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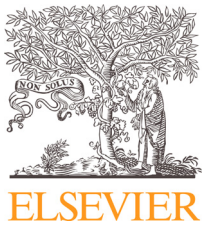

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Review

Systematic review: The platelet-rich plasma use in female androgenetic alopecia as effective autologous treatment of regenerative plastic surgery

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KEYWORDS
Female androgenetic alopecia;
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PRP in hair loss;
PRP hair re-growth;
PRP hair;
Plastic surgery;
Regenerative plastic surgery

Summary *Background:* The number of clinical trials evaluating platelet-rich plasma (PRP) efficacy in female androgenetic alopecia (F-AGA) has exponentially increased during the last five years. A systematic review focused on this specific field has been performed by assessing the local infiltrations of PRP compared with any control for F-AGA in the selected studies.
Objectives: The aim of this study was to evaluate the safety and efficacy of the use of PRP in F-AGA.
Methods: The protocol was developed in accordance with the Preferred Reporting for Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. A multistep search of PubMed, MEDLINE, Embase, PreMEDLINE, Ebase, CINAHL, PsycINFO, Clinicaltrials.gov, Scopus database, and Cochrane databases has been performed to identify papers on female pattern hair loss (FPHL) treatment with PRP. Of the 63 articles initially identified, 11 articles focusing on AGA were selected and, consequently, only 5 articles focused exclusively on F-AGA were analyzed. Of this amount, 3 articles were randomized-controlled trials (RCTs), 1 clinical trial, and 1 double-blind placebo-controlled pilot study (DBPCPS). The studies included had to match predetermined criteria according to the PICOS (patients, intervention, comparator, outcomes, and study design) approach.

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Results: Eight percent of the articles selected and analyzed, reported a positive effect of PRP for F-AGA treatment. The information analyzed highlights the positive effects of PRP on F-AGA, without major side effects and thus, it may be considered as a safe and effective alternative procedure to treat hair loss compared with traditional drugs as Minoxidil® and Finasteride®.
Conclusions: The use of PRP in F-AGA was safe and effective for F-AGA.
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Contents

Introduction

A scientific-clinical need exists for the development of biotechnologies to improve hair re-growth (HR-G) in androgenetic alopecia (AGA).

The number of investigations evaluating the efficacy of autologous platelet-rich plasma (PRP) and adult stem cell-based therapy (A-SC-BT) in AGA, commonly considered regenerative plastic surgery procedures have exponentially increased during the last decade (2010–2020).

AGA is a dynamic and chronic hair loss disorder, affecting 80% of white men, identified as male-androgenetic alopecia (M-AGA) and 40% of women, identified as female androgenetic alopecia (F-AGA), before age 70, in which lymphocytes and mast cells have been seen around the miniaturizing follicle detailed in the stem cell-rich lump zone.[1–4] Miniaturization of the follicles is characterized by a diminishment of the anagen phase, with an improvement in the number of resting hair follicles, telogen, containing microscopic hairs in a hairless scalp.[5–7]

In hair loss scalp, hair follicle stem cell numbers stay unaltered, though the number of more actively proliferating progenitor cells particularly diminishes.[8]

F-AGA is gradually increasing among young women and may bring serious psychological impacts. Women may present with a reduction in hair density (HD), hair thinning, and widening of the area especially on the center of the scalp, which may lead to a serious psychological impact on one's self-esteem, interpersonal relationships, and social status.

Although surgical hair transplant and multiple non-surgical therapeutic methods like topical Minoxidil®, oral Finasteride®, and low-level laser therapy (LLLT) had been introduced to the treatment of F-AGA, further randomized-controlled trial (RCT) treatments must be performed.[2,9]

In this field, the aim of regenerative strategies must be the development of new autologous biotechnologies to involve HR-G by *ex vivo* and *in vitro* culture or by *in vivo* regeneration and bio-stimulation. Autologous A-SC-BT has been of great interest for application in HR-G. Some early efforts in the field focused on isolating primary cells from a biopsy of the tissue of interest and growing the cells *ex vivo* for subsequent introduction back into the patient.

One year ago, (2019), the preliminary outcomes related to the use of a new regenerative technique to provide autologous micro-grafts (MCGs) containing human follicle mesenchymal stem cells (HF-MSCs) to be used in patients affected by AGA, have been reported.[10] The MCGs were obtained by multiple procedures of fragmentation, centrifugation, and filtration of a 2 mm punch biopsy of the scalp.[10] However, a major limitation encountered in this area has been the difficulty in expanding cells to sufficient numbers for human use, the necessity to perform this expansion in good manufacturing practices (GMP) laboratories, and the

viability of the expanded cells.[10] For this reason, the clinical use of HF-MSCs and A-SC-BT to improve HR-G has not been adequately considered.

