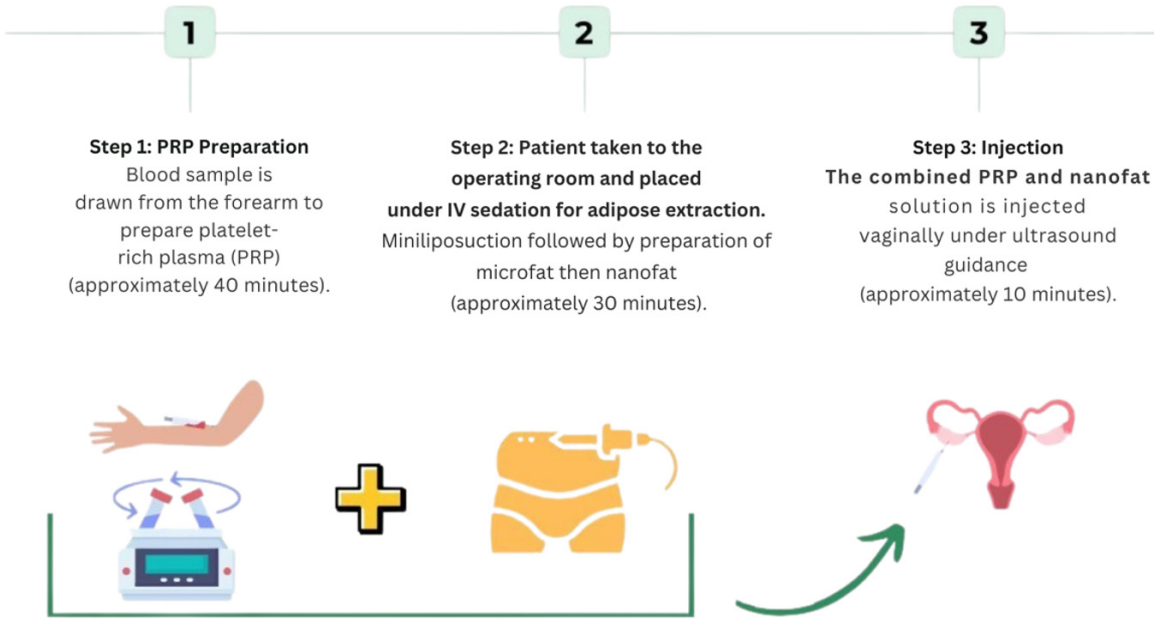

Figure 1. Summary of the timeline of the adipose and platelet-rich plasma (PRP) preparation and administration.

adipose tissue contains a mean of 400,000 ADSCs [12].

The adipose tissue was aspirated from subabdominal fat pads through a small 2 mm incision below the umbilical area. A Klein's tumescence solution, that contains lidocaine (1%), epinephrine 1 mg/mL (1:1,000), sodium bicarbonate (10 mEq/L), and normal saline, was infiltrated slowly with a tumescent infiltrator of 2.1 mm × 20 cm dimensions. Then using a 60-ml syringe, 20 mL of mixed fat with a tumescent solution was harvested from subcutaneous fat manually using a 2.4 mm × 20 cm cannula harvester with sharp holes of 1 mm diameter.

The Progenikine® Concentrating System (Emcyte corporation, Fort Myers, Florida USA), an FDA-approved device [13], was used to prepare the concentrated adipose tissue microfat. This system is used in medical procedures involving the harvesting and transferring of autologous adipose tissue. It is used to prepare an adipose treatment sample that gets purified, emulsified and condensed. It is designed to quickly and completely remove inflammatory oil and infranatant contaminants, leaving a clinically pure treatment sample. As seen in **Figure 2**, the adipose was injected through the bottom port of the disposable Progenikine® Concentrating kit (**Figure 2**, step 1). The kit was then placed in the centrifuge machine with a counterbalance device placed at opposite ends of the centrifuge buckets, after which the centrifuge was set at 1.5 RPM for 3.5 minutes (**Figure 2**, step 2). Following centrifugation, the adipose was separated into oil lipids (upper layer), condensed adipose (middle layer), and infranatant fluid (lower layer) (see **Figure 2**). Then a 20 mL syringe onto the top port was placed to aspirate the oil lipids (**Figure 2**, step 3) and a 20 mL syringe was used to aspirate the infranatant fluid (**Figure 2**, step 4). Both the oil lipids and the infranatant fluid were discarded following aspiration. Finally, a 10 mL syringe was placed at the bottom port to aspirate the final 6 mL volume of adipose tissue microfat (**Figure 2**, step 5).

