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Review Article

Innovative Therapeutic Strategies for the Treatment of Repeated Implantation Failure - An Update

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Abstract

Inspite of the hurdles in evaluation of Recurrent implantation failure, there has been forward progression existent with regards to therapeutic strategies for aiding in these RIF patients. Of the maximum attractive approaches three like utilization of I) peripheral blood mononuclear cells (PBMC), ii) Subcutaneous administration of Granulocyte Colony –Stimulating Facto (G-CSF)r iii) Platelet rich plasma (PRP) hold major attraction. Here we have Concentrated mainly on these 3 innovative strategies besides detailing certain other immune therapies utilized in the past like Intrauterine Insemination of hCG, ii) intravenous immuoglobulins (IVIG), iii) intravenous intralipid as well as iv)heparin in addition to how they act.

Keywords: Recurrent Implantation Failure; PBMC; PRP; G-CSF

Introduction

Recurrent implantation failure (RIF) patients in addition to the treating physicians face a constant dilemma as to what should be undertaken further without attempting any separate interventions. Hence subsequently those patients that present without any structural uterine abnormalities, various separate management options have been attempted, usually with minimal proof with regards to effectiveness, with occasionally no advantages, or certain deteriorating actions as well.

In the context of causes, assessment, studies conducted with regards to management of RIF usually do not correspond to the usual norms accepted for an appropriate research in view of absence of Standard criteria for RIF, ii) absence of excluding aneuploid fetuses, in addition to no classification for certain parameters like total number of earlier transfers. In case of prior in addition to short publications mostly controls role is played by patients themselves or contrasted with a small cohort of patients. Subsequent to any interceding treatment, the post interceding treatment might result in pregnancy just by coincidence. This statistical event referred to as regression towards the mean details the transfer towards the average that might make natural, variability amongst recurrent data appear like actual alterations. Additionally, present meta-analysis in which the assessment, of the effectiveness, of the treatment approaches for RIF usually pool data from heterogenous patient populations along with treatment approaches. Nevertheless, inspite of the, existence of numerous hurdles in giving the definition of RIF, obtaining the etiology beneath, in addition to conduction of randomized controlled trial (RCT), further movement with regards to innovative therapeutic

strategies, for the ones with RIF is getting achieved. Here 3 of the maximum lucrative treatment approaches for RIF therapy are detailed. Besides that certain interposing treatments have not documented any advantages, or rather might prove to be deleterious, yet still get utilized rarely.

Intrauterine administration of autologous peripheral blood mononuclear cells (PBMC)

With regards to attainment of success as far as implantation is concerned the local maternal immune tolerance is significant. A posit has been detailed in context of patients with RIF might not possess the capacity of enrollment of the essential lymphocytes whose requirements exists with regards to achieving successful implantation, however infusion of lymphocytes that belong to the patient herself might possess the capacity of restoration of the balance of the immune system in addition to the enhancement of endometrial receptivity along with implantation possess T as well as B lymphocytes along with monocytes. These cells cause stimulation of generation of cytokines, interleukins as well as growth factors, that have been illustrated in certain studies to have a positive influence on endometrial thickness (ET) along with endometrial receptivity [2]. In case of studies with the aim of RIF therapy, blood samples were classically collected from patients 3-5 days prior to the posted embryo transfer as well as PBMC were segregated that was followed by infusion. (Figure 1) [2-7].