Alternatively, the use of autologous platelets-derived growth factors (PDGFs), contained in PRP, represented by basic fibroblast growth factor (b-FGF), PDGF, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor-β (TGF-β), and insulin-like growth factor-1 (IGF-1),[11-13] may represent a valid regenerative strategy for their capacity to promote cell proliferation, differentiation, and neo-angiogenesis, favoring, *in vivo*, the wound healing process.[14] *In vitro*, antiapoptotic effects of PRP have been identified as one of the major contributing factors stimulating hair growth (HG) via the Bcl-2 protein's activation (antiapoptotic regulator) and Akt signaling, prolonging the survival of dermal papilla cells during the hair cycle. In particular, the up-regulation of fibroblast growth factor-7 (FGF-7)/b-catenin signaling pathways with PRP treatment is suggested to stimulate HG by inducing HF-MSCs differentiation as well as prolonging the anagen phase of the HG cycle.[14]

Comparing with traditional therapies as Minoxidil® and Finasteride®[13] and hair transplantation, PRP appears as a novel and promising regenerative treatment both in F-AGA and M-AGA, with lower cost and fewer adverse effects.[13,14] The hypothesis addressed in the present study is that PRP might represent an alternative, non-invasive, autologous, and effective treatment for female AGA patients. Even though a limited number of publications about the PRP used in F-AGA, have been reported, a systematic review regarding the use of PRP in F-AGA has been the aim of the present work.

Methods

Search strategy and literature screening

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis ((PRISMA; http://www.prisma-statement.org).[15]

The research was conducted by two investigators (P.G. and S.G.) in accordance with the PRISMA guidelines and the Cochrane handbook.[16] A multistep search of PubMed, MEDLINE, Embase, PreMEDLINE, Ebase, CINAHL, PsycINFO, Clinicaltrials.gov, Scopus, and Cochrane databases was performed to identify studies, published before of November 1, 2020, on F-AGA treatment with PRP searching without a language or publishing time restriction.

A total of 687 articles using the keyword "female androgenetic hair loss", 63 articles using the keyword "platelet-rich plasma female hair loss", and 32 using the keyword "platelet-rich plasma female androgenetic hair loss" were found. The articles related to "platelet-rich plasma female hair loss" ($n = 63$) and "platelet-rich plasma female androgenetic hair loss" ($n = 32$) were contained in the total amount initially resulted ($n = 687$).

Of the 63 articles initially identified, 11 articles focusing on AGA were selected and, consequently, 7 articles focused exclusively on F-AGA were analyzed. In fact, 5 articles were identified as bias (not correctly match with the keyword used). Additionally, of the 7 articles selected, 2 articles were excluded (1 comment and 1 systematic review). Only 5 articles were finally considered. Of these amounts, 3 articles were RCTs, 1 clinical trial, 1 double-blind placebo-controlled pilot study (DBPCPS).

Study assessment

The aim of this systematic review has been to assess the selected articles comparing local injections of PRP compared with any control for F-AGA. Articles included in this work had to match predetermined criteria according to the PICOS (patients, intervention, comparator, outcomes, and study design) approach (https://ro.ecu.edu.au/cgi/viewcontent.cgi?referer=https://www.google.it/&httpsredir=1&article=1010&context=ecupres). Study assessment was based on inclusion and exclusion criteria.

Inclusion criteria:

- **P**—Patients (age 18–79 years, females who showed AGA in stages I-III controlled by the Ludwig classification scale);
- **I**—Intervention (local application of autologous PRP);
- **C**—Comparator (any type of control, internal, external and different product);
- **O**—Outcomes (HD, hair count-HC, hair thickness-HT, and hair color improvement; hair loss reduction);
- **S**—Study design (clinical trial, randomized placebo-controlled trial/randomized, double-blind, placebo- and active-controlled, half-head study/DBPCPS/blinded, randomized clinical trial).

