MODERN CONCEPTS OF TREATMENT OF ENDOMETRITIS WITH CLINICAL APPLICATION OF PLATELET-RICH PLASMA IN THE FEMALE REPRODUCTIVE SYSTEM

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Annotation: Platelet-rich plasma is an autologous plasma containing platelets prepared from fresh whole blood drawn from a peripheral vein. Through processing, it can be prepared to contain supraphysiologic levels of platelets at three to five times greater than the level of normal plasma. PRP has been explored both in vivo and ex vivo in the human endometrium model in its ability to harness the intrinsic regenerative capacity of the endometrium. Intrauterine autologous PRP infusions have been shown to increase endometrial thickness and reduce the rate of intrauterine adhesions. In the setting of recurrent implantation failure, intrauterine infusion of PRP has been shown to increase clinical pregnancy rate. PRP also appears to hold a potential role in select patients with premature ovarian insufficiency, poor ovarian responders and in improving outcomes following frozen–thawed transplantation of autologous ovarian tissue. Further studies are required to explore the potential role of PRP in reproductive medicine further, to help standardise PRP protocols and evaluate which routes of administration are most effective.

Keywords: gynaecology; platelet-rich plasma; infertility; endometrium; uterus

СОВРЕМЕННЫЕ КОНЦЕПЦИИ ЛЕЧЕНИЯ ЭНДОМЕТРИТА С КЛИНИЧЕСКИМ ПРИМЕНЕНИЕМ БОГАТОЙ ТРОМБОЦИТАМИ ПЛАЗМЫ В ЖЕНСКОЙ РЕПРОДУКТИВНОЙ СИСТЕМЕ

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Аннотация: Богатая тромбоцитами плазма – это аутологичная плазма, содержащая тромбоциты, полученная из свежей цельной крови, взятой из периферической вены. Благодаря обработке ее можно приготовить так, чтобы она содержала супрафизиологические уровни тромбоцитов, в три-пять раз превышающие уровень нормальной плазмы. PRP исследовалась как in vivo, так и ex vivo на модели эндометрия человека в отношении ее способности использовать внутреннюю регенеративную способность эндометрия. Было показано, что внутриматочные инфузии аутологичной PRP увеличивают

толщину эндометрия и снижают частоту внутриматочных спаек. Было показано, что в случае рецидивирующей неудачи имплантации внутриматочная инфузия PRP увеличивает частоту клинической беременности. PRP также, по-видимому, играет потенциальную роль у некоторых пациенток с преждевременной недостаточностью яичников, плохим ответом яичников и в улучшении результатов после замороженно-размороженной трансплантации аутологичной ткани яичника. Необходимы дальнейшие исследования для дальнейшего изучения потенциальной роли PRP в репродуктивной медицине, чтобы помочь стандартизировать протоколы PRP и оценить, какие пути введения наиболее эффективны.

Ключевые слова: гинекология; богатая тромбоцитами плазма; бесплодие; эндометрий; матка

AYOLLAR JINSIY TIZIMIDA TROMBOTSITLARGA BOY PLAZMANI KLINIK QO‘LLASH ORQALI ENDOMETRITNI DAVOLASHNING ZAMONAVIY KONTSEPTSIYALARI

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Annotasiya: Trombotsitlarga boy plazma - periferik tomirdan olingan yangi qondan tayyorlangan trombotsitlarni o'z ichiga olgan otologik plazma. Qayta ishlash orqali u trombotsitlarning suprafiziologik darajasini normal plazma darajasidan 3-5 baravar yuqori bo'lishiga tayyorlanishi mumkin. PRP inson endometrium modelida ham in vivo, ham ex vivo o'rganilgan, uning endometriumning ichki regenerativ qobiliyatidan foydalanish qobiliyati. Intrauterin otolog PRP infuziyalari endometrium qalinligini oshirishi va intrauterin yopishish tezligini kamaytirishi ko'rsatilgan. Takroriy implantatsiya etishmovchiligi sharoitida PRPning intrauterin infuzioni klinik homiladorlik darajasini oshirishi ko'rsatilgan. PRP, shuningdek, tuxumdonlarning muddatidan oldin etishmovchiligi bo'lgan tanlangan bemorlarda, tuxumdonlarning yomon javob berishida va tuxumdonning avtonom to'qimalarining muzlatilgan-eritilgan transplantatsiyasidan keyingi natijalarni yaxshilashda potentsial rol o'ynaydi. PRP ning reproduktiv tibbiyotdagi potentsial rolini o'rganish, PRP protokollarini standartlashtirish va qaysi yuborish yo'llari eng samarali ekanligini baholash uchun qo'shimcha tadqiqotlar talab etiladi.

