Dydrogesterone Sustained Release in Different Gynecology Indications

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Background and Objective of the Survey

Dydrogesterone, a synthetic analog of natural progesterone, is extensively used in gynecology for its effectiveness and safety across various indications. Its sustained-release formulation offers consistent hormone levels, enhancing its therapeutic benefits and patient compliance. In assisted reproductive technology (ART), dydrogesterone supports the luteal phase by maintaining adequate progesterone levels crucial for embryo implantation and pregnancy maintenance, with studies confirming its efficacy comparable to other forms of progesterone. For endometriosis, dydrogesterone alleviates symptoms like pelvic pain and dysmenorrhea by counteracting estrogen's proliferative effects on endometrial tissue, without the androgenic side effects common with other progestins. It is also effective in managing menstrual disorders, such as irregular cycles and heavy bleeding, by stabilizing progesterone levels, thereby regulating the menstrual cycle and reducing excessive bleeding. Additionally, dydrogesterone is beneficial for premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), as it mitigates mood swings and irritability, significantly improving the quality of life. In cases of secondary amenorrhea, dydrogesterone helps restore regular menstruation by mimicking the natural progesterone peak. With minimal side effects and no significant androgenic, estrogenic, or glucocorticoid activity, dydrogesterone sustained-release is suitable for long-term use, making it a preferred choice for managing various chronic gynecological conditions effectively and safely.

The objective of the survey is:

To evaluate the role of dydrogesterone sustained release in different gynecology indications

Methodology of the Survey

A survey was conducted to evaluate the role of dydrogesterone sustained release in different gynecology indications. A total of 100 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Increased Estradiol Production and Progesterone Resistance in Endometriosis
- Angiogenesis and Vasculogenesis in Endometriosis
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- Is oral administration preferred by the physician over vaginal administration?
- Is oral dydrogesterone safe and well tolerated by the patient?
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- Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis
- Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Endometriosis is a gynaecological condition characterized by the growth of endometrium-like tissues within and outside of the pelvic cavity. Almost 50% of adolescents with intractable dysmenorrhea or pelvic pain and 4% of women undergoing tubal ligation are diagnosed with endometriosis. It has been well established that many women have a delay in diagnosis of endometriosis despite having significant dysmenorrhea and the other related symptomatology starting at a young age. An important factor that contributes to the diagnostic delay is the lack of noninvasive methods for detecting endometriosis. Although endometriosis can be asymptomatic, chronic pelvic pains that are aggravated during the period of menstruation, as well as subfertility, prompt women to seek help. Based on scientific evidence that endometriosis is dependent on estrogen for growth, current pharmaceutical interventions focus on estrogen inhibition by means of either contraceptive usage or the use of drugs that inhibit ovarian secretion of estrogen. These interventions have been effective in managing pain and diminishing endometriotic lesions to some extent. However, the high rate of recurrence of endometriosis after pharmaceutical treatment or surgical ablation of the lesions drives researchers to seek other therapeutics that can effectively treat endometriosis, in terms of both symptom resolution and cure from the disease.

Increased Estradiol Production and Progesterone Resistance in Endometriosis[1]

The most widely accepted theory of retrograde menstruation postulates the pathogenesis of endometriosis to begin with the invasion and proliferation of menstrual effluents in the PF. From there, studies suggest that aberrant immune mechanisms and responses to ovarian steroids found in only a subset of women would lead to the development of endometriotic foci in the peritoneal membrane. Interestingly, in a baboon model of endometriosis, menstrual phase endometrium injected intraperitoneally displayed enhanced adherence to the peritoneal membrane compared to the luteal phase endometrium. This suggests that menstrual phase endometrial fragments express selective factors that are yet to be characterized, allowing for subsequent implantation in aberrant locations. Under normal physiological circumstances, human endometrium is under cyclical regulation by estrogen and progesterone, with the

superficial, functionalis endometrial layer undergoing proliferation, differentiation, and shedding if implantation does not occur. However, the cellular components of the ectopic endometriotic lesions respond to ovarian steroids in a different manner when compared to normal eutopic endometrium. Macroscopically apparent structural malformation of the endometrial epithelium of women with endometriosis lends clues to increased incidence of infertility in women with endometriosis and perhaps offers an explanation as to why only a subset of women develop endometriosis.

Estradiol (E2), a biologically active form of estrogen, plays a critical role in the reconstruction of the endometrium after menstruation. Proliferation of endometrial cells and reestablishment of vasculature of the functionalis endometrial layer are driven by the actions of E2 interacting with its nuclear receptors, ER-α and ER-β. Endometrial E2 arises mainly from the ovaries and also from extraovarian tissues such as the adrenal gland and adipocytes which arrive at tissue via circulation. Aromatase P450 (aromP450) is an enzyme that catalyzes the conversion of ovarian androstenedione into estrone. From there, 17β-hydroxysteroid dehydrogenase type 1 (17β-HSDT1) further catalyzes the conversion of estrone into E2. Prostaglandin E_2 (PGE_2) is synthesized from arachidonic acid by the activity of rate limiting enzyme cyclooxygenase-2 (COX-2). PGE_2 induces aromP450 production via the cAMP cell signaling cascade in the ectopic endometriotic stromal cells in a dose dependent manner. In the endometrium of healthy women, the activity of aromP450 is undetectable. However, both endometrium and the ectopic endometriotic lesion of women with endometriosis express this enzyme in significantly high amounts, allowing local production of E2. The ability of the lesion to produce E2 *de novo*, in addition to manufacturing the enzymes required for its production, may facilitate the implantation of endometrial fragments in the peritoneal cavity.

Due to widely implicated roles of E2 in the pathogenesis of endometriosis, a variety of pharmaceutical interventions targeting the inhibition of estrogen production are administered to women with endometriosis, but with mixed success. Most of all, the symptoms of pain may be managed while on treatment; however, pain often reappears promptly with the discontinuation of the treatment. Around half of patients using progestins reported recurrence of pelvic pain after treatment cessatio. Furthermore, long term usage may be deterred by the undesirable side effects consisting of breakthrough bleeding, weight gain, and bone mineral density loss from treatments including GnRH (gonadotropin releasing hormone) agonists and depot progestins (medroxyprogesterone acetate). A third-line treatment, aromatase inhibitors (AI), can be used in conjunction with other types of inhibitors targeted towards estrogen

suppression. However, with some women showing development of resistance to current hormonal therapies, further investigations are needed targeting improvements to current therapeutic interventions.

In addition to the enhanced local production of E2 in both eutopic endometrium and ectopic endometriotic lesions in women with endometriosis, resistance to progesterone contributes to the pathogenesis of endometriosis. Progesterone, which is mainly produced during the secretory phase of the menstrual cycle, inhibits the action of estrogen and prepares the endometrium for implantation. The process of decidualization, whereby the endometrial epithelial and stromal cells begin to differentiate, is facilitated by progesterone. Similar to estrogen, progesterone interacts with two receptor isoforms, PR-A and PR-B, each with distinct functions. Gene ablation of PR-A in mice leads to uterine and ovarian abnormalities, while ablation of PR-B does not affect uterine or ovarian function. Furthermore, both PR-A and PR-B transcripts are made from a single gene with a shorter PR-A transcript than PR-B, which results in the ability of PR-A to become transrepressor of PR-B and other nuclear receptor. Interestingly, endometriotic lesions lack PR-B, and the transrepressor PR-A is barely expressed. This is evidence that progesterone resistance in endometriosis may lie at the molecular level. Decreased responsiveness to progesterone is further substantiated by Bulun et al.which showed decreased responsiveness of endometriotic stromal cells to progesterone by measuring the levels of prolactin mRNA, which is normally induced by progesterone. Treatment of endometriotic stromal cells with medroxyprogesterone acetate (MPA), a synthetic variant of progesterone, resulted in much lower levels of prolactin mRNA compared to eutopic endometrial stromal cells. Such resistance to progesterone treatment ensures increased local concentration of E2 due to the inability of progesterone to activate 17β-hydroxysteroid dehydrogenase type 2 (17β-HSDT2), which catalyzes deactivation of E2 to estrone. Normally, progesterone mediated factors from endometrial stromal cells induce expression of 17β-HSDT2 from the endometrial epithelial cells in a paracrine manner. This mechanism was suppressed in Ishikawa endometrial epithelial cell line cultured with conditioned medium from the ectopic endometriotic stromal cells. Thus, studies show that, unlike eutopic endometrium, progesterone resistance is prevalent in the ectopic endometriotic lesions, which may contribute to the increased concentration of local E2 that may further promote the growth of the endometriotic lesions.

Angiogenesis and Vasculogenesis in Endometriosis[1]

Angiogenesis refers to a complex process of new blood vessel formation from previously existing vessels. This process plays a fundamental role in reproduction, development, and wound repair. In adults, endothelial cell proliferation is a highly regulated process established by a balance between angiogenic and angiostatic factors that are activated when necessary and then inhibited completely when the need is eliminated. Cases of increased rate of endothelial cell proliferation are often linked with cancer and tumor development which are known to be dependent on angiogenesis for growth and metastasis. Vasculogenesis, on the other hand, refers to a process of *de novo* formation of blood vessels arising from migration, proliferation, and incorporation of angioblasts or endothelial progenitor cells (EPCs) from the bone marrow, usually occurring during embryogenesis. The survival of endometriotic implants on the peritoneal membrane within the peritoneal cavity relies upon the establishment of blood supply for the provision of oxygen and nutrients to the developing lesions. Endometriotic lesions are densely vascularized, fueling the notion that angiogenesis and/or vasculogenesis may be involved. Analogous to the process of vascularization of tumors, endometriosis may utilize mechanisms of both angiogenesis and vasculogenesis to establish its own vascular network to sustain its survival.