Exclusion criteria:

- **P**—Patients (other types of alopecia, alopecia areata, cicatricial alopecia, lichen planopilaris, patient with platelets disorders, thrombocytopenia, anti-aggregating therapy, use of pharmacological therapeutics targeting AGA as Finasteride®, similar drugs, and/or antiandrogens in the earlier year, bone marrow aplasia, uncompensated diabetes, sepsis, cancer, use of topical medicines for AGA as lotions as Minoxidil® (excepted if Minoxidil® was tested as the control in PRP studies), prostaglandin analogs, retinoid, or corticosteroids in the earlier year);
- **I**—Intervention (combined use of PRP with other products);
- **C**—Comparator (not applied);
- **O**—outcomes (not applied);
- **S**—study design (expert opinion, comments, letter to the editor, single case report, preclinical model (animal studies), *in vitro* studies, articles identified as bias—not correct match with the keyword used—group of study $<$ 10 patients, shorter follow up than 3 months, review and systematic review). No limitations were applied on ethnicity or method of PRP processing.

This systemic review, performed on the PICOS approach is considered an evidence-based medicine (EBM) 1a level study according to the Oxford center for Evidence-Based Medicine (OCEBM), March 2009 (https://www.cebm.net/2009/06/oxford-center-evidence-based-medicine-levels-evidence-march-2009/).

Study selection

Original studies include research articles, observational studies (i.e., case series, cross-sectional, case–control, and cohort) and randomized trials of PRP and AGA in woman patients in Italian, English, German, Swedish, Norwegian, Spanish, Danish, Turkish, American, and Chinese were all eligible for inclusion.

Exclusion criteria were studies only included male patients, abstracts, unpublished studies, and lack of raw data. Conference reports were also excluded for insufficient details for analysis. The titles and abstracts of the identified studies were performed by the two investigators (P.G. and S.G.). If the information provided in the abstracts was not sufficient to access the eligibility, a full-text evaluation was conducted. The two authors also (P.G. and S.G.) also evaluated the quality of the included studies independently. Any disagreement was resolved through discussion.

In total, 687 articles focused on female androgenetic hair loss were initially identified and selected using PRISMA Flow (www.prisma-statement.org; Scheme 1). A total of 624 articles were excluded. Of this amount, 385 were duplicates and/or not adequate. Consequently, it was decided to include only clinical trials with female patients diagnosed with AGA, also referred to as female pattern hair loss (FPHL).

For this reason, 239 articles not correctly matched with the topic (alopecia areata, $n = 13$; cicatricial alopecia, $n = 3$; lichen planopilaris, $n = 2$; pre-clinical model, $n = 2$; *in vitro*, $n = 19$; bias, $n = 15$; not related to PRP in AGA, $n = 185$) were excluded.

Of the 63 studies initially identified, 52 articles were excluded as related to other treatments represented by micro-needling ($n = 3$), Minoxidil® and Finasteride® ($n = 32$), A-SC-BT ($n = 13$), and LLLT ($n = 4$).

Eleven articles apparently related to the use of PRP in female androgenetic hair loss were selected. Of these, 5 articles were identified as bias (not a correct match with the keyword used). Additionally, of the 7 articles selected, 2 articles were excluded (1 comment and 1 systematic review).

Consequently, only 5 articles strictly and exclusively focused on F-AGA treated with PRP were analyzed and included in this systematic review. Of this amount, 3 articles were RCTs, 1 clinical trial, and 1 DBPCPS.

These 5 studies were evaluated and summarized by their study characteristics and study outcomes (Table 1).

Data extraction

Data were independently extracted by the first investigator (P.G.) and checked the same day by the second investigator (S.G.), only from the retrieved articles. The literature search has been conducted until January 15, 2021. Any disagreement on the extracted data has been settled by a consensus among P.G. and S.G. No attempt was made to obtain specific or missing data from the authors. The following data have been extracted: First author, year of publication, study design, number of patients, type of procedure, and primary and secondary outcomes.

The quality of the included investigations was independently assessed using two investigators (P.G. and S.G.) using the Cochrane collaboration's risk of bias assessment tool for RCTs[16] while using the Newcastle–Ottawa Scale to evaluate the individual non-randomized studies.[17]

Endpoint definition

The efficacy of PRP was primarily evaluated by an increase in HD, and secondarily, by an increment of HC, improvement in the hair-pull test, the satisfaction of patients from the surveys, and changes of HT compared with pictures and TrichoScan analysis taken before and after the treatment sections. Given that various test methods were taken through the studies we included, only the most widely used methods would be set at the endpoints for all pooled studies. All side effects, including local injection pain, headache, increasing scalp sensitivity, and any allergic effects have been analyzed.