Kalit so‘zlar: ginekologiya; trombotsitlarga boy plazma; bepushtlik; endometrium; bachadon

The use of cell-based therapies, such as platelet-rich plasma (PRP), has gained considerable momentum over the last decade due to their ability to promote tissue

regeneration through cell differentiation and trophic activities. The first clinical application of PRP was as a transfusion product to treat thrombocytopenia. It has since been used across numerous medical fields, including maxillofacial and plastic surgery, orthopaedic surgery, dermatology, urology and more recently gynaecology .This review aims to summarise the use of PRP within the reproductive setting by conducting an evidence-based evaluation of its preparation, classification systems, mechanism of action and clinical applications. We aim to explore the potential benefits of PRP on endometrial receptivity and regeneration, embryo implantation and ovarian function.PRP is an autologous plasma containing platelets prepared from fresh whole blood drawn from a peripheral vein. Through processing, it can be prepared to contain supraphysiological levels of platelets at three to five times greater than the level of normal plasma. Platelets are produced by megakaryocyte cells within the bone marrow. They are anucleate and have the smallest density amongst all blood cells with a diameter of 2 μL. Their physiologic count ranges from 150,000 to 400,000 platelets per μL. Given their small density, centrifugation methods result in platelets settling at the top of an aggregate, which allows for efficient extraction and subsequent clinical use.PRP contains alpha granules storing cytokines and growth factors, which are key to tissue regeneration. Growth factors within the alpha granules include vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), connective tissue growth factor (CTGF) and fibroblast growth factor (FGF). These growth factors regulate cellular migration, differentiation and proliferation through autocrine and paracrine effects. The alpha granules containing growth factors are released within ten minutes of platelet activation at the site of injury or inflammation, resulting in a net flow of neutrophils and macrophages, which leads to angiogenesis and re-epithelialisation. Specifically within the human endometrial model, the release of PDGF has proven to be key to endometrial progenitor cell activity. PDGF isoforms have been demonstrated to significantly improve endometrial stromal cell proliferation and contractility.The outer membrane of platelets consists of a phospholipid bilayer which provides the structural foundation of the platelet cell membrane. Phospholipids within the serum have been demonstrated to negatively correlate with the level of phospholipid within the follicular fluid within the ovarian follicles during controlled ovarian stimulation cycles in patients undergoing IVF. This has been hypothesised to result from the increased consumption of platelets secondary to increased membranogenesis taking place during follicular growth. Therefore, an increased serum level of platelets through the addition of PRP, resulting in an increased level of serum phospholipid, may benefit follicular growth and thus improved oocyte during IVF cycles. To add to this, Fayezi and colleagues discovered that the amounts of phospholipid and the

phospholipid/apoA-I ratio in follicular fluid were associated negatively with the percentage of fertilised oocytes.

Types of PRP

The growth factors secreted by platelets which are available to tissues have been shown to be directly proportional to the platelet concentration. Bone and enhanced soft-tissue healing have been proven to occur at platelet concentrations of 1,000,000 plate-lets/μL within a 5mL volume of plasma; thus, this is often used as a working definition of therapeutic PRP. In the presence of varying concentrations of platelets within a platelet gel, human endothelial cells have displayed induced proliferation, motility and enhanced invasiveness in the pattern of a bell-shaped distribution, whereby higher concentrations have resulted in a reversal of the processes. The optimal concentration for platelet stimulation and proliferation was reported to be 1.25 × 106 and for angiogenesis, 1.5 × 106 platelets/mL.