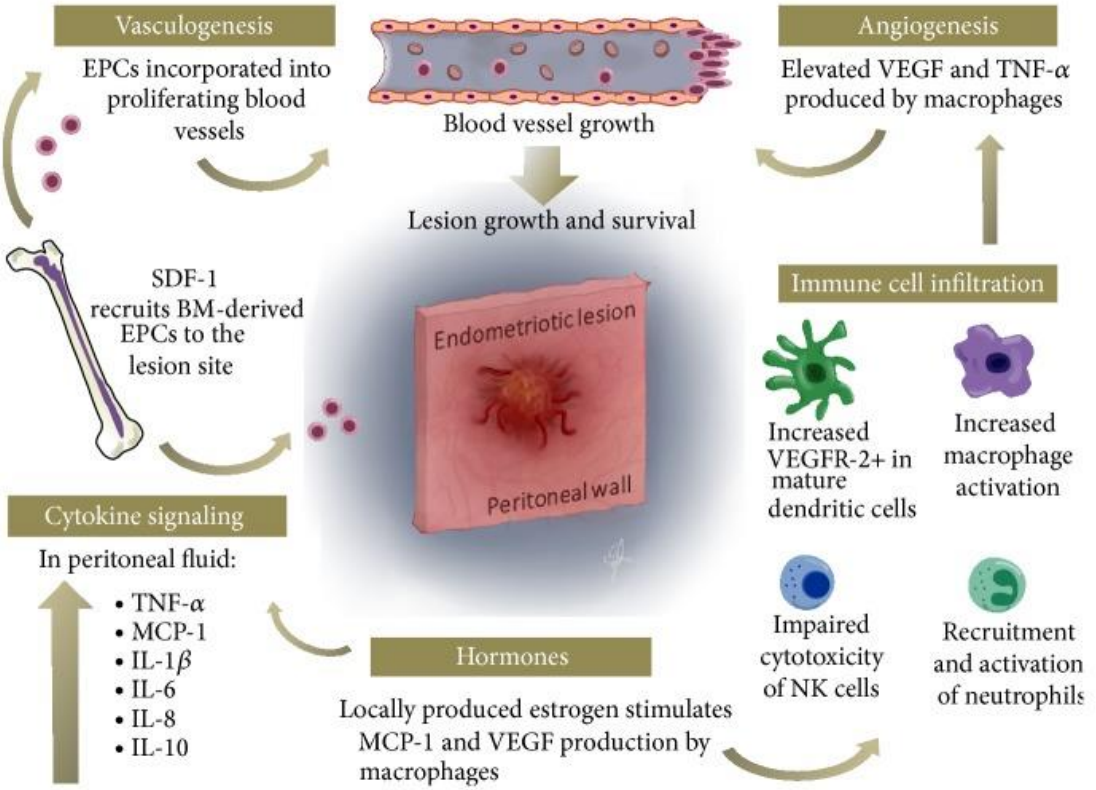

Figure 1. An overview of immune cells and mediators involved in the promotion of neovascularization and endometriotic lesion growth on the peritoneal membrane.

In women with endometriosis, high levels of angiogenic factors and inflammatory cytokines are found in the peritoneal fluid (PF). Development of blood vessels of the lesions depends on two processes: vasculogenesis and angiogenesis. Vasculogenesis is mediated by recruitment and incorporation of the bone marrow- (BM-) derived endothelial progenitor cells (EPCs) to proliferating blood vessels in the endometriotic lesions. Recruitment of BM-derived EPCs is facilitated by stromal cell-derived factor- (SDF-) 1. Vascular endothelial growth factor (VEGF) and other angiogenic factors including interleukin- (IL-) 6, IL-8, and tumor necrosis factor- (TNF-) α mediate the process of angiogenesis by activating angiogenic switch of endothelial cells. Local production of estradiol by the lesion maintains the expression of VEGF and promotes the production of VEGF and monocyte chemoattractant protein- (MCP-) 1 by the macrophages. In women with endometriosis, natural killer (NK) cell cytotoxicity is diminished, which may be due to increased expression of IL-10 in the PF. Immature dendritic cells (DCs) express VEGFR-2 on the surface and thus are theorized to play a role in angiogenesis by interacting with VEGF. The integrated role of immune cells and mediators is a complicated process and requires further studies to piece together the details available to fully appreciate their role in the pathogenesis of endometriosis.

The endometrial fragments sloughed off from the endometrium of the uterus may harbour innate angiogenic potential due to the following characteristics. The human endometrium, composed of functionalis and basalis layer, is a unique organ that undergoes proliferation, differentiation, and regeneration with each menstrual cycle under the regulation of ovarian steroid hormones, estrogens, and progesterone. Along with the growth of the endometrium, the vasculature of the endometrium will experience proliferation and regeneration each cycle under the influence of the ovarian steroids, specifically E2. Shifren et al. measured increased expression of vascular endothelial growth factor (VEGF) mRNA in the functionalis layer of the endometrium through proliferative and secretory phase of the menstrual cycle, indicating angiogenesis is in play. In the same study, E2 was responsible for the stimulation of VEGF expression from isolated human endometrial cells, as administration of E2 led to an increase in VEGF mRNA expression compared to the endometrial cells without E2 stimulus. Endometriosis is theorized to arise from implantation of endometrial fragments in the

peritoneal cavity. With healthy endometrium showing innate angiogenic potential under the regulation of E2, it is evident that aberrantly regulated VEGF expression and E2 level may facilitate the neovascularization of endometriotic lesions that fuels its establishment in aberrant locations.

Indeed, VEGF plays a crucial role in facilitating the process of angiogenesis in endometriosis. It is a vasoactive substance involved in a variety of normal physiological processes including wound healing and revascularization of endometrium by mediating endothelial cell proliferation and migration. In tumorigenesis, VEGF concentration is typically correlated with increased vascularity in various types of tissue associated tumors (reviewed in). In normal endometrium, VEGF mRNA and protein expression can be driven by hypoxia. Not surprisingly, the PF of women with advanced stages of endometriosis contains higher concentrations of VEGF compared to women with mild endometriosis or healthy patients. In addition, this elevated level of VEGF concentration in both PF and serum in endometriosis patients is positively associated with increased proliferative activity and microvessel density of the endometriotic lesions, indicating its involvement in the development of blood vessels. Various sources of VEGF have been indicated, including endometriotic lesions and PF macrophages in endometriosis, which increase VEGF expression when treated with ovarian steroids such as E2 and progesterone, solidifying the notion that VEGF is involved in angiogenesis associated with endometriotic lesions. Other angiogenic cytokines including IL-1β, IL-6, and IL-8 will be further discussed in other sections of this review.

Vasculogenesis was generally accepted to be only prevalent during embryogenesis and that postnatal neovascularization of tissues occurred solely through angiogenesis. The paradigm has shifted with the discovery of CD34+ and Flk1+ circulating endothelial progenitor cells (EPCs) in adult peripheral blood with phenotypic characteristics of endothelial cells *in vitro*. This study in addition to the results published two years later definitively showed the presence and active involvement of bone marrow-derived EPCs in neovascularization of tissues including the endometrium. Becker et al. (2011) confirmed the incorporation of the bone marrow-derived EPCs into the vasculature of the endometriotic lesion by transplanting GFP+ bone marrow-derived cells into mice with surgically induced endometriosis. Laschke et al. (2011) further visualized the recruitment of the bone marrow-derived EPCs into the site of the endometriotic lesion development by elucidating the involvement of stromal cell-derived factor-1 (SDF-1) in the mobilization of bone marrow-derived EPCs into the lesions. To confirm the chemotactic ability of SDF-1, Laschke et al. (2011) showed that, by antagonizing SDF-1

receptor—CXCR-4—with AMD3100, the number of recruited EPCs and the subsequent vascularization of endometriotic lesions significantly decreased. These results were confirmed by another study that demonstrated SDF-1 to be a chemokine capable of trafficking hematopoietic stem cells and EPCs whereby its focal concentration leads to increased vascularity of that region. Our group recently demonstrated that blocking of SDF-1 in an alymphoid mouse model of endometriosis resulted in a decrease in endometriotic lesion vascularization and growth. Collectively, these studies confirm that vasculogenesis in addition to angiogenesis is taking place, as demonstrated by the capacity of the lesion to mobilize and incorporate EPCs from the bone marrow into the vasculature of the lesions.

Furthermore, different types of immune cells are involved in the process of angiogenesis by producing proinflammatory and angiogenic cytokines and by increasing their concentration within the PF that bathes the endometriotic lesions (reviewed i). Lin et al. elucidated the importance of immune cells by demonstrating that angiogenesis of endometriotic lesions occurs after infiltration of VEGF secreting neutrophils and macrophages into the lesions as well as within the peritoneal cavity, indicating the essential role played by infiltrating leukocytes in the mouse model of endometriosis. In addition, dendritic cells (DCs) have shown their involvement in angiogenesis. A study conducted by Fainaru et al. supports this argument by demonstrating increased perivascular distribution of VEGFR-2 expressing immature DCs in the endometriotic lesions with the ability to induce the migration of endothelial cells *in vitro.* The presence of DCs in the peritoneal cavity resulted in endometriotic lesion growth and vascularization of endometriotic lesion in this mouse model of endometriosis. In another study utilizing transgenic mouse model with conditional DC depletion (diphtheria toxin-treated B6.FVB-Itgax-hDTR-EGFP^{tg}), researchers found that endometriosis lesions in DC depleted mice were significantly greater in size compared to control and showed decreased expression of CD69, a marker for T and natural killer cell activation. Based on these findings, it is apparent that DCs directly participate and regulate angiogenic process as well as subset of immune activation during endometriosis lesion development.