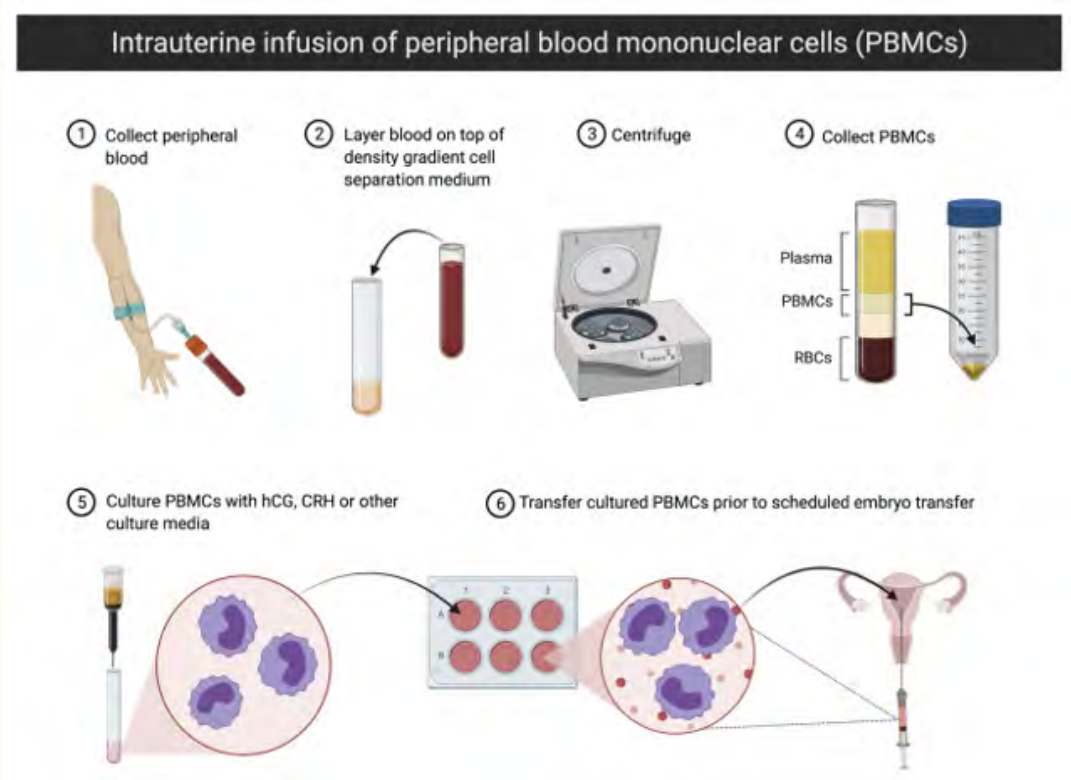

Figure 1: Courtesy ref no-7 - Intrauterine infusion of peripheral blood mononuclear cells (PBMCs) is a potential immunotherapy for patients with repeated implantation failure (RIF). Blood samples are collected from individual patients, layered on top of a density gradient cell separation medium and centrifuged (Ficoll-Paque procedure). PBMCs are collected and may be cultured with human chorionic gonadotropin (hCG), corticotropin-releasing hormone (CRH) or other culture media prior to transfer into the uterine cavity (Images created with BioRender).

During one of the initial observational studies where utilization of PBMC was carried out for RIF, autologous PBMC were infused in the uterine cavity of RIF patients prior to fresh embryo transfer [6]. Prior to infusion PBMC culture was done with human chorionic Gonadotrophins (hCG), since it has been illustrated by in vitro studies that on activation by hCG escalation of liberation cytokines as well as chemokines from PBMCs takes place, which is required for an implantation with success [8]. In contrast to the nontreated group escalation of implantation in addition to clinical pregnancy rate, live birth rates (LBR) were seen in patients who received treatment with PBMC [6]. The escalation of utilization of frozen embryo transfer (FET), 2 extra observational studies further conducted these studies prior to FET, with an observation of enhancement of implantation in addition to Clinical pregnancy rates in patients with RIF [6,8]. Okitsu., *et al*. [6] repeated akin experiment without utilization of culture of PBMCs with hCG, that apparently activates them subsequent to Intrauterine insemination with different molecules that are existent in the uterine cavity already.

Furthermore, small RCTs have validated the advantages of PBMCs with regards to therapy of RIF patients. A RCT was conducted by Yu., *et al*. [2], with the utilization of this autologous PBMCs that had been stimulated by hCG prior to day 3 of frozen/thawed embryo transfer. Their observation was a greater implantation in addition to clinical pregnancy rates as far as the PBMCs group was concerned (clinical pregnancy, 46% in PBMC streated group, in contrast to 21% in the control group; $p < 0.05$; $n = 198$). Akin to this Nobjiari., *et al*. [4], observed a significant escalation of clinical pregnancy rates in one more RCT subsequent to Intrauterine delivery of PBMCs, prior to frozen/thawed embryo transfer in case of patients with a minimum of earlier three implantation failures (clinical pregnancy, 39%in PBMCs treated group, in contrast to20% in the control group; $p = 0.01$; $n = 138$) [4]. In this study subsequent to Identification, culture of PBMCs was done in a basic culture medium whose constituents, were mitotic factors, cytokines, interleukins as well as growth factors along with corticotrophin -releasing hormone (CRH). CRH gets expressed robustly during embryoimplantation, besides result in the liberation of T helper 2 cytokines, that aid in implantation [4].