Endometritis

Chronic endometritis is defined as persistent inflammation of the endometrial mucosa caused by bacterial pathogens. Diagnosis of chronic endometritis is made through sampling of the endometrium at hysteroscopy and the presence of plasma cells within the endometrial stroma on histological analysis. The level of proinflammatory cytokines interleukin-6, interleukin-1β and tumour necrosis factor α are increased in women with chronic endometritis, which may affect cell migration and proliferation. It has been associated with repeat implantation failure and recurrent miscarriage. Current treatment for chronic endometritis rests largely on oral antibiotics. However, although antibiotic treatment has been shown to improve the implantation and clinical pregnancy rates, those with ongoing chronic endometritis may continue to experience fertility issues compared to women successfully treated. Autologous PRP represents a novel treatment approach for chronic endometritis. One recent case study demonstrated a successful live birth following intrauterine infusion of PRP in a patient with a history of chronic endometritis and six failed embryo transfers. Microbiological and scanning electron microscopy analysis during a subsequent menstrual cycle following an intrauterine PRP infusion revealed no evidence of chronic endometritis. In the bovine model in vitro, PRP has been shown to downregulate the expression of proinflammatory cytokines IL-1β, IL-8 and iNOS. Additionally, PRP has been shown to upregulate the expression of ER-α, ER-β and PR genes, which are vital for pregnancy. Furthermore, in the equine model in vivo, intrauterine infusion of PRP displayed a reduction in the intrauterine inflammatory response as measured by the percentage of neutrophils in uterine cytology and the nitric oxide concentration within the uterine fluid. In clinical settings such as endometritis where endometrial regeneration is impaired, PRP has been shown to increase the expression of matrix metalloproteinases (MMP) MMP3, MMP7 and MMP26 within the endometrial stromal fibroblasts and mesenchymal stem cells.

MMPs have been shown to be vital for successful wound healing—an important step in recovery from endometritis. As provisional, albeit limited, outcomes from animal studies appear promising, there is a further need for well-designed studies in humans.

Refractory Endometrium

In each menstrual cycle, there exists a period of four to five 'opportune' days for the human embryo to implant when the endometrium remains receptive. The endometrial microenvironment determines endometrial receptivity. This is governed by changes to the uterine luminal and glandular cells, decidualisation of the endometrial stroma and increased leukocyte activity. Sonographic markers, such as endometrial thickness and uterine artery blood flow, have proven to have a high negative predictive value and a low positive predictive value for a receptive endometrium. Nevertheless, studies have demonstrated an endometrial thickness of 7 mm and above to be optimal for implantation and to result in improved clinical pregnancy rates. An endometrial thickness <7 mm, which is unresponsive to hormonal therapy, has been defined as a refractory endometrium and is associated with suboptimal fertility rates. A severe deficiency in angiogenic-related markers has been demonstrated in patients with a refractory endometrium, specifically leukemia inhibitory factor, vascular endothelial growth factor (VEGF) and β 3 integrin.Thus, given the proangiogenic potential of autologous PRP, its application in the setting of subfertility secondary to refractory endometrium presents an exciting opportunity for patients who are unresponsive to conventional treatment methods.

RESULT

Intrauterine infusion of PRP represents a novel strategy for the treatment of the endometrium in its ability to promote biological processes for endometrial regeneration. Data on the benefit of PRP within the reproductive setting still remain scarce. However, the theoretical benefits and positive preliminary findings suggest great potential in other indications within reproductive medicine . PRP offers an exciting opportunity to enhance ovarian reserve in the context of POI, poor ovarian response and potentially in the context of ovarian cortex transplantation. PRP remains a relatively low-cost therapeutic intervention given that it can be prepared at the patient's bedside with minimal equipment and can be administered in the office setting quickly and effectively. The use of autologous blood to produce PRP has eliminated the risk of immunological reactions and presents a widespread opportunity for its use in the field of gynaecology. However, differences in PRP preparation can produce a heterogenous injectate, which may vary in quality, purity and quantity. One such example is the variation of centrifugation speed and duration where higher speeds can result in a greater concentration of platelets but may also result in more contaminants or disruption in the platelet integrity. Future studies should define the cellular content of PRP, including the white and red cell counts, the concentration factor and the platelet yield—a valuable step in producing a robust product for clinical

application. Moreover, further studies need to evaluate the optimal methods and routes of administration. Despite the clear potential of the role of PRP in reproductive medicine, well-designed, randomised, prospective studies are essential before usage can be recommended. One particularly valuable area of focus is the effect of PRP in the activation and growth of ovarian follicles in addition to the potential for reversal of ovarian ageing.

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