Nanofat preparation from microfat

The microfat collected was then processed using the Tulip System (Tulip Medical Products, San Diego, CA) to produce the nanofat. As seen in **Figure 3**, the emulsification process of microfat was carried out with 3 transfers using the Tulip System device. The cleaned microfat was loaded into 10 mL syringes and mechanically emulsified by shifting the contents 20 times back and forth between two 10 mL syringes connected to each other by a 2.4-mm Tulip transfer. This process was repeated 20 times back and forth with the smaller diameter 1.4-mm Tulip transfer and finally 20 times back and

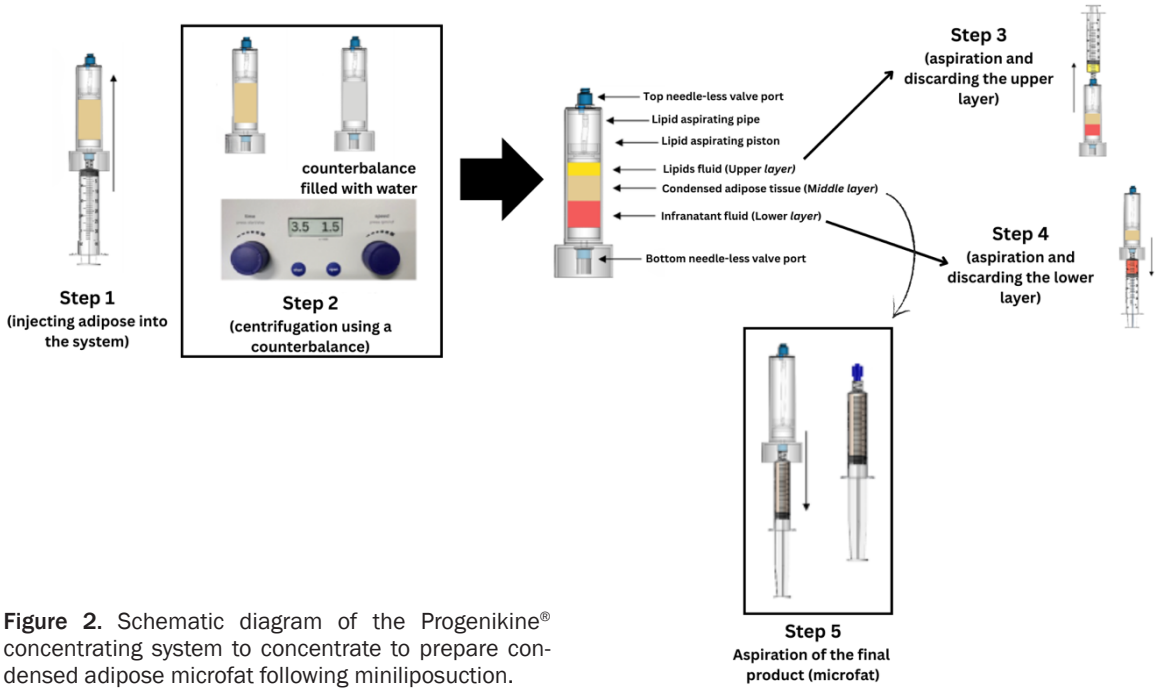

Figure 2. Schematic diagram of the Progenikine® concentrating system to concentrate to prepare condensed adipose microfat following miniliposuction.