Results

Literature search

A total of 687 articles have been initially identified. A total of 624 articles have been excluded for several reasons, including duplicates ($n = 385$) of which, not correct match after the title's/abstract's screening ($n = 194$), not human studies ($n = 45$), not related to AGA ($n = 64$), not related to PRP ($n = 82$), and not correct match with the topic after full-text reading ($n = 239$). Sixty-three articles have been initially assessed for eligibility; of this amount, 52 articles have been excluded due to not correct match with the treatment PRP, including Micro-needling ($n = 3$), Minoxidil® and Finasteride® ($n = 32$), A-SC-BT ($n = 13$), LLLT ($n = 4$). For the above-mentioned reasons, 11 articles have been selected but only 5 were articles strictly correlated with the use of PRP in F-AGA.[18-22]

Patients' analysis

Among all 63 studies, only 5 studies that recruited all female participants have been found. The mean age of the total enrolled female patients was above 19 years old and between 23 and 38 years old. Most female patients had a history of AGA for at least 2–6 years with grades I–III on the Ludwig scale. Females who had previous hair transplantation, who suffered from systemic disease, cancer, immunomodulatory disease, erythema, scars, or who had applied Minoxidil or any additional drugs for hair loss have been excluded. At the same time, puerperal patients or pregnant patients, have been excluded.

Laboratory tests were checked to exclude alternative causes of hair loss,[18-22] such as poor nutrition, anemia (i.e., complete blood count—including platelet count, platelet volume, hemoglobin, serum iron, serum ferritin, total iron-binding capacity, and folic acid), thyroid dysfunction (i.e., tri-iodothyronine (T3), free T3 (FT3), thyroxine (T4), free T4 (FT4), and thyroid-stimulating hormone (TSH), antithyroid peroxidase, and testosterone), syphilis (i.e., a

Table 1 The study design and results of the included studies.