More recently, a meta-analysis conducted on RIF therapy utilized a combination of three RCTs along with 3 observational studies with regards to PBMCs, with the findings of advantages of Intrauterine PBMC administration on clinical pregnancy rate (risk ratio, 2.18; 95% confidence interval [CI], 1.58-3.9; $p < 0.0001$; odds ratio 2.03; 95% CI1. 22-3.36. $p = 0.06$) along with live birth rates (LBR) (riskratio, 2. 41;95%confidence interval [CI], 1.40-4.16; $p = 0.002$; odds ratio 3.73; 95% CI1. 13-12. 29. $p = 0.03$) [2-4,6,8,9]. Moreover, whereas, these data were attractive with maximum studies documented an escalation of LBR subsequent to PBMCs infusion in contrast to the ones in the placebo/ control group, the studies in total are presently still quite small, comprising of heterogenous study populations, variations with regards to the preparation of PBMCs, in addition to separate protocols for treatment (fresh vis a vis frozen, day3 vis a vis 5 transfers). Additionally, greater insight with regards to the safety of utilization of human blood components is still required.

Intrauterine administration of platelet rich plasma

Platelet rich plasma (PRP) represents autologous blood components that are comprised of a markedly concentrated composition of platelets existent in a small plasma volume. Numerous bioactive molecules like growth factor, transforming growth factor beta (TGF-β) platelet-derived growth factor (PDGF), Fibroblast growth factor 2 (FGF) vascular endothelial growth factors (VEGF), cytokines, cell adhesion molecules get stored in platelets α granules [8]. The liberation of these α granules from the platelets that are activated aids in the provision of these factors in great amounts towards the target tissues, that aids in cell proliferation along with differentiation, angiogenesis, chemotaxis in addition to modulation of the local immune response [9,10]. Utilization of PRP at present is being done in numerous branches that is inclusive of orthopaedics, ophthalmology, dentistry along with wound repair besides many more [11,12] along with new data have documented in in vitro fertilization (IVF), transfers in case of women that possess a thin endometrium [10,14].

For evaluation of utilization of Intrauterine administration of PRP might cause enhancement of implantation rates in case of women having a history of a minimum of three failed embryo transfers, that were of high quality. A double blind RCT was conducted by Nazari., *et al*. [15] where 97 women got randomly divided into Intrauterine insemination of PRP 48 hr prior to embryo transfer or to a control group [15]. The chemical in addition to

Clinical pregnancy rates were greater in the PRP group (chemical pregnancy, 53% visa vis 27%; p = 0.09; Clinical pregnancy, 45% visa vis 17%; p = 0.003) in contrast to control group [15].

Recently Zamaniyan., *et al*. [16], performed a randomized as well as physician blinded cinical trial in women who were going through a FET, having failed to achieve a pregnancy subsequent to embryo transfer following a minimum of three failed high quality embryo transfers. Here as well PRP administration conducted 48 hr prior to embryo transfer. For the intention to treat evaluation, the implantation along with clinical pregnancy rates along with ongoing pregnancy rates were greater in the PRP group in contrast to control group (58.3% visa vis 25%; p = 0.09; 48% visa vis 23%; 47% visa vis 12% respectively; all with p ≤ 0.01). Hence whereas larger RCT's is the need of the hour, the initial data holds promise.

Subcutaneous administration of Granulocyte Colony - Stimulating Factor

Granulocyte Colony –Stimulating Factor (G-CSF) represents a glycoprotein that gets generated by immune cells like monocyte along with macrophages, endothelial cells, bone marrow cells. G-CSF causes stimulation of proliferation, differentiation, survival in addition to function of neutrophils [17]. Recombinant G-CSF utilization at present for the treatment of haematological disorders like aplastic anemia as well as neutropenia [18]. Furthermore, G-CSF gets expressed as well as generated by decidual cells, thus have been evaluated as IVF adjunctive therapy that is delivered either locally or systemically for the women that possess a thin endometrium, history of repeated pregnancy loss RPL or RIF [19].

During a multicenter, randomized, open label, controlled trial, 112 women were randomized by Aleyasin., *et al*. [20], for getting 300 mcg of G-CSF that was delivered by Subcutaneous injection I hr prior to fresh embryo transfer or to a control group. Greater implantation rates along with clinical pregnancy rates were documented, in the ones that got Subcutaneous G-CSF in contrast to controls (Clinical pregnancy, 37.5% visa vis 14.3%; p = 0.005; implantation, 18% visa vis 7.2%; p = 0.007; n = 112) [20]. Validation of 2 earlier conference abstracts was done by his study along with demonstrated an advantage in patients with RIF that had receipt of G-CSF systemically [21].