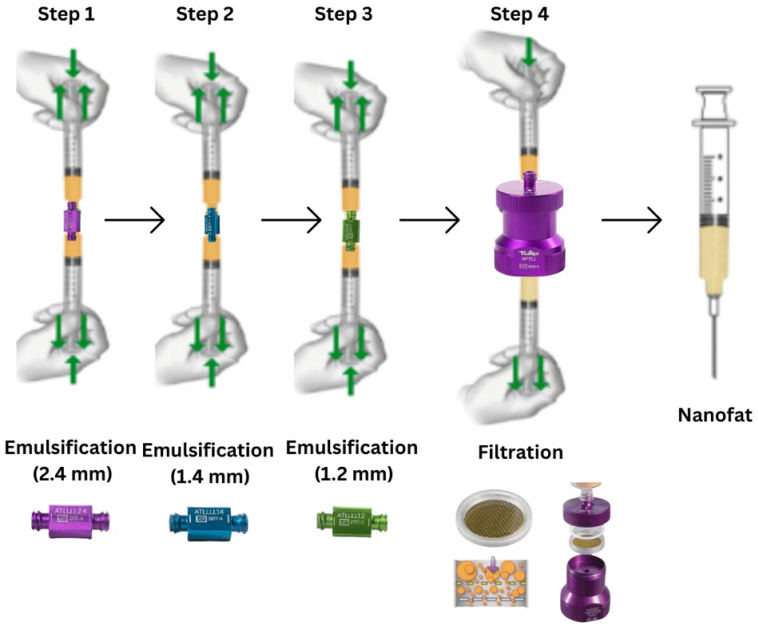

Figure 3. The emulsification process of condensed adipose microfat to nanofat using the Tulip system.

forth with the smallest diameter 1.2-mm Tulip transfer until the fat was liquefied, acquiring a pale-yellow appearance. The emulsified fat was then passed one time through the nanotransfer block, which contains a double filter of 400 µm and 600 µm single-use cartridge net (Filtration step) into a 10 mL syringe containing 6 mL nanofat which was the final product.

Preparation of PRP

PRP was prepared as we previously described [14]. Approximately 30 mL of blood was collected from the patient by peripheral venipuncture. After centrifugation (1500 × *g* for 5 minutes), the upper layer containing platelet-poor plasma was aspirated and discarded, after which the PRP layer was aspirated and placed in a separate tube for a second round of centrifugation. The process was repeated a second time. A total of 4 mL of PRP was collected from the tubes, and no activators were used.

Nanofat and PRP combination injected into the ovaries

The 6 mL of nanofat (400,000 ADSCs/mL) was added to the 4 mL of PRP in a sterile cut and mixed thoroughly by shaking the container. Of the total of 10 mL, 6 mL was aspirated into a 10 mL syringe. Under IV sedation and transvaginal ultrasound guidance, intraovarian injection of approximately 3 mL of nanofat + PRP combination per ovary was performed. The injection was performed in multifocal spots and the diffusion of

the nanofat with the PRP in the subcortical layers was achieved by applying 5 to 8 punctures per ovary transvaginally using a 22-gauge needle and guide.

Results

Case 1

The patient continued monitoring with her local clinic and engaged in timed intercourse monthly using ovulation predictor kits. By June 2024 (six months following the adipose-PRP procedure), she underwent an ultrasound that showed her AFC had increased significantly from 2 to 14, and she conceived naturally. She had an uncomplicated term pregnancy and delivered a healthy infant via spontaneous vaginal delivery at age 47.

Case 2

Three months following the adipose-PRP procedure, the patient underwent a third minimal stimulation IVF cycle using the same oral pills as previously used in her IVF cycles. Four mature oocytes were collected and produced 2 blastocysts (1 euploid and 1 aneuploid) after PGT-A. The patient initiated a frozen embryo transfer cycle on 5/24/2024 for her euploid embryo that led to a successful pregnancy. Her pregnancy progressed without complications and, on 2/4/2025, delivered a healthy female infant via cesarean section.

Discussion

These two reports are among the first to document successful pregnancies and healthy live births in women aged 45 and older following intraovarian administration of adipose nanofat and PRP combination. Notably, conception occurred approximately six months after the procedure in the patient #1 who conceived naturally, and within nine months in patient #2 who conceived via frozen embryo transfer of her only euploid embryo that was produced within three months following adipose-PRP administration. This relatively rapid post-treatment conceptions suggest a possible temporal relationship between adipose-PRP administration and restoration of ovarian function.