Human endometrium has the unique ability to undergo cyclical proliferation and regeneration of the functionalis layer after physiological shedding of the endometrium. Thus, endometrial fragments exuded from the uterus will retain angiogenic capabilities in the peritoneal cavity. Postnatal neovascularization was once thought to be only possible in limited circumstances. It is now apparent that, in endometriosis vascularization, both angiogenesis and vasculogenesis are taking place at the site of the lesion. Under the regulation of E2, which augments expression

of VEGF from the peritoneal macrophages, neovascularization of endometriotic lesion seems to mainly occur from the preexisting blood vessels of the peritoneal membrane under the process of angiogenesis. The complete elucidation of mechanisms underlying the process of angiogenesis remains complex due to other immune cells and mediators that are involved in neovascularization. In comparison, the process of vasculogenesis seems more concise, as demonstrated by studies that clearly showed the incorporation and recruitment of bone marrow-derived EPCs to the vasculature of endometriotic lesion. Indeed, neovascularization of the lesion utilizes both processes of angiogenesis and vasculogenesis. Knowing the mechanisms behind the establishment of vasculature will further aid in the development of therapies targeted towards lesion ablation, which may prove to be more beneficial compared to currently existing hormonal therapies used in treatment of endometriosis.

Immune Dysfunction and Endometriosis[1]

Although endometriosis is common among women of reproductive age, the incidence of endometriosis is small compared to the occurrence of the retrograde menstruation that is experienced by most women of the same category. One hypothesis that arises then is that the women that develop endometriosis compared to those that do not have a defective immune system that is unable to recognize and properly mount immune response to the endometrial fragments within the pelvic cavity. It is speculated that endometrial fragments themselves acquire the ability to evade the immune system as they enter the pelvic cavity. We cannot exclude the possibility that both the fragments and the immune system are aberrant in women with endometriosis. In this section, we summarize the potential implication of the innate (macrophages, neutrophils, DCs, and NK cells) and adaptive immune cells (T and B cells) in the pathogenesis of endometriosis.

The menstrual endometrial fragments induce inflammation within the peritoneal cavity. In response to the presence of these fragments, the sentinels of the immune system such as neutrophils and macrophages are among the first to be recruited to the area. Indeed, macrophage concentration and proportion are increased in the PF of women with endometriosis, and they are the primary contributors to the elevated proinflammatory and chemotactic cytokines found in the P. In addition to partaking in the growth of peritoneal implants, macrophages are a major source of angiogenic mediators including TNF-α and IL-8. Furthermore, macrophages are involved in the regulation of hypoxia-induced angiogenesis by

producing VEGF. Macrophage depleted Balb/C mice display endometriotic lesions that not only are smaller in weight and size compared to the control mice but also display reduced vascularization of the lesion, indicating that macrophages are involved in the process of growth and development of blood vessels. The same study, however, found that macrophage depletion does not prevent endometrial cells from implanting onto the peritoneal membrane, which suggests different mechanisms are involved in the process of implantation in the pathogenesis of endometriosis.

More recently, neutrophils have gained much attention and have been hypothesized to play an important role in the pathogenesis of endometriosis. Amongst most leukocytes implicated in inflammation, neutrophils have the shortest life span and contribute significantly to the resolution of inflammatory reaction. Neutrophils from disease-free women, when incubated with plasma or PF from women with endometriosis, displayed decreased rate of apoptosis compared to control women. This study clearly indicated a potential existence of antiapoptotic factors in the plasma and PF in women with endometriosis that is not as concentrated in women without the disease. IL-8 was one of the potential factors investigated given its well established role as a proinflammatory cytokine and a key factor involved in the chemotaxis of neutrophils during inflammation. However, treatment with anti-IL-8 antibody prior to adding PF or plasma from endometriosis patients did not have marked difference in apoptosis rate of neutrophils, which may indicate the presence of other factors that may be in play. This study also showed that neutrophils from women with endometriosis may be more resistant to spontaneous apoptosis than the neutrophils from control. These findings further contribute to the notion of dysregulated immune response in women with endometriosis.

Dendritic cells (DCs), a type of antigen presenting cells (APCs), are paramount in the activation of adaptive immunity through antigen presentation to naïve T cells. Dendritic cells, like macrophages, differentiate from monocytes in the presence of IL-4/GM-CSF *in vitro*. However, *in vivo*, DCs only require as low as picomolar to nanomolar concentrations of antigens for presentation; thus they are powerful in detecting and initiating adaptive immunity on foreign or self-antigen. Once an antigen is captured, maturation of DCs occurs, whereby they gain the ability to activate the naïve T cells into cytotoxic or T helper state. DCs also play a vital role in the prevention of autoimmunity by acting as mobile sentinels that bring self-antigens to the lymphoid organ-resident naïve T cells to promote induction of self-immunity. Immature DCs are nonexistent in the peritoneal membrane of healthy women; however, they are found within the endometriotic lesions and the surrounding peritoneal membrane of women

with endometriosis. Furthermore, the numbers of mature DCs are significantly decreased in both functionalis and basalis layers of endometrium of women with endometriosis throughout the menstrual phase compared to the healthy endometrium. The implication of low distribution of immature DCs in the endometrium or the diminished numbers of the mature DCs in both functionalis and basalis layer throughout the menstrual phase in women with endometriosis is unclear; however they likely promote angiogenesis of the lesion. Furthermore, conflicting findings from two independent investigations obscure the role of DCs in the pathogenesis of endometriosis. Stanic and colleagues (2014) reported on the depletion of DCs leading to the growth of the endometriotic lesion, whereas Pencovich and colleagues (2014) reported on the exact opposite—the depletion of DCs attenuated the development of endometriosis. One possible explanation of the differing results despite utilizing a similar transgenic mouse model using diphtheria toxin (DT) (B6 FVB-Itgax-hDTR-EGFP^{tg}) and B6.FVB-Tg(Itgax-DTR/EGFP) may be that the time for lesion retrieval was delayed by 3 days and that the receptor for DT was human compared to simian DT receptor. Investigations into the role of DCs need further fine-tuning as they appear to play a crucial role in the pathogenesis of endometriosis, in particular by promoting angiogenesis and inducing activation of adaptive immunity.

Diminished cytotoxicity of natural killer (NK) cells within the peritoneal cavity has also been well documented. Somigliana et al. reported on the presence of immunosuppressants in both the conditioned media (CM) of normal endometrial stromal cell and of endometriotic stromal cells. This implies that the normal endometrium harbours innate immunosuppressive ability against cytotoxic activity of NK cells, possibly to allow the implantation of the embryo. In women with endometriosis, this immunosuppressive effect on NK cell cytotoxicity was greater, which in peritoneal environment may allow endometrial fragments to develop into lesions. Such reduction in NK cytotoxicity seems to stem not due to decrease in quantity but due to functional defect, as the number of NK cells did not seem to differ between patients and control. Recently, IL-6 in PF of women with endometriosis has been identified as a possible immunosuppressant towards NK cell cytotoxicity against autologous endometrial fragments. These studies indicate possible association of NK cells with immune dysfunction in endometriosis.

The role of adaptive immunity, particularly T helper cells and B cells, is less defined. In brief, cell mediated immunity is facilitated by T helper type 1 cells (Th1) that target intracellular pathogens whereas humoral-mediated or T helper type 2 cells (Th2) target extracellular

pathogens and are involved in B cell activation and antibody secretion. In women with endometriosis, a polarization towards Th2 cells has been observed due to strong intracellular expression of IL-4 and absence of IL-2 from the lymphocytes isolated from the ectopic lesions. Furthermore, increased activation of B cells was also detected from the eutopic endometrium as well as the lesions compared to healthy endometrium. Indeed, endometriosis is sometimes categorized as an autoimmune disease due to anti-endometrial antibodies being detected in the serum of women with endometriosi. The balance of T helper cells in women with endometriosis remains controversial with some studies reporting diminished activation of both Th1 and Th2 in the PF of women with endometriosis. Furthermore, in contrast to Szyllo et al., another study failed to detect any difference in the intracellular concentration of IFN-γ and IL-4 from PF lymphocytes between endometriosis patients and healthy controls. In particular, genome-wide gene array and immunostaining for B (CD20+) and T (CD3+) cells in ovarian endometriomas failed to detect gene expression and presence of either of cell types despite overexpression of B lymphocyte stimulato. Contradictions in results between independent studies are likely due to different experimental methods and thus warrant further investigation.

Cytokines and Chemokines in Endometriosis[1]

Cytokines are the main mediators and communicators of the immune system. Although these polypeptides are mostly produced by immune cells, most nucleated cells also produce cytokines, albeit in lesser quantities. Immune cells use cytokines to coordinate the host response to infection or trauma via autocrine and paracrine signaling. Based on their immune-regulatory role, cytokines are broadly classified as either pro- or anti-inflammatory. Proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF) primarily initiate and amplify the inflammatory response to infection or trauma by signaling the recruit of additional immune cells and proinflammatory mediators to the site of injury. Anti-inflammatory cytokines such as IL-4, IL-6, and IL-10 primarily regulate the intensity and duration of the inflammatory response by suppressing the effects of proinflammatory cytokines, although some have inflammatory roles as well. Chemokines, such as monocyte chemoattractant protein-1 (MCP-1), IL-8, and stromal cell-derived factor-1 (SDF-1), are capable of recruiting immune cells to the site of injury and stimulate them to produce additional cytokines. The cascade of events that comprises the inflammatory response is an important

aspect of endometriosis development. The normal immune response to pathogens or injury entails a delicate balance of inflammatory and anti-inflammatory cytokines and regulators in order to be effective and remain safe for the host. Thus, cytokine dysregulation is recognized as an important aspect of the pathogenesis of numerous conditions, including endometriosis. Previous studies have found increased total leukocyte concentrations in addition to noticeable disruption of the immune activity in women with endometriosis. Peritoneal fluid contains higher concentration of proinflammatory and angiogenic cytokines presumably produced from immune cells such as macrophages and from the lesion itself, which contribute to the pathogenesis of endometriosis. Furthermore, the PF from women with endometriosis has components that polarize monocytes into macrophages instead of DCs, which are potent antigen presenting cells compared to macrophages even in the presence of dendritic cell polarizing cytokines *in vitro* . In this section, we examine various cytokines and chemokines that seem to play a significant role in the establishment and survival of lesions in endometriosis.

