PHARMACOTHERAPY OF ASHERMAN SYNDROME

An adjuvant treatment (hormonal, antibiotics) used with surgical therapy in order to promote regeneration of endometrium and to prevent infections.

About Pharmacotherapy of Asherman syndrome

Pharmacotherapy of Asherman's syndrome (AS, intrauterine adhesions, IUA) is used as an adjuvant (add-on) therapy to maximize effectiveness of surgical therapy. Most of the patients have a sclerotic (stiffening) or destroyed endometrium (an inner epithelial layer of uterus) after surgical removal of adhesions and they need to promote endometrium regeneration and a means of continued separation of the uterine cavity walls to prevent the reformation of adhesions.

In a setting of low-circulating estrogen levels in the postpartum period the endometrium fails to regenerate following damage to the basalis layer, which has been postulated to harbor endometrial stem/progenitor cells responsible for its remarkable regenerative capacity. Infection and inflammation may contribute to the inability of traumatized endometrium to regenerate and are important processes involved in the deposition of fibrotic tissue (formation of excess fibrous connective tissue in an organ or tissue).

Failure of the endometrial functional layer to regenerate in Asherman's syndrome results from deep trauma involving the underlying uterine muscular layer (myometrium) with concomitant loss of basalis endometrium and its population of adult stem cells (undifferentiated cells). Indeed, dense fibrotic areas of the uterine cavity show no endometrial lining and in regions where endometrium is present, it is thin and atrophic with inactive glands and little stroma (the connective, functionally supportive framework of a biological cell,
tissue, or organ). Patients with fibrotic lesions around the cervix or with loss of functional endometrium present with menstrual abnormalities, particularly amenorrhea, while women with dense adhesions obliterating the tubal ostia are infertile. Repeated pregnancy loss is often due to partial blockages of the ostia (small opening) and uterine cavity with fibrotic adhesions and a poorly vascularised and diminished endometrium.

**Hormonal therapy**

In order to restore basal endometrium and rebuild the normal endometrial layer inside the uterine cavity, hormonal treatment is proposed to promote endometrial regeneration and healing after surgery.

Adjunctive hormonal therapy for uterine adhesions consists of high dose estrogen for 30-60 days, depending on the extent of uterine cavity occlusion and the type of adhesions found. The more extensive and old the adhesions, more prolonged the hormonal treatment must be. In the last 10 days of this artificial cycle, oral progestin is given to induce withdrawal bleeding.

The use of sildenafil citrate intravaginally was documented as possible pharmacological treatment to restore endometrial thickness. In a prospective observational study, sildenafil citrate improved endometrial thickness in 92% of cases who presented thin endometrium (endometrial thickness <8 mm). Other encouraging results came from IVF where the combination of oestradiol and sildenafil citrate improved endometrial blood flow and endometrial thickness in 4 women with prior failed assisted reproductive cycles due to poor endometrial response.

**Prophylactic antibiotics**

Prophylactic antibiotics are used to prevent infections in surgical procedures. They are frequently used in AS patients in view of a traumatized endometrium and the extensive surgical manipulation typically required. Antibiotic prophylaxis is referred to the prevention of infection complications using antibiotics and is necessary in the presence of mechanical barriers (intrauterine device, Foley catheter, saline-filled Cook Medical Balloon Uterine Stent) to reduce the risk of possible infections.

Antibiotic choice is most often in the form of cephalosporins (cefazolin 1g) intravenously 30 minutes before surgery, followed by cephalexin 500mg four times daily by mouth for a week, should an intrauterine splint be placed.

Alternatively, doxycycline 100mg twice daily for the duration of the stent or balloon placement may be used post-operatively. In cases of tuberculous endometritis, i.e. an inflammation of the endometrium due to infection by
Mycobacterium tuberculosis, adequate antibiotic treatment must be completed prior to proceeding with surgical intervention.

**Success or failure factors**

Many different AS treatments have been suggested and there is no shared consensus about the time of the administration of hormonal therapy (preoperative and/or postoperative) and the type of regimen (estradiol or combined estradiol and progesterone). The general idea is to encourage fast growth of any residual endometrium immediately after surgery with the dual purpose of preventing new scar formation and restoring a normal uterine environment. It is supposed that this goal can only be achieved with supraphysiological (greater than normally present in the body) hormonal levels.

**Complications**

A common pharmacological method for preventing reformation of adhesions is sequential hormonal therapy with estrogen followed by a progestin to stimulate endometrial growth and prevent opposing walls from fusing together. However, there have been no randomized controlled trials (RCTs) comparing post-surgical adhesion reformation with and without hormonal treatment and the ideal dosing regimen or length of estrogen therapy is not known. The absence of prospective RCTs comparing treatment methods makes it difficult to recommend optimal treatment protocols. Furthermore, diagnostic severity and outcomes are assessed according to different criteria (e.g. menstrual pattern, adhesion reformation rate, conception rate, live birth rate). Clearly, more comparable studies are needed in which reproductive outcome can be analysed systematically.

**Prognosis**

Upon completion of the hormonal treatment and once withdrawal bleeding has ceased, hysterosalpingography (HSG) and/or office hysteroscopy is performed to assess the results of the operation and decide on further therapy or initiation of attempts at conception. However, estrogen therapy needs to be combined with ancillary treatment to obtain maximal outcomes, in particular in patients with moderate to severe IUA.
Mild to moderate adhesions can usually be treated with success. Extensive obliteration of the uterine cavity or fallopian tube openings (ostia) and deep endometrial or myometrial trauma may require several surgical interventions and/or hormone therapy or even be uncorrectable. If the uterine cavity is adhesion free but the ostia remain obliterated, in vitro fertilization (IVF) remains an option. If the uterus has been irreparably damaged, surrogacy or adoption may be the only options.

Find more about related issues

Diagnoses

Asherman’s syndrome
A medical condition, where the walls of the uterus stick to one another due to bands of scar tissue.
Learn more at: www.fertilitypedia.org/therapy/diag/asherman-s-syndrome

Sources

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