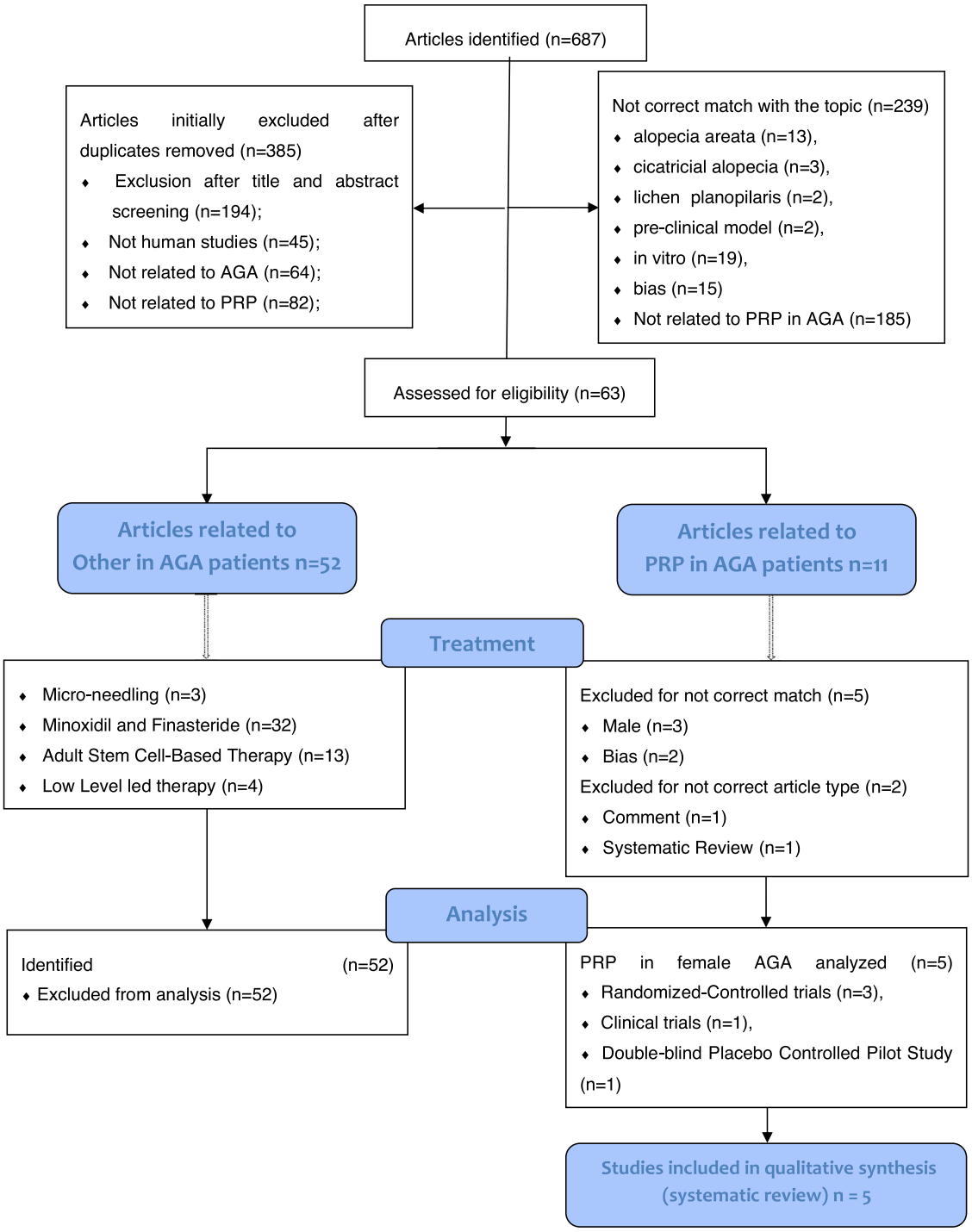
Authors	Study Type				Characteristics of Enrolled Subjects (Completed Study)	Objective Measures	Objective Assessment of Hair Growth	Subjective Assessment of Hair Growth	Year	Ref.
	Randomized	Controlled	Blinded	half-head						
Puig et al.	Yes	Yes	Yes	No	26 (26) 26 F, stage II	1. HC (Ph) 2. Hair mass index (Cohen's HairCheck® system)	1. No ($p = .503$) 2. No ($p = .220$)	13.3% of SG vs 0% of CG reported substantial improvement in HLs, rate of HLs, HT, and ease of managing/styling hair; 26.7% of SG vs 18.3% of CG reported feeling coarser/heavier hair	2016	[19]
Starace et al.	No	No	No	No	10 (10) 10 F, stage II	1. HD (median relative percentage change -%RC, TrichoScan) 2. Hair diameter (TrichoScan,%RC)	2. Yes (12 wks, $p < .05$); (24 wks, $p < .05$)	After 12 wks, the medium hair diameter in frontal area showed a significant increase (%RC = 12.5), and after 24 wks (%RD = 14.6). The vellus relative change showed a decrease, in the front and the central area, (−6.6%)	2019	[18]
Tawfik and Osman	Yes	Yes	Yes	Yes	30 (30) 30 F, stages I-III	1. HD (folliscope) 2. HT (folliscope) 3. Pull test 4. Global (pictures)	1.2.3. Yes, there was a statistical significant difference between PRP and placebo areas ($p < .005$) regarding both HD and HT as measured by a folliscope. The hair pull test became negative in PRP-injected areas in 25 patients (83%) with average number of three hairs%	Global pictures showed a significant improvement in hair volume and quality together with a high overall patient satisfaction in PRP-injected sites. The results were maintained during the 6-mo. follow-up	2017	[20]

(*continued on next page*)

Table 1 (*continued*)

Authors	Study Type				Characteristics of Enrolled Subjects (Completed Study)	Objective Measures	Objective Assessment of Hair Growth	Subjective Assessment of Hair Growth	Year	Ref.
	Randomized	Controlled	Blinded	half-head						
Dubin et al.	Yes	Yes	Yes	No	30 (30) 30 F, stages I-III	1. HD 2. Hair caliber 3. Pull test 4. Blinded global (assessment)	1. Yes, mean HD in the SG was increased vs the CG at wk 8 (+ 71.1 vs -26.7 hairs/cm^2; $p < .01$) and wks 24 (+ 105.9 vs -52.4 hairs/cm^2; $p < .01$) 2. Yes, mean HT (caliber) in the SG was increased vs the CG at wk 8 (+ 0.0043 vs -0.0034 mm; $p < .01$) and wk 24 (+ 0.0053 vs -0.0060 mm; $p < .01$). Adverse effects included headache, scalp tightness, swelling, redness, and post-injection bleeding	Blinded global Ph assessment indicated that 57% of patients receiving PRP versus 7% of patients receiving saline improved at wks 24 from baseline ($p < .01$)	2020	[21]
Bruce et al.	Yes	Yes	No	No	20 (20) 20 F, stages I-III	1. HC TrichoScan 2. Vellus HD Trichoscan3. Terminal HD TrichoScan 4. Cumulative thickness 5.Quality-of-life surveys	1.2. Yes, After PRP, significant increases from baseline to wks 12 in TrichoScan analysis HC ($p = .002$) and vellus HD ($p = .009$) occurred.	Several quality-of-life responses improved from baseline to wks 12 after PRP treatment, whereas no improvements were noted after Minoxidil	2020	[22]