IL-1 is an acute phase inflammatory cytokine that exists in three main forms—IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra). The release of IL-1α and IL-1β by mononuclear and epithelial cells in response to injury leads to inflammation, while IL-1Ra release attenuates this response by blocking IL-1α and IL-1β binding. Various studies have reported higher concentrations of IL-1α , IL-1β , and total IL-1 in the PF of women with endometriosis compared to normal women, thus supporting the notion of a local inflammatory environment in endometriosis. This idea is further supported by studies reporting impaired expression of the soluble decoy receptor IL-1-RII in the endometrium and PF of women with endometriosis, which would help attenuate the effects of IL-1α and IL-1β. Similarly, decreased levels of IL-1Ra have been reported in the PF of patients with early stage endometriosis. These results may reflect an initial but failed attempt to attenuate the local inflammation caused by endometrial fragments in the pelvic cavity. The fact that shed endometrial fragments would trigger such a strong inflammatory response points to either a reduced capacity of immune cells to clear these fragments or a potential autoimmune condition that would cause peritoneal resident immune cells to be more sensitive to endogenous damage signals. A study by Bergqvist and colleagues found that endometriotic lesion expresses higher levels of IL-1β than eutopic endometrium of both normal women and women with endometriosis, which indicates that the inflammation in endometriosis is locally induced.

Tumor necrosis factor alpha (TNF-α) is the most studied protein of the TNF family and is primarily produced by activated macrophages, NK cells and Th1 cells. TNF-α appears to act

synergistically with IL-1, as they both activate the canonical NF-κB inflammatory pathway. Harada and colleagues found increased levels of TNF-α in the PF of women with endometriosis and detected a positive correlation between TNF-α concentrations and endometriotic lesion size. Others have also reported higher levels of TNF-α in the endometrium and PF of women with endometriosis but only in mild or early stages of the disease, which suggests that TNF-α plays a role in the early stages of endometriosis when the lesions are establishing. Interestingly, both TNF-α and IL-1 are capable of inducing the expression of cyclooxygenase-2 (COX-2), the enzyme that regulates the synthesis of prostaglandin E_2 (PGE_2). Unlike the constitutive COX-1 enzyme, COX-2 is undetectable under normal conditions and only becomes upregulated in response to infection or injury. In women with endometriosis, COX-2 has been found to be overexpressed in isolated peritoneal macrophages, but not in isolated peripheral macrophages, which supports the idea that local inflammatory factors are responsible for the upregulation of COX-2 in macrophages. Furthermore, PGE_2 itself can induce COX-2 expression, creating a positive feedback cycle that promotes inflammation and pain via overproduction of PGE_2. PGE_2 can also attenuate macrophage cytotoxicity and promote local estrogen synthesis, cell proliferation, and angiogenesis.

Dydrogesterone: background and pharmacology[2]

Dydrogesterone is a potent orally active progesterone receptor agonist that was developed in the 1950s and that has been widely used since the 1960s for menstrual disorders such as premenstrual syndrome, cycle irregularity, endometriosis, threatened miscarriage, and habitual miscarriage, and for postmenopausal hormone therapy. Unlike other members of the progestin family, dydrogesterone and its main active metabolite, 20α-hydroxydydrogesterone, do not have any clinically relevant agonistic or antagonistic activity on the androgen, estrogen, and glucocorticoid receptors and only mild antimineralocorticoid properties. Safety concerns owing to receptor cross-activation have precluded the use of the majority of the progestins in fertility treatment and pregnancy. Only bioidentical progesterone, 17-hydroxy-progesteronecaproate and dydrogesterone are considered to be sufficiently safe for the developing fetus.

Interestingly, dydrogesterone has only little effect on gonadotropin release and therefore hardly interferes with follicular growth and corpus luteum formation and maintenance. At clinically used doses (5–30 mg), ovulation is not suppressed in the human, although recently

dydrogesterone (20 mg/d) has been used as an alternative to chlormadinone acetate for preventing premature LH surges in the context of controlled ovarian stimulation (COS).

In contrast to natural progesterone, dydrogesterone has good oral bioavailabilty (~28%). The half-life of dydrogesterone has been estimated to be 5–7 hours and the half-life of 20α-hydroxydydrogesterone to be 14–17 hours. Prereceptor regulation of action happens mostly by conversion of dydrogesterone to its biologically active 20α-hydroxymetabolite by aldoketo reductase 1C1, an enzyme that also converts progesterone to its less potent metabolite 20α-hydroxyprogesterone.

Dydrogesterone is currently not available in the United States; it was withdrawn from the market for commercial reasons. Likewise, the product was withdrawn from the United Kingdom market in 2008 and from the Australian market in 2011 for commercial reasons. For the United States, dydrogesterone was registered in 1961 and the license transferred over the years to several companies. In 1997, the current new drug application owner, Solvay, withdrew the product because the registered indications were no longer commercially viable and/or there were potentially conflicting interest regarding other products of which Solvay was the license holder. For the United Kingdom and Australia, low sales of a comparatively cheap drug and the lack of new and commercially interesting indications motivated the withdrawal from the markets.

However, dydrogesterone is currently licensed for use in more than 100 countries globally, with more than 20 European countries having at least one label for use of dydrogesterone in pregnancy.

Dydrogesterone has long been used for exogenous support of endogenous progesterone production by the corpus luteum and placenta. Although definitive proof of luteal phase defect being an independent entity causing infertility has never been established, luteal phase defect is a well described iatrogenic phenomenon in the context of COS with multifollicular development and oocyte retrieval for in vitro fertilization (IVF). Studies comparing progestogen usage versus nil or placebo in COS IVF treatment cycles have reported that the use of progestogen is associated with an improvement in ongoing pregnancy or live birth rate. Accordingly, luteal phase support (LPS) with the use of progestogens is routinely performed in IVF treatment cycles.

Is oral administration preferred by the patient over vaginal administration?[3]

Studies on the administration of, for example, vaginal versus oral misoprostol have consistently reported the oral route to be preferred by the majority of patients. Preference for oral administration may be even higher in the context of LPS, with a minimum intake duration of 10 days and often treatment extension into early pregnancy. Furthermore, patients exposed to once daily or three times daily administration of a vaginal progesterone prefer once daily application, because this was considered to be easier, more convenient, and less messy. It is also noteworthy that in a recent phase III trial program comparing vaginal progesterone gel once daily with subcutaneous progesterone injection once daily for LPS, no difference in patient preference for one of the two administration routes could be seen, despite the fact that injectable drugs are usually less tolerated, especially when self-injected. In that trial, the incidence of vaginal irritation, inflammation, dryness, pruritus, discharge, or pain was 50.8% in patients on daily vaginal gel administration compared with 10.4% in patients on subcutaneous progesterone.

Chakravarty et al. reported, based on questionnaires handed out in the context of one of their randomized studies, that satisfaction of patients with the tolerability of oral dydrogesterone for LPS (2 × 10 mg) was significantly higher compared with micronized vaginal progesterone (3 × 200 mg). In another RCT on 831 patients undergoing IVF, patients were found to be significantly more often satisfied with oral dydrogesterone (2 × 10 mg) and more often significantly dissatisfied with once daily vaginal progesterone gel when ranking the drugs on scale from 1 to 5. No such difference was seen, however, in a recent study from Iran on 240 patients, in which total satisfaction and total dissatisfaction was equally distributed between 2 × 10 mg oral dydrogesterone and 2 × 400 mg vaginal micronized progesterone for LPS.

The above results illustrate that the preference for a route of administration in an individual patient is likely a function of personal habits and cultural circumstances. It has been suggested that patients may believe that they are receiving a “stronger” medicine when the administration is by injection or other uncomfortable route of administration and that such expectations may even influence the response to a drug. Although the latter is unlikely in the context of LPS, implicit judgments on a medication by an individual patient (efficacy beliefs), concerns about potential adverse reactions, and personal preferences should be taken into account to achieve good compliance and treatment adherence.

Is oral administration preferred by the physician over vaginal administration? [3]

Luteal phase support with the use of progesterone is usually started within the time interval between oocyte pick-up and embryo transfer. When the embryo transfer catheter passes through the cervical canal, there is a risk of introducing not only progesterone itself, but also excipients of tablets, suppositories, or gel into the uterine cavity. Furthermore, the supraphysiologic progesterone concentrations in the vagina may alter the local microbiome, which has become a recent focus of interest in the context of IVF.

Although a negative effect of drug excipients or high doses of progesterone on the endometrium, embryo, or the microbiome have never been documented, doctors usually take great care in cleaning the outer cervical os before the embryo transfer. A formal physician preference study has not been done, but an educated guess is that most doctors prefer a cleaner vagina (and therefore oral or injectable administration) when doing the embryo transfer or when performing a transvaginal scan at later stage.

Is oral dydrogesterone safe and well tolerated by the patient? [3]

Bioidentical orally administered progesterone has been associated with the formation of sedative metabolites due to a first pass effect in the liver. These metabolites act centrally, and side-effects of oral progesterone, such as fatigue, headache, and urinary frequency, in addition to safety concerns regarding intrahepatic cholestasis with oral progesterone intake, have prompted the development of vaginal preparations for LPS in IVF. The most important tolerability issue with vaginal progesterone is, however, discharge and irritation.

An objective assessment of the tolerability of dydrogesterone (20 mg/d) compared with vaginal micronized progesterone (600 mg/d) was done by Chakravarty et al.. Liver function tests were performed at baseline (before administration) and on the day of pregnancy test (e.g., after ~14 days of intake). The percentage of patients with abnormal liver function tests and the mean serum glutamate-pyruvate transaminase, bilirubin, and alkaline phosphatase levels were highly similar between the groups. In 10.5% of patients given micronized progesterone, vaginal discharge or irritation was confirmed, whereas 0% of dydrogesterone patients had those side-effects.

Tomic et al. reported that perineal irritation, vaginal bleeding, vaginal discharge, and interference with sexual activity was significantly higher in patients receiving vaginal

progesterone gel compared with oral dydrogesterone. No difference was seen for dizziness, headache, nausea, breast tension, or bloating.

