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Platelet rich plasma as a minimally invasive approach to uterine prolapse

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ABSTRACT

Pelvic organ prolapse (POP) is a major health problem that affects many women with potentially severe physical and psychological impact as well as impact on their daily activities, and quality of life. Several surgical techniques have been proposed for the treatment of POP. The FDA has published documents that refer to concerns about the use of synthetic meshes for the treatment of prolapse, in view of the severe complications that may occur. These led to hesitancy in use of these meshes and partial increase in use of other biological grafts such as allografts and xenografts. Although there seems to be an increasing tendency to use grafts in pelvic floor reconstructive procedures due to lower risks of erosion than synthetic meshes, there are inconclusive data to support the routine use of biological grafts in pelvic organ prolapse treatment.

In light of these observations new strategies are needed for the treatment of prolapse. Platelet rich plasma (PRP) is extremely rich in growth factors and cytokines, which regulate tissue reconstruction and has been previously used in orthopaedics and plastic surgery. To date, however, it has never been used in urogynaecology and there is no evidence to support or oppose its use in women who suffer from POP, due to uterine ligament defects. PRP is a relatively inexpensive biological material and easily produced directly from patients' blood and is, thus, superior to synthetic materials in terms of potential adverse effects such as foreign body reaction. In the present article we summarize the existing evidence, which supports the conduct of animal experimental and clinical studies to elucidate the potential role of PRP in treating POP by restoring the anatomy and function of ligament support.

Introduction

Prolapse is a common condition that is the result of progressive weakening of the supportive structures of the uterus. It is estimated that approximately thirty per cent of women over the age of 50 have uterine prolapse [1]. In the U.S. nearly 200,000 women undergo surgery for prolapse annually, with a cost that exceeds one billion dollars [2]. Every woman has an 11.1% lifetime risk of undergoing surgery for uterine prolapse, until the age of 80 years [3]. Scientists estimate that in the next 30 years there will be an increase by 45% in women who seek treatment for prolapse.

The dysfunction of ligaments that support the uterus is multifactorial. Specifically, current evidence suggests that the duration of labour, the neonatal birthweight and parity are independent factors that increase the risk of uterine prolapse [4,5]. Chronically increased intra-abdominal pressure is also triggered by conditions such as obesity, chronic bronchitis, bronchiectasis, asthma and constipation and may affect the integrity of the pelvic floor. Besides, the transition to menopause alone is associated with urogenital atrophy, which results in ligament atrophy, relaxation of the pelvic floor and uterine prolapse, while it appears that the incidence of prolapse increases with age [6].

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Prolapse is a condition that affects quality of life, with implications in psychology, self-esteem, sexual and social life. As the average life expectancy of women increases, more and more women will seek medical assistance for prolapse repair. In this context, it seems that the introduction of new therapeutic modalities in the field becomes urgent.

Various surgical techniques have been used for the treatment of prolapse, with recurrence rates up to 30% [3]. Vaginal meshes have been widely used in recent years, but due to the high rates of complications [7], the FDA published reports informing patients and physicians about the complications that accompany their use and underlined the importance of investigating innovative methods for the treatment of prolapse [8].

The hypothesis

The uterosacral (USL) and cardinal ligaments (CL) provide support to the uterus and pelvic organs, and the round ligaments (RL) maintain their position in the pelvis. In women with pelvic organ prolapse (POP), the connective tissue, smooth muscle, vasculature, and innervation of the pelvic support structures are altered [9]. Both laparoscopic and vaginal procedures that involve USL suspension have been developed and widely used, but complications have been reported, usually secondary to their proximity to the ureter, vessels, rectum and sacral nerve roots [10].

An alternative approach for the management of prolapse could be the implementation of an injectable agent, which could primarily enforce the ligaments. This regenerative principle with autologous substances could potentially limit the side effects of synthetic materials. Interestingly, fibrin adhesives and PRP have been used in various fields in the past 30 years [11], but the substances have not been used for treatment of urogynaecological problems.

Research projects investigating the regenerative abilities of plasma offer options of using an autologous substance with adhesive, healing, and haemostatic properties at low cost [12–14].