Abbreviations: F, female; HC, hair count; HD, hair density; HT, hair thickness; HLs, hair loss; Ph, photography; SG, study group; CG, control group; wks, weeks; mo., months.



Scheme 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

venereal disease research laboratory blood test), autoimmune, or systematic diseases (anti-ENA and anti-ANA). Circulating levels of cortisol, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), D4-androstenedione, 17-hydroxyprogesterone, 3-↵-diol glucuronide, prolactin, and gonadotropins (i.e., FSH and LH) were analyzed. Finally, urinalysis was used to detect levels of 17-idrocorticosteroid, 17-ketosteroid, DHEA, free cortisol, pregnanetriol (PTL), and testosterone (T). The stage of individual participant alopecia was evaluated according to the Ludwig scale.

Platelet-rich plasma protocols

Different protocols of PRP preparation have been found in the analyzed articles. In detail, several commercial PRP kits, products from different companies were commonly used, associated with different centrifugation and filtration protocols. Activators and anticoagulation used it depended on PRP kits and investigation purposes. In all enrolled studies, calcium chloride ($CaCl_2$) or calcium gluconate $(C_6H_{11}O_7)_2Ca$, in 1 μmol /ml and a 10:1 ratio has

been mostly added as activators, respectively. Sodium citrate ($Na_3C_6H_5O_7$) has been mostly used as an anticoagulant. Moreover, platelet concentration was improved from 1.3 times to 5-fold as whole blood depending on PRP preparation procedures.[18-22]

Procedures and techniques

About 0.1% octenidine hydrochloride spray or 70% alcohol was used for cleaning the scalp area to treat, while local injection of anesthesia as lidocaine or naropin have been commonly used. Only in the studies of Gentile et al.,[3,4,9-14] local anesthesia has not been used.

Two studies used anesthesia in cream form, one used the head's soft massage, and one conducted cold air anesthesia before the infiltrations. The majority of the investigations displayed the use of 22–30-G gauge needles with insulin syringes to perform the infiltrations while sterile-microneedling and mesotherapy guns were also used in several clinical trials. [4,9-14,18-22] The "nappage technique" was taken by most studies with a 1–3 cm distance between each injection point. PRP at a concentration from 0.2 to 1 ml has been infiltered within each gridded injection point. The depth of intradermal injections was approximately 1.5–2.5 mm deep, but 0.5 mm deep for a sterile micro-needling procedure. Intra-follicular injections and intra-perifollicular injections were also carried in several studies. In the studies of Gentile et al. [3,4,9-14], the depth of inter-follicular injection was 5 mm using mechanical and controlled injection via the mesotherapy gun.[4] Usually, 3–5 treatment sessions with 4–6 intervals were performed. The time of follow-up observed was commonly from 9 weeks to 15 months.[18-22]

Outcome evaluation

In addition to the Ludwig scale, outcomes evaluation methods included photographic evaluation via global photographs, phototrichogram analysis with TrichoScan® to evaluate HD, HC, and HT, physician global assessment score (PhGAS), patient global assessment score (PaGAS), pull test, and biopsy with ki-67 immunochemistry stain.[18-22] The females' satisfaction surveys and physician satisfaction surveys were also used to evaluate the efficacy of PRP in several recruited studies.[18-22]

Eighty percent of the studies analyzed showed positive responses and an improvement compared with the baseline. No significant adverse effects have been reported. Few patients reported mild headache, scalp sensitivity bruise, mild pain on injection sites after 12–72 h which would resolve spontaneously in the second to fourth post-operation day. In detail, only Dubin et al.[21] reported mild adverse effects, like headache, scalp tightness, swelling, redness, and post-injection bleeding

Discussion

As reported, in the last decade, and in particular in the last five years, the PRP injection has been proposed many times in several fields of regenerative plastic surgery, and in particular, as a potential adjuvant therapy to treat AGA. A great part of the studies regarded male or male and female patients,[3,4,9-14] but very few studies are focused strictly on F-AGA. Starace et al.,[18] in a recent study published 1 year ago (2019) investigate the efficacy, tolerability, and clinical improvement of PRP for the treatment of F-AGA.