The most comprehensive and robust insight into the maternal safety and tolerability of oral dydrogesterone comes from the LOTUS I trial, in which doctors and patients were blinded and each patient was randomized to oral dydrogesterone or micronized vaginal progesterone and received a dummy medication with placebo. In addition, the patients were monitored for adverse events during later stages of pregnancy. Treatment emerging adverse events leading to study termination were reported in 12.4% of subjects in the dydrogesterone group and in 16.0% of subjects in the micronized vaginal progesterone group. Liver enzyme analysis was normal in nearly all patients in both groups. Because most adverse events leading to study termination or discontinuation of the study drug were infrequent, events were grouped by organ system (e.g., gastrointestinal, nervous system, reproductive organ system, vascular system). No differences were identified, and no new safety or tolerability issues were found in this large study.

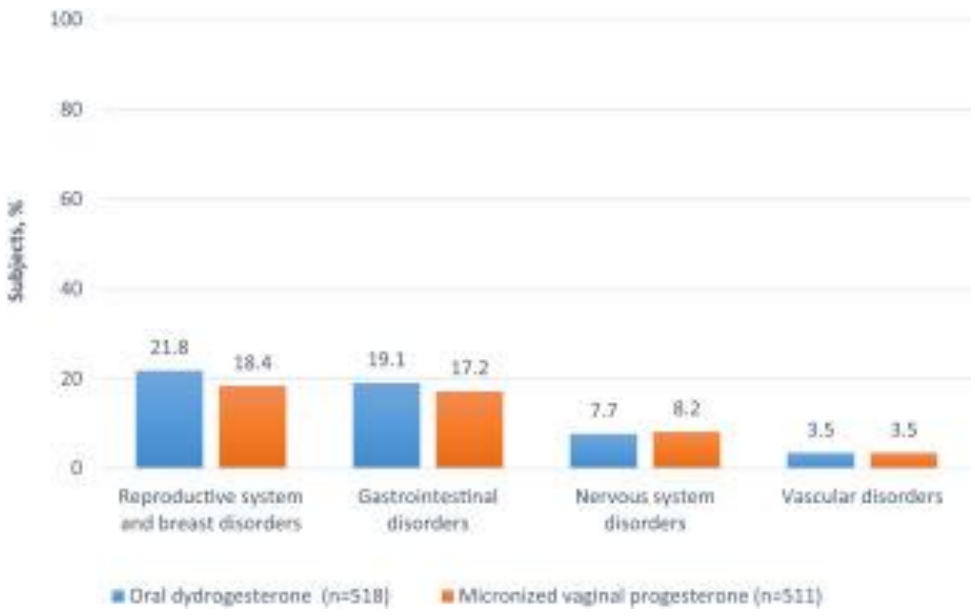

Figure 2. Proportion of female subjects reporting treatment emerging adverse events according to organ system in the two groups of the LOTUS I trial.

In summary, the use of oral dydrogesterone avoids the frequently reported and negatively perceived side effects of vaginal preparations, whereas no systemic tolerability difference from micronized vaginal progesterone has been identified in a large, double-blind, double-dummy randomized trial.

Is dydrogesterone safe for the fetus? [3]

Dydrogesterone has been on the market since the 1960s and is labeled for use in pregnancy (e.g., for recurrent miscarriage or threatening abortion) in numerous countries worldwide. From sales figures, it has been estimated that more than 8 million fetuses must have had in utero exposure to dydrogesterone during more than half a century of use on a global scale.

In view of this extensive use, a substantial fetal risk of dydrogesterone can be ruled out, although a low-level risk could be detected only via sophisticated and large observational studies.

A review and in-depth analysis of available pharmacovigilance data identified 28 cases of congenital defects with a potential link to dydrogesterone exposure in pregnancy recorded within the time span from 1977 to 2005.

Malformation rates associated with a drug can not be calculated from pharmacovigilance data, but the low number of reported cases (some of which occurred within controlled studies) in relation to the (estimated) number of pregnancies exposed makes a relevant teratogenic risk of dydrogesterone highly unlikely. Moreover, the types of defects potentially associated with dydrogesterone in the pharmacovigilance data were very diverse, with no evidence of a pattern of abnormalities.

In the LOTUS I trial, child health was recorded at birth for the total maternal population and 6 months after birth in a subset of 216 patients who had been treated in Russia. Overall, 213 and 158 children were recorded in the oral dydrogesterone and vaginal progesterone group, respectively. The incidences of congenital, familial, and genetic disorders were <2% in both treatment groups. No difference in the incidence of congenital malformations was found, and no distinct pattern of defects with the use dydrogesterone or progesterone was observed.

Further safety data stem from RCTs on dydrogesterone use in threatened miscarriage and recurrent miscarriage. None of those studies revealed a safety concern with dydrogesterone use.

In 2015, a retrospective case-control study compared exposure to dydrogesterone in pregnancy in 202 children born with congenital heart disease and a control group of 200 healthy children born from 2010 to 2013 in the Gaza strip of Palestine.

Dydrogesterone exposure was defined as any reported use (by recall) in the first trimester of pregnancy. A higher rate of dydrogesterone intake was found in mothers of children with a heart defect (38%) compared with control children (18%), and the authors concluded that there was a positive association between dydrogesterone use during early pregnancy and congenital heart disease in the offspring (adjusted odds ratio 2.71, 95% CI 1.54–4.24; *P*<.001). However, this study violated numerous basic principles of epidemiologic research. First, all comparisons should have been made within the same study base, that is, women who have had an indication for dydrogesterone and who did or did not receive that drug. Second, because dydrogesterone is often prescribed for miscarriage prevention, all women should have had a similar risk background; the difference in maternal population leads to the issue of confounding: There is evidence from the literature that previous miscarriages are an important and strong risk factor for congenital heart defects. Third, the authors did not confirm exposure (at least retrospectively based on medical records) but instead relied on recollection of the mothers. However, mothers are likely to recollect any event in pregnancy better if their child has an abnormality. Finally, different heart defects were pooled into one group and socioeconomic status was ignored, as were comorbidities. In summary, a causal relationship of dydrogesterone and heart defects can not be inferred from this study.

Congenital heart defects are common, with an estimated incidence of 1%. A study verifying or refuting the hypothesis of a threefold increased risk of a heart defect in offspring exposed to dydrogesterone would require >3,000 infants to be studied in a 1:1 randomized trial. With a live birth rate of 30% in patients undergoing IVF, a two-armed study on women receiving dydrogesterone or a control drug for LPS in IVF treatment would therefore require a total sample size of ≥10,000 patients (alpha error <5%, beta error <20%). It is unlikely that a study of such dimension will soon be performed, and physicians therefore will have to rely on the available pharmacovigilance data. Of note, larger-size randomized studies assessing the risk of bioidentical progesterone have not been conducted, despite the fact that a theoretic risk of bioidentical progesterone in supraphysiologic doses can not be ruled out.

Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis[5]

Abstract

Background: This study aimed to explore the clinical efficacy of dydrogesterone in treating recurrent spontaneous abortion (RSA), analyze the influence of dydrogesterone on cellular immune factors, and provide evidence for clinical medication.

Methods: We used the China National Knowledge Infrastructure (CNKI) platform, Wanfang Data resource, PubMed, Web of Science, and Embase database to conduct a literature search to screen clinical studies published between 2005 and 2021 concerning dydrogesterone treatment for RSA. Stata 16.0 was used for meta-analysis and sensitivity analysis, and Begg's funnel chart was used to test publication bias.

Results: Only 13 studies, which included a total of 2,454 RSA patients, met the study inclusion criteria. The experimental group was treated with dydrogesterone, and the control group was treated with progesterone, human chorionic gonadotropin (hCG), placebo, or active immunization. Meta-analysis showed that the pregnancy success rate of the experimental group was higher than the control group, and the adverse reaction rate was lower than the control group. In addition, subgroup analysis also revealed that the experimental group had a higher pregnancy success rate than the control group and a lower adverse reaction rate. Levels of progesterone and hCG in the experimental group were dramatically higher than the control group after treatment. The experimental group also had higher levels of interleukin 4 (IL-4) and interleukin 10 (IL-10) than the control group, while levels of interferon-gamma (IFN-γ) were lower.

Discussion: Dydrogesterone, a safe and effective synthetic progesterone drug, had a significant clinical effect on RSA and effectively improved hormone levels and related cellular immune factors in RSA patients.

Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion[5]

Abstract

Background: Threatened abortion is a relatively common complication during pregnancy. Inadequate production of endogenous progesterone is implicated as a risk factor for miscarriages. Thus, supplementation of external progesterone can be used as a preventive strategy in these women. Dydrogesterone a stereoisomer of progesterone has a good safety and tolerability profile and is known to effectively prevent pregnancy loss in women with threatened miscarriage, however, real-world data safety and effectiveness analysis of dydrogesterone in Indian patients was lacking. Therefore, this real-world retrospective analysis of the case reports was done to evaluate the safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the treatment of women with threatened abortion.

Methods: Data was collected from 194 obstetricians and gynaecologists in India, on the use of oral dydrogesterone in women presenting with threatened abortion in the first trimester of pregnancy.

Results: Completed case report forms of patients who met the eligibility criteria (n = 617) were considered for the analysis. The main presenting symptom was vaginal bleeding/spotting with an additional symptom of abdominal cramp/pelvic pain/low back pain in 364 (69.07%) patients. Miscarriage was reported in 45 (7.29%) patients and 23 (3.98%) patients needed surgical intervention before 20 weeks of gestation with dydrogesterone treatment. The median time for relief of symptoms from the start of dydrogesterone tablets was 3.32 days for low back pain, 3.9 days for abdominal pain, and 4.37 days for the establishment of hemostasis. Treatment with dydrogesterone was found to be well-tolerated and adverse events were reported in 3.72% of the patients.

Conclusions: This retrospective analysis suggests that dydrogesterone is safe and effective in reducing the incidence of pregnancy loss in women with threatened abortion.