In this context, injecting an autologous adhesive factor to the ligaments might have promising, results in the treatment of POP, by enforcing the ligaments and restoring normal anatomy, with minimal, if any, complications.

Confirmation of the above beneficial effects of PRP will provide the necessary knowledge for the design and conduct of clinical studies aimed for the reinforcement of USL. The purpose of this article is to summarize available evidence in the field and construct a robust hypothesis, which could potentially drive the research agenda towards conducting experimental and clinical studies in this field.

Current evidence

Uterosacral ligament

The USL plays an important role in pelvic organ support, and is used as corrective support in pelvic reconstructive surgery [15,16]. In a 15-month follow up women after modified high uterosacral ligament suspension (HUSLS) women report excellent objective, subjective and sexual function [17], and a 5 year follow up with only 8/42 women having recurrence of vault prolapse [18].

It was previously thought that the USL consists only of connective tissue, but a study that focused on the proximal to the cervix part of the USL showed that it also consists from smooth muscle cells [19]. Another study by Ramanah et al. suggested that USL is a ligamentous complex, which encompasses the inferior hypogastric plexus, the hypogastric nerves and vascular elements, which are surrounded by a fine connective sheath [19].

A previous study suggested that patients with POP have an intrinsic deficit of a gene responsible for the development of the USL [20]. In the USL of women with POP, there is higher expression of collagen III and matrix metalloproteinase 2 (MMP-2) [21,22]. It is known that collagen III plays role in tissue elasticity and extensibility, therefore can be responsible for the tissue laxity in these patients.

Biomechanics

Data concerning the biomechanical properties of USL, especially from human live tissue are scarce in the literature. Martins et al. observed that the maximum stress value of prolapsed vaginal tissue was significantly higher compared to values from previous studies (3-8 MPa vs 0.27–0.42 MPa) [23–25]. In another study on fresh female cavaders, researchers showed that the USL is more rigid than the round and broad ligaments [26]. Studies on USL in an experimental animal model showed that hormone replacement (using conjugated equine estrogens plus medroxyprogesterone acetate (CEE/MPA), or ethinyl estradiol plus norethindrone acetate (EE/NA)) increases the tensile stiffness in USL [27].

PRP and ligament healing

After tissue injury is established, platelets are the first that arrive at site and trigger the early inflammatory phase of the healing process [28]. They help with homeostasis, through cell membrane adherence, aggregation, clot formation, and release of substances that promote tissue repair and that affect the reactivity of blood vessels and blood cell types involved in angiogenesis and inflammation [29,30]. PRP contains several growth factors (GFs) that contribute to the pathophysiology of ligament reconstruction including VEGF, IGF-I, PDGF, HGF, TGF-β and FGF [31–34]. Besides that, platelets also contain antibacterial and fungicidal proteins, metalloproteinases, coagulation factors, and membrane glycoproteins, which may affect the inflammation process by inducing the synthesis of other integrins, interleukins, and chemokines [35]. Although many GFs are associated with wound healing, PDGF and TGF-β 1 appear to be two of the more integral modulators [36]. More specifically, TGF-β seems to be active in every stage of tendon healing as it stimulates cell migration, regulates the production of proteinases and collagen. After tissue injury, the expression of TGF-β mRNA rapidly increases and seems to suppress matrix metalloproteinases production and to increase the synthesis of extracellular matrix [37]. Separate analyses of GFs in PRP have shown significant increases in PDGF, VEGF, TGF-β1, and EGF, compared with their concentrations in whole blood [38–42]. However, there are conflicting results with regard to IGF-I [38–41,43].

Platelet derived growth factor is essential in early wound healing (during the acid tide) [44,45]. Several studies support that a single injection of PDGF significantly enhances tendon repair [46–48].

Insulin-like growth factor-I (IGF-I) is also important for wound healing and tissue repair. It has been proposed that systemic administration of IGF-I with or without growth hormone enhances healing of collagenous tissue, by increasing maximum force, ultimate stress, and elasticity in biomechanical tests [49].

Animal models

There is little information regarding the biomechanics of pelvic floor on humans, because of the difficultly of performing controlled, longitudinal studies in human patients along with ethical issues. Animal models, on the other hand, afford the opportunity to test hypotheses more rigorously in a controlled environment.