In 2021, the first phase I non-randomized clinical trial in humans evaluated the safety and potential benefits of injecting autologous ADSCs into the ovaries of women with POI [5]. Nine patients received varying escalating doses of ADSCs (5, 10, or 15 million cells) and were followed for up to 12 months. There were no serious side effects reported and menstruation resumed in 4 out of 9 patients while serum FSH levels decreased in 4 patients, thus indicating some hormonal improvement. Additionally, ovarian volume, AMH, and AFC showed variable results with no significant differences between the groups. That study concluded that intraovarian ADSC therapy was safe and feasible, with some signs of improved ovarian function.

The novelty of our report lies in its demonstration that combining autologous adipose tissue, rich in ADSCs, with PRP may yield reproductive benefits even in older women with extremely diminished ovarian reserve and advanced reproductive age (older than 45). While PRP has been studied as a standalone intervention and ADSCs have been studied in women POI, reports of combining these modalities, particularly using minimally processed, mechanically emulsified nanofat in compliance with U.S. FDA regulatory restrictions, are rare in the literature [15, 16]. Furthermore, this is the first report, to our knowledge, of natural conception in a woman over 45 following such adipose-PRP treatment.

Adipose mesenchymal stem cells and PRP therapies for improvement of ovarian function appears to act primarily through paracrine signaling and immunomodulation. Adipose mesenchymal stem cells secrete growth factors (e.g., VEGF, IGF-1, and others), cytokines, and exosome-derived microRNAs that promote angiogenesis, reduce granulosa cell apoptosis, modulate immune activity, and enhance folliculogenesis/steroidogenesis [6]. By suppressing pro-inflammatory cytokines and fostering an immunomodulatory environment, ADSCs can improve the ovarian microenvironment and hormonal profiles [17]. Limited evidence suggests possible differentiation into ovarian-like cells, but the predominant therapeutic effect is mediated through regenerative signaling pathways such as PI3K/Akt/mTOR and MAPK/ERK [18].

There are important limitations to consider. First, as an observational report of two patients, causality cannot be established thus there is a need for larger studies. The spontaneous con-

ception in patient #1 without the adipose-PRP procedure, although rare at that age, cannot be excluded. Second, ovarian reserve markers and follicular dynamics were not serially measured at short intervals, limiting the ability to fully characterize ovarian reserve changes post-treatment. Third, there was no control group, and the follow-up period was limited to the index pregnancies.

In conclusion, intraovarian adipose nanofat combined with PRP may represent a promising regenerative strategy for older women with diminished ovarian reserve who wish to conceive using their own oocytes. The short interval from treatment to conception in both cases underscores the potential for clinically meaningful improvement in reproductive potential. While these findings are encouraging, larger controlled studies are essential to confirm these preliminary observations and assess safety, efficacy, and optimal patient selection.

Disclosure of conflict of interest

None.

Abbreviations

ADSC, Adipose-Derived Stem Cells; AFC, Antral Follicle Count; AMH, Anti-Müllerian Hormone; ART, Assisted Reproductive Technology; bFGF, Basic Fibroblast Growth Factor; FET, Frozen Embryo Transfer; FSH, Follicle-Stimulating Hormone; hCG, Human Chorionic Gonadotropin; HGF, Hepatocyte Growth Factor; ICSI, Intracytoplasmic Sperm Injection; IGF-1/IGF-2, Insulin-like Growth Factor 1/2; IUI, Intrauterine Insemination; IVF, In Vitro Fertilization; MAPK/ERK, Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase; PDGF, Platelet-Derived Growth Factor; PGT-A, Preimplantation Genetic Testing for Aneuploidy; PI3K/Akt/mTOR, Phosphatidylinositol 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin; POI, Premature Ovarian Insufficiency; PRP, Platelet-Rich Plasma; TGF-β, Transforming Growth Factor Beta; VEGF, Vascular Endothelial Growth Factor.

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