A study group composed of 10 female patients affected by AGA and not responding to treatment with Minoxidil® and/or oral antiandrogens have been enrolled. The clinical improvement was evaluated by pull test, global photographs, and TrichoScan® at weeks 9, 12, and 24, and hair measurements were performed at baseline and 12 and 24 weeks after the first session. After 24 weeks, the median relative percentage change (%RC) for all the parameters of HD was mostly positive. After 12 weeks, the medium HT in the frontal area showed a significant increase (%RD = 12.5, with p-value<0.05), and after 24 weeks (%RD = 14.6, p-value<0.05), the vellus relative change instead showed a decrease, especially in the front and the central area, while for the vertex, the decrease was mainly visible at the end (-6.6%). No adverse events were reported.

On the contrary, only the study of Puig et al.[19] did not display a statistically significant improvement in the results assessed. Puig et al.[19] performed a double-blind randomized placebo-controlled multicenter trial involving 26 patients with FPHL. Fifteen females were randomized to the PRP group (study group) and 11 to the placebo group (control group). Researchers marked a 4 cm^2 area in the central part of the scalp, where hair was repeatedly evaluated during the work using the HairCheck®. Patients of the study group received one infiltration of either PRP or normal saline within 4 cm from this area at week 0. At week 26, no statistically significant difference was found between the study and control groups in terms of HC. Patients of the study group did, however, report a subjective reduction of the hair loss rate, and an improvement of HT, and ease of hair styling, which none of the control group participants noted. This work was the only study published in which the patients received only one PRP or placebo treatment.

As known, hair is an essential part of a woman's appearance and attractiveness. This is reflected in the predominantly psychological morbidity that can be associated with FPHL. More invasive procedures, like hair transplant, could be not indicated in the treatment of F-AGA and for this reason, always more frequently, PRP has received growing attention as a potential therapeutic tool for hair loss.

Tawfik and Osman [20] evaluated the efficacy and safety of autologous PRP in the treatment of 30 patients who suffered FPHL. Female patients, in this study, were randomly assigned to receive autologous PRP injection into a selected area, while another area was injected with normal saline as a placebo. Sessions were performed weekly for a maximum total of four sessions. Patients were followed up 6 months after the end of the last session. The outcome was assessed both subjectively and objectively. A statistically significant difference between PRP and placebo areas ($p < 0.005$) regarding both HD and HT as measured by a folliscope, has been reported. The hair pull test became negative in PRP-injected areas in 25 patients (83%) with an average number of three hairs. Global pictures showed a significant improvement in hair volume and quality together with high overall

patient satisfaction in PRP-injected sites, and these results were maintained during the 6-month follow-up.

Dubin et al.[21] in a very recent study, published in the current year (2020) affirmed that PRP may be considered a useful treatment for F-AGA, although additional and more objective studies are needed. They conducted a prospective RCT of 30 women diagnosed with AGA. Patients received subdermal scalp injections of Eclipse system PRP or placebo saline at weeks 0, 4, and 8. Outcome measures were changes in HD (hair/cm^2), hair caliber (mm), and blinded global photographic assessment (improved or not improved) at week 24. The blinded global photographic assessment indicated that 57% of female patients receiving PRP versus 7% of female patients receiving saline improved at week 24 from baseline ($p < .01$). Compared to baseline, there was improvement in mean density in the PRP group versus the placebo group at week 8 (+ 71.1 vs -26.7 hairs/cm^2; $p < .01$) and week 24 (+ 105.9 vs - 52.4 hairs/cm^2; $p < .01$). Compared with baseline, there was improvement in mean caliber in the PRP group versus the placebo group at week 8 (+ 0.0043 vs -0.0034 mm; $p < .01$) and week 24 (+ 0.0053 vs -0.0060 mm; $p < .01$). Mild adverse effects, consequent to the PRP injections, included headache, scalp tightness, swelling, redness, and post-injection bleeding have been described in this study. Additionally, two patients have been lost during the follow-up.