As compared to subcutaneous G-CSF delivery, 2 RCTs did not observe, statistically significant variations In implantation rates along with clinical pregnancy rates in patients with RIF subsequent to Intrauterine administration of G-CSF [22]. In view of no advantages visualized subsequent to local delivery of G-CSF it was posited that advantages of G-CSF administration systemically was secondary to the action of G-CSF on oocyte maturation in addition to embryonic generation instead of enhancement of endometrial receptivity [20,22]. Greater studies with regards to better quality that document LBR are required further. Furthermore, studies conducted in future as per G-CSF need to document adverse actions also in view of localized re actions in certain cases of escalation of leukocyte counts have been illustrated by G-CSF earlier [19,23].

More immune treatments

The other treatments for RIF that are being evaluated are Intrauterine insemination of hCG, ii) intravenous immuoglobulins (IVIG), iii) intravenous intralipid as well as iv) heparin [24-26,32]. A meta-analysis conducted more recently demonstrated that infertile women as well as patients that were in receipt of Intrauterine administration of hCG prior to embryo transfer had greater implantation in addition to LBR [9,27]. These evaluation pooled data from small studies, besides utilize separate volumes along with dosages of hCG, that restricts the capacity of contrasting data from different trials with the final conclusions that one wonders if any advantageous action is existent actually.

Intravenous immuoglobulins represents a purified form of the pooled plasma that gets obtained from healthy volunteers, that has got evaluated with regards to therapy of RIF with the posit that IVIG results in enhancement of regulatory T cells, cause reduction of T helper 1 cytotoxic reactions in addition to being associated with natural killer cells (NK) cell actions [28,29]. More recently, an observational study conducted by Ho., *et al*. [25], observed that infusion of IVIG proved to be advantageous for patients with RIF that possessed lower peripheral NK) cell populations in the early follicular phase. Total proof that corroborate utilization of IVIG is still least, with requirements for greater studies.

Utilization of intravenous intralipid has been done in the form of provision of calories in addition to essential fatty acids with regards to patients in need of parenteral nutrition. Although the precise mode by which intralipids act on uterus is not clear, however it is posited that intralipids might change the uterine milieu that promotes T helper type 2 cytokines as well as subsequent to uterine

NK cell phenotype towards the one that facilitates pregnancy [29]. AlZabewidy., *et al*. [26], observation was an enhancement of clinical pregnancy rates along with live birth rates (LBR) in the groups of RIF patients in receipt of intravenous intralipid infusion, however, statistical significance was not achieved in the outcomes (clinical pregnancy, 36.6% vs 28.2%; p = 0. 282; live birth rates 18.3% vs 14.1%; p = 0.49).

Furthermore, heparin has been evaluated in the form of adjunctive therapy. Trophoblast adhesion along with invasion gets impacted by heparin by its action on Matrix Metalloproteinases (MMP's), Tissue inhibitors of Matrix Metalloproteinases (TIMPs), cadherin-E, heparin binding epidermal growth factor along with free insulin like growth factor [31]. To our misfortune meta-analysis have been unable to illustrate advantages of heparin on clinical pregnancy rates, other than in patients already having a diagnosis of earlier thrombophilia or antiphospholipid syndrome [9,32].

Additionally, we reviewed the role of Endometrial Mesenchymal Stem Cells Regenerative Therapy in cases of RIF possessing Resistant Endometrium [33].

Nevertheless, studies that have been well fashioned, enough powered with proper population selection with treatment protocols that are consistent are required prior to advocating hCG, IVIG, or intralipid infusion for RIF patients. The adverse actions of these therapies have to be evaluated in future studies for being sure of sufficient studies without proof of deleterious actions.

Conclusions

Besides being tough for the treating physician in addition to the emotional condition of the couples facing the wrath of RIF apart from the economical burden of the continued treatment needed for them. Management of RIF holds lot of challenges with restricted presence of treatment approaches giving success with absence of proof of high quality. Usually treating physician is pressurized to try anything and everything feasible that makes these RIF patients subjected to expensive therapies that have not been validated by results. Couples with RIF require lot of emotional aid in addition to reassurance with regards to despite the etiology not clear, finally clinical pregnancy would be attained in more than 95% of patients on persistence of repeated embryo transfer of high quality [34]. With escalation of insight of embryo, endometrium along with early pregnancy more work on treatment strategies for RIF should be pursued further that can aid our clinical decisions. Having the promise offered by upcoming treatment s like PBMCs, we might soon be able to manage this key problem in the coming future.

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