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2. Griesinger G, Blockeel C, Tournaye H. Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard?. *Fertil Steril*. 2018;109(5):756-762.
3. Griesinger G, Blockeel C, Tournaye H. Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard?. *Fertil Steril*. 2018;109(5):756-762.
4. Guo H, Lu Q. Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis. *Ann Palliat Med*. 2021;10(10):10971-10985.
5. Nagarkatti, Rajendra & Mehra, Dolly & Mandal, et al. (2022). Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 11. 10.18203/2320-1770.ijrcog20221833.

Survey Form

1. **In your clinical practice, how frequently do you encounter cases of Endometriosis in patients visiting to your clinic every month?**
    a. <5%
    b. 5 - 20%
    c. 21– 30%
    d. >30%

2. **In what percentage of your patients do you prefer progestins?**
    a. 20-40%
    b. 41-60%
    c. 61–80%
    d. >80%
    e. All patients

3. **In your clinical practice, which type of progesterone do you prefer the most?**
    a. Oral progesterone and its derivative
    b. Vaginal Progesterone
    c. Injectable

4. **In what percentage of your patients with endometriosis do you prescribe Dydrogesterone?**
    a. <10%
    b. 10-20%
    c. 21-30%
    d. 31–40%
    e. 41-50%
    f. >50%

5. **What is the preferred dose of dydrogesterone in patients with endometriosis?**
    a. 10 mg once daily
    b. 10 mg BID
    c. 10 mg TID
    d. 10 mg QID

6. **In your clinical practice, what could be the possible reasons of non-adherence to dydrogesterone in patients of Endometriosis?**
    a. Frequent dosing (TID)
    b. Side effects
    c. Any other_____

7. **Would you prefer sustained release formulation of dydrogesterone in patients with Endometriosis?**
    a. Yes
    b. No

    If yes, what would be the preferred dose in these patients?
    a. 20 mg Dydrogesterone SR (OD)
    b. 20 mg Dydrogesterone SR (BID)
    c. 30 mg Dydrogesterone SR (OD)

8. **In your opinion which are the patient profiles most suitable for Dydrogesterone SR therapy ? (you can select more than one option)**
    a. Endometriosis
    b. Recurrent pregnancy loss
    c. Luteal phase support
    d. Threatened Miscarriage
    e. Habitual abortion

9. **In your clinical practice, what is the average duration of the treatment with dydrogesterone in patients of Endometriosis?**
    a. 1 month
    b. 1-3 months
    c. 3-6 months
    d. 6 months-1 year
    e. More than 1 year

10. **In your clinical practice, what benefits do you observe with dydrogesterone/SR over micronized progesterone? [you may tick more than one options]**
    a. Increased efficacy
    b. Less side effects
    c. Better tolerability
    d. Patient convenience
    e. All of them

11. **Which of the following is your most preferred type of progestogen in recurrent pregnancy loss?**
    a. Oral micronized progesterone
    b. Vaginal micronized progesterone
    c. IM/SC progesterone
    d. Dydrogesterone

12. **Do you use dydrogesterone in Recurrent Pregnancy Loss (RPL)?**
    a. Yes
    b. No

13. **How do you use dydrogesterone in your patients with RPL?**
    a. As a monotherapy
    b. In combination with oral/vaginal micronized progesterone
    c. Any other, please specify_____

14. What is the preferred dose of dydrogesterone in RPL?

a. 10 mg BID from the onset of bleeding until 1 week after bleeding has stopped

b. 10 mg BID from the onset of bleeding until the 16th week of pregnancy

c. 40 mg loading dose followed by 20–30 mg/day until 7 days after bleeding stops

d. 40 mg immediately, followed by 10 mg every 8 h until symptoms abate; then continue oral dydrogesterone for 1 to 2 weeks

e. Any other, please specify_____

15. Which of the following dydrogesterone formulation would you prefer in patients of RPL?

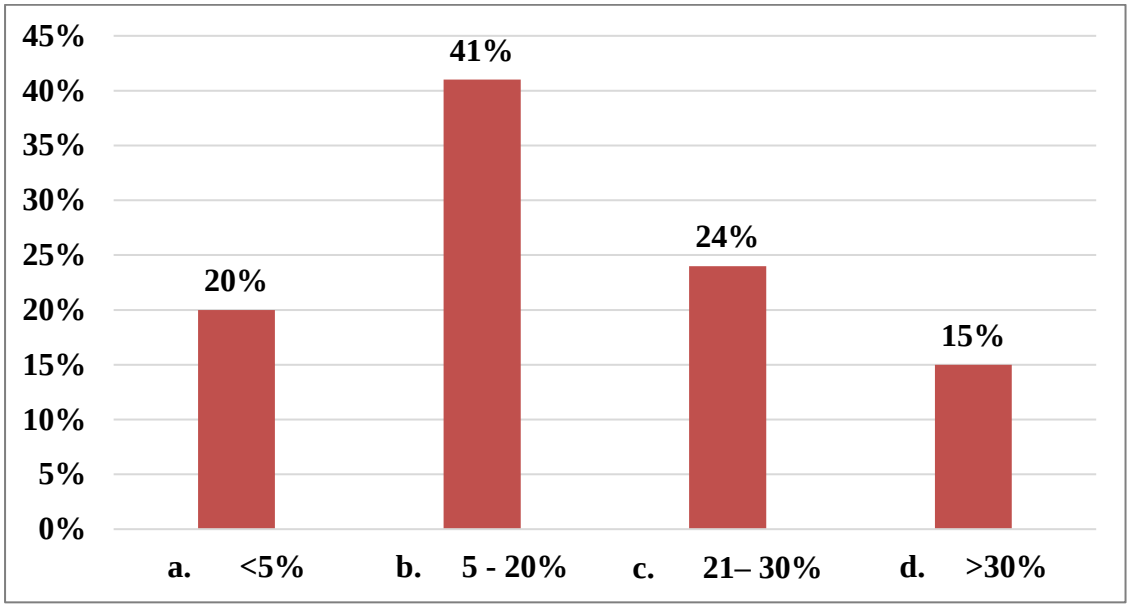
a. Dydrogesterone 20 mg sustained release tablets

b. Dydrogesterone 30 mg sustained release tablets

c. Dydrogesterone 10 mg immediate release tablets

Survey Findings

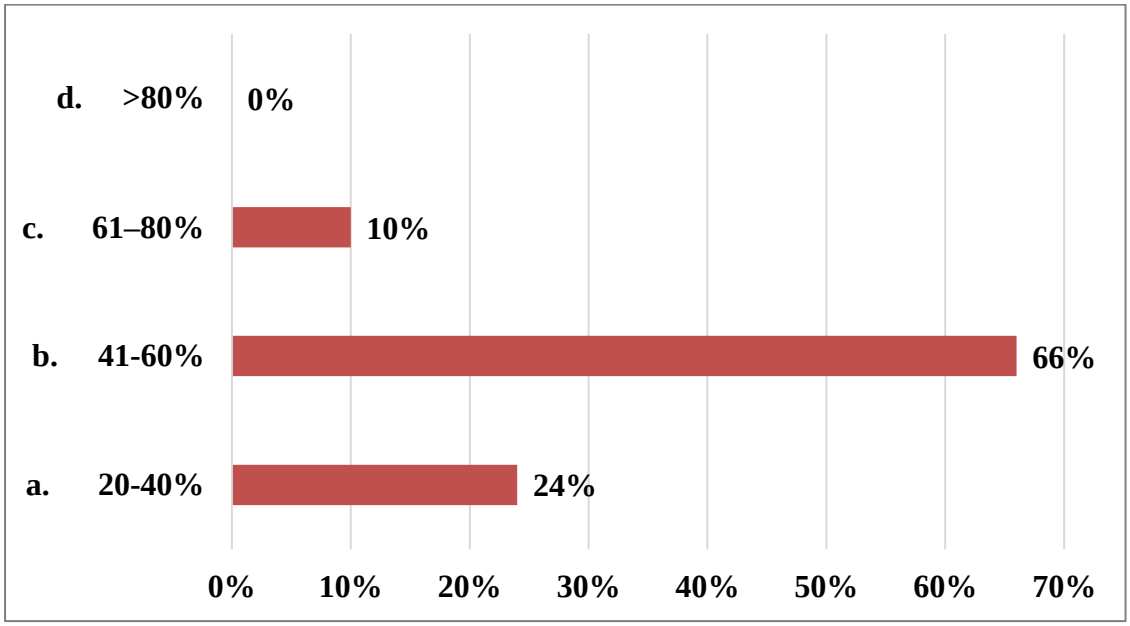
1. **In your clinical practice, how frequently do you encounter cases of Endometriosis in patients visiting to your clinic every month?**
    a. <5%
    b. 5 - 20%
    c. 21– 30%
    d. >30%



According to 41% of doctors, they encounter of 5 - 20% cases of Endometriosis in patients visiting to their clinic every month.