Bruce et al.[22] in another contemporary study (2020), pushed by the demonstrated successful treatment with PRP in men, evaluated PRP in the treatment of F-AGA, compared with topical Minoxidil®. Here, 20 women suffering from AGA received topical Minoxidil® for 12 weeks and injectable PRP for 12 weeks in a randomized crossover design with an 8-week washout between treatments. Standardized TrichoScan analysis and quality-of-life surveys were assessed at baseline and 12-week follow-up for each treatment. After PRP, significant increases from baseline to week 12 in TrichoScan analysis HC ($p = .002$) and vellus HD ($p = .009$) occurred. However, Minoxidil® resulted in significant increases in HC ($p < .001$), vellus HD ($p = .03$), terminal HD ($p = .004$), and cumulative thickness ($p = .004$). Several quality-of-life responses improved from baseline to week 12 after PRP treatment, whereas no improvements were noted after Minoxidil®. For the above-mentioned outcomes obtained, Bruce et al. [22] concluded, that PRP is an effective treatment for HR-G in F-AGA, although not as effective as Minoxidil®. However, the improved quality-of-life responses after PRP, but not Minoxidil®, suggest a potential overall greater degree of satisfaction with PRP.

This systematic review demonstrated a relative efficacy and safety for PRP in the treatment of F-AGA from the analysis for RCTs and observational studies, especially for those patients who had unresponsive to the topic Minoxidil® application, offering another new effective treatment method for FPHL. Only mild adverse effects (not significative) have been described in only one study, and therefore, the PRP injections can be regarded as an alternative for the treatment of FPHL with minimal morbidity and a low cost-to-benefit ratio. During a deeper analysis of the literature, on the potential side effects of PRP treatment, two works[25,26] reported hyperalgesia after PRP injections. Yildirim et al.[25] reported hyperalgesia in patients treated with repeated PRP injections. The development of hyperalgesia in these patients may be due to the growth factors contained in PRP, but further experimental and clinical studies are needed to determine the effective cause of hyperalgesia occurring after repeated PRP injections.

Ince et al.[26] in a pre-clinical study reported both non-activated and activated PRP resulted in greater hypersensitivity than saline and sham treatment. They suggest that the development of hyperalgesia may be associated with an increase in nerve growth factor (NGF) as well as increased inflammatory mediators.

In every case, further human clinical studies are needed to confirm, and determine the effective cause of hyperalgesia.

Only one study did not display a statistically significant improvement in the results assessed, but at the same time, it is the only study in which the female patients received only one PRP or placebo treatment.

The HD represented the most common endpoint between the studies to perform an analysis of the outcomes. Although there were several systemic reviews[13,23] and meta-analyses on AGA,[24] systematic reviews and meta-analyses mainly focus on women patients were scarce.

The major strengths of the study were provided the efficacy of PRP just for F-AGA highlighting different PRP preparing methods and treatment regimes.

In the author's opinion, the need for large-scale RCTs and extensive meta-analysis precedes a considerable heterogeneity challenge. Heterogeneity anticipated is mainly because of the different treatment regimes, different PRP preparation methods, injection details, as well as PRP concentration. Although efforts had been made to solve these issues, adapting the application protocols of new studies on the basis of the outcomes published in the previous studies, the introduction of the concept to respect rules and institutional guidelines (as suggested by the authors P.G. and S.G. in a recent systematic review), a widely shared protocol of both PRP preparation and application lack.

Additionally, whether divergences exist in the efficacy of PRP through races remains unclear. Besides, the majority of randomized studies were set in half headed. In fact, more frequently, patients received PRP on half scalp and placebo on the other half. Both injected spots showed improvement of HG or HD although PRP showed a more obvious effect, which may result in a smaller difference between PRP and placebo, and whether PRP had a growth effect for the opposite side of the scalp remains obscure.

Conclusions

In conclusion, this systematic review showed the efficacy of PRP in the therapy of F-AGA through HD, HC, and HT evaluations. Although the mechanism of action on hair follicles is still under debate, it has been proved that PRP to be a promising option for F-AGA treatment. Given the current treatments differ in methodology and treatment technique, further studies are needed to define standardized protocols and large-scale randomized trials still need to be conducted to confirm its efficacy. For these reasons, the authors invite all the audience to improve the level of publi-

cations in this field by focusing prevalently on EBM level 1 studies.

CRediT authorship contribution statement

Pietro Gentile: Visualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Methodology, Validation, Supervision, Conceptualization, Software, Resources, Data curation, Project administration, Funding acquisition. **Simone Garcovich:** Methodology, Software, Validation, Formal analysis, Data curation, Project administration, Funding acquisition.

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Ethical approval

Not required.

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