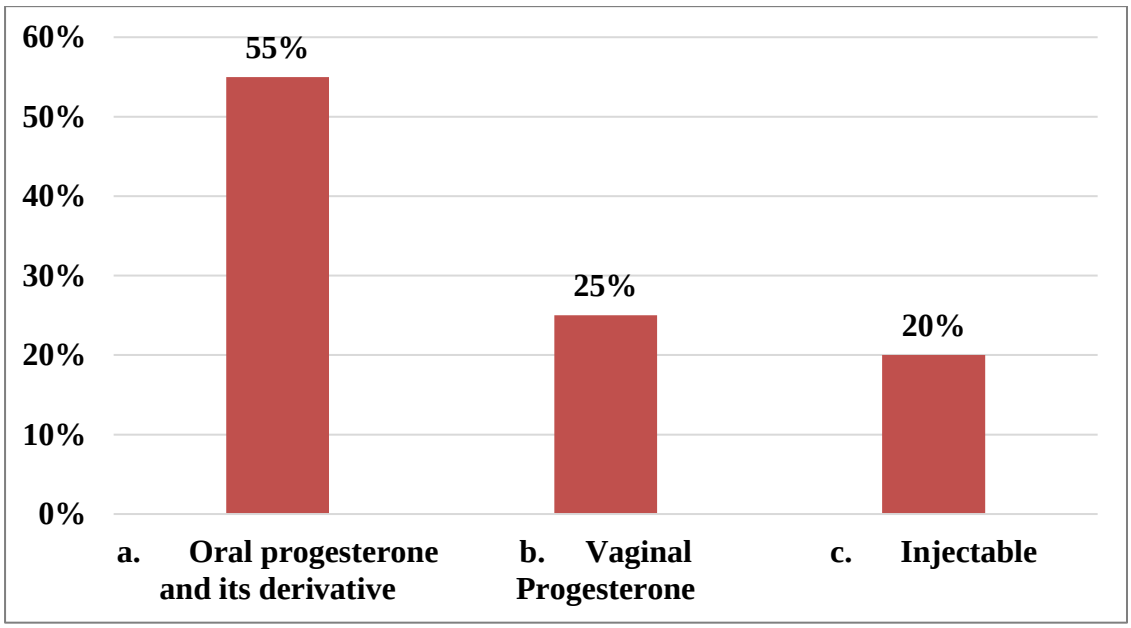
2. In what percentage of your patients do you prefer progestins?

a. 20-40%
b. 41-60%
c. 61–80%
d. >80%
e. All patients



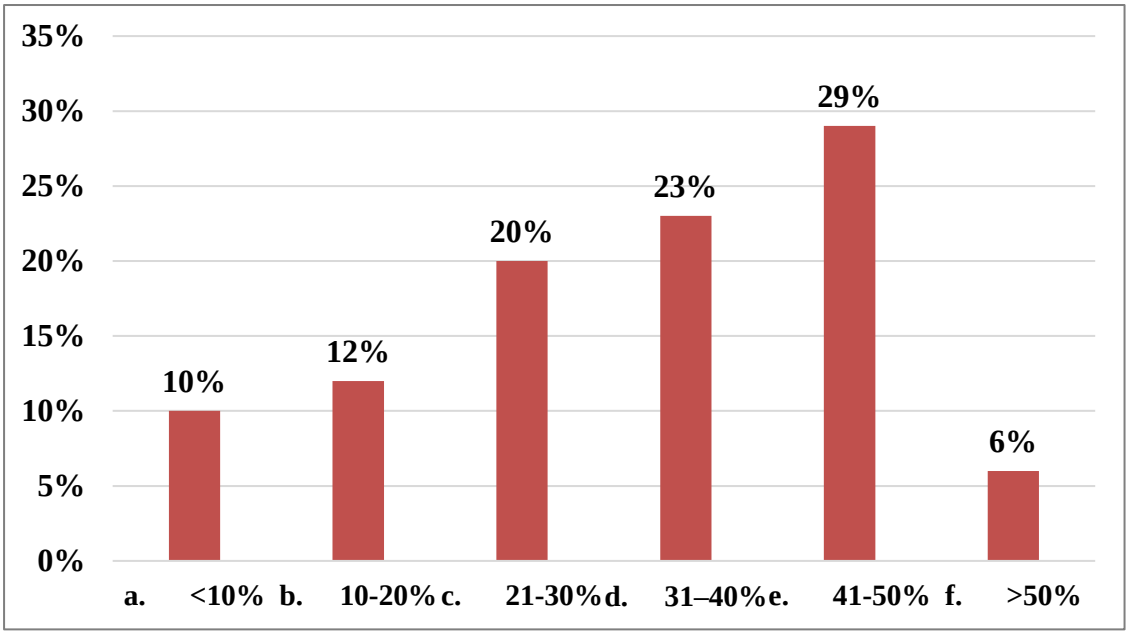
As per 66% of doctors, in 41-60% of their patients they prefer progestins.

3. **In your clinical practice, which type of progesterone do you prefer the most?**
    a. Oral progesterone and its derivative
    b. Vaginal Progesterone
    c. Injectable



According to 55% of doctors, they prefer oral progesterone and its derivative the most.

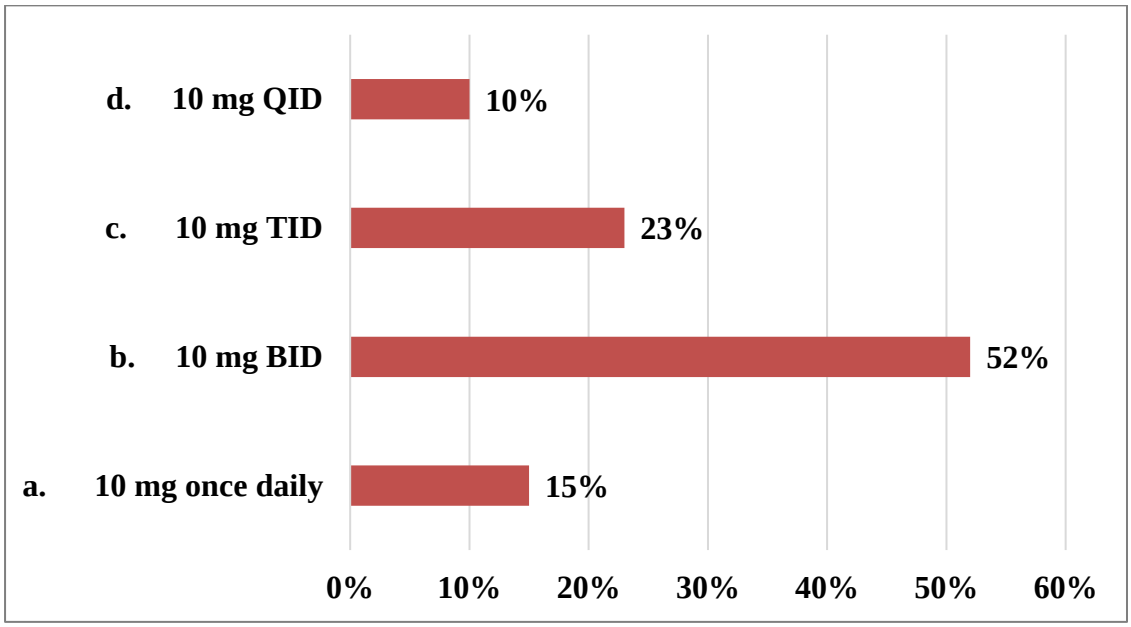
4. **In what percentage of your patients with endometriosis do you prescribe Dydrogesterone?**
    a. <10%
    b. 10-20%
    c. 21-30%
    d. 31–40%
    e. 41-50%
    f. >50%



According to 29% of doctors, in 41-50% of patients with endometriosis they prescribe Dydrogesterone.

5. What is the preferred dose of dydrogesterone in patients with endometriosis?

a. 10 mg once daily
b. 10 mg BID
c. 10 mg TID
d. 10 mg QID



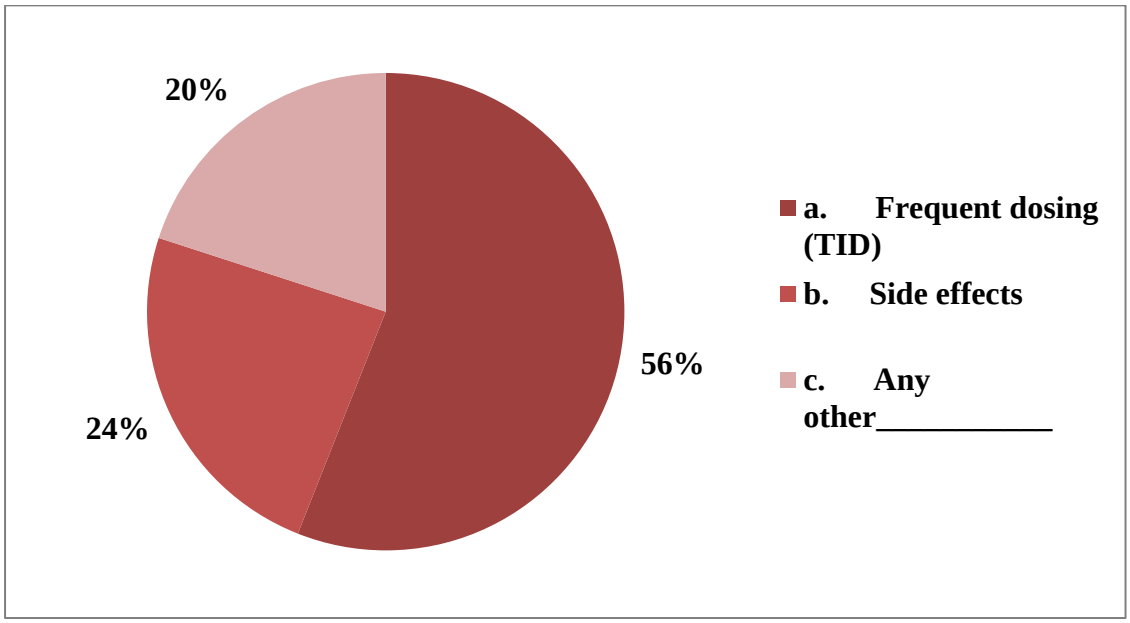
As per 52% of doctors, 10 mg BID is the preferred dose of dydrogesterone in patients with endometriosis.

6. **In your clinical practice, what could be the possible reasons of non-adherence to dydrogesterone in patients of Endometriosis?**

    d. Frequent dosing (TID)

    e. Side effects

    f. Any other_____



As per 56% of doctors, frequent dosing (TID) could be the possible reasons of non-adherence to dydrogesterone in patients of Endometriosis.

7. **Would you prefer sustained release formulation of dydrogesterone in patients with Endometriosis?**

    a. Yes

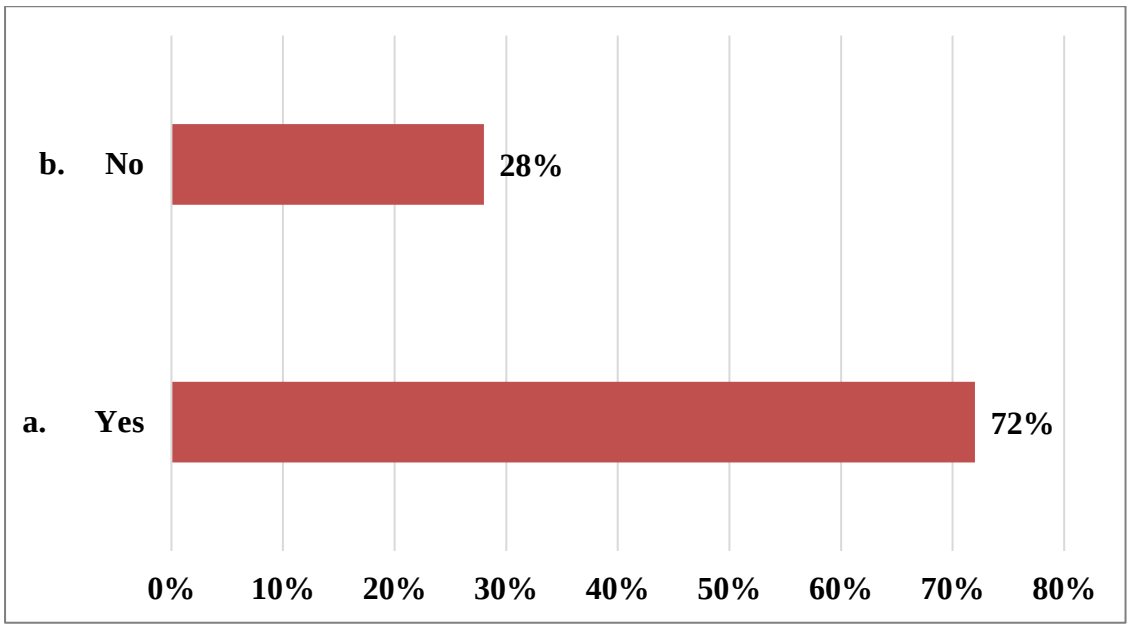
    b. No

    If yes, what would be the preferred dose in these patients?

    a. 20 mg Dydrogesterone SR (OD)

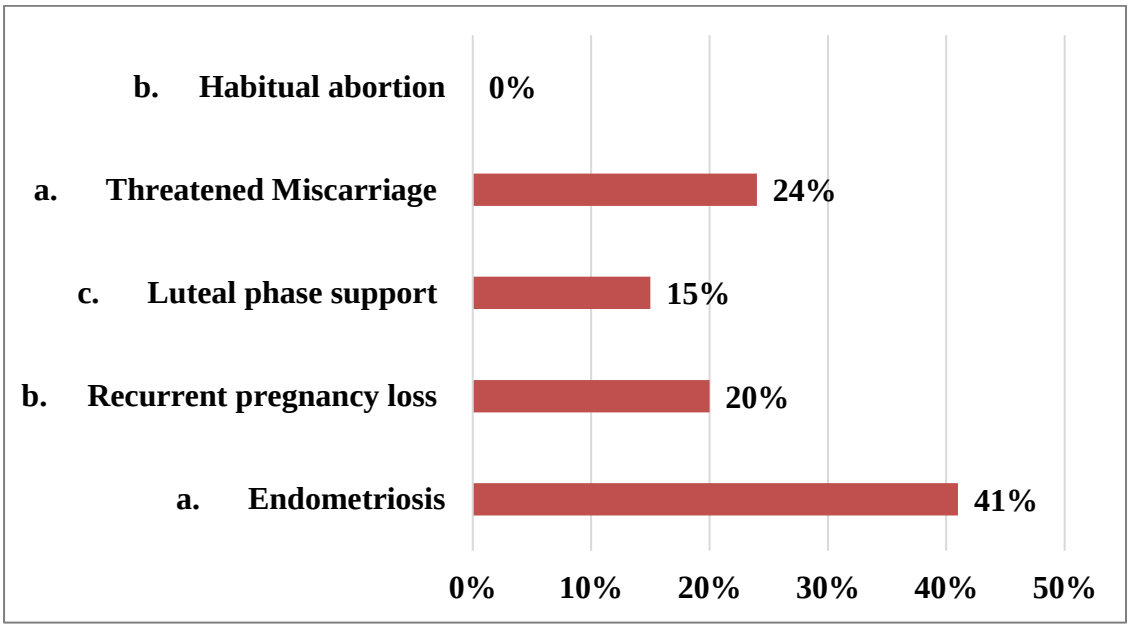
    b. 20 mg Dydrogesterone SR (BID)

    c. 30 mg Dydrogesterone SR (OD)



According to 72% of doctors, they prefer sustained release formulation of dydrogesterone in patients with Endometriosis, with 20 mg Dydrogesterone SR (BID) being the preferred dose.

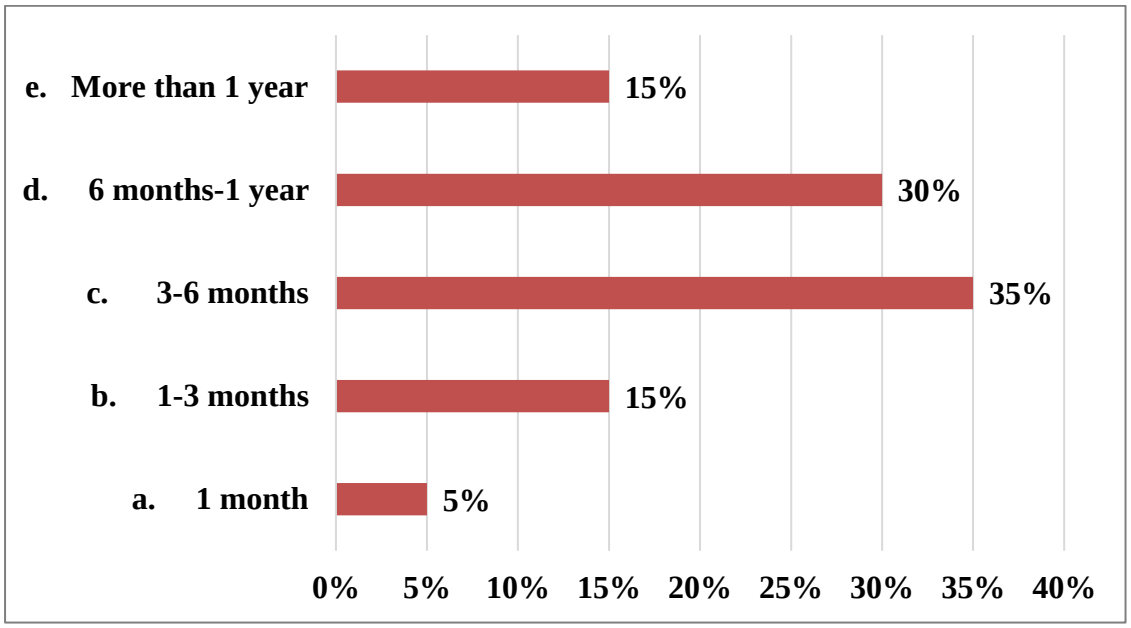
8. **In your opinion which are the patient profiles most suitable for Dydrogesterone SR therapy ? (you can select more than one option)**
    a. Endometriosis
    b. Recurrent pregnancy loss
    c. Luteal phase support
    d. Threatened Miscarriage
    e. Habitual abortion



As per 41% of doctors, the patient profiles most suitable for Dydrogesterone SR therapy is endometriosis.

9. **In your clinical practice, what is the average duration of the treatment with dydrogesterone in patients of Endometriosis?**

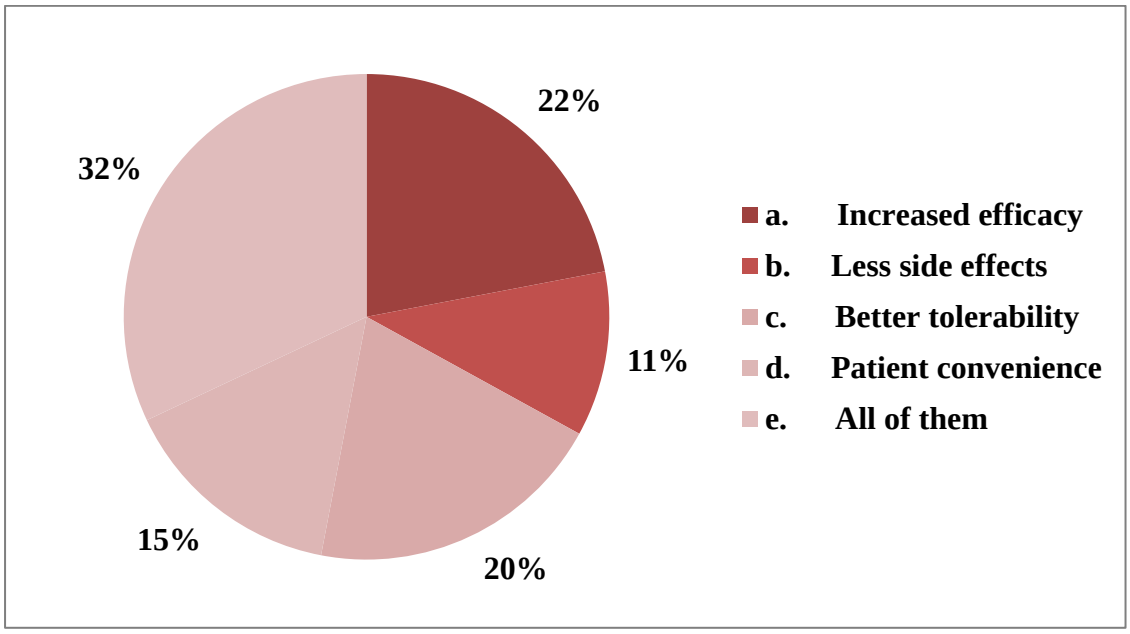
   a. 1 month
   b. 1-3 months
   c. 3-6 months
   d. 6 months-1 year
   e. More than 1 year



According to 35% of doctors, 3-6 months is the average duration of the treatment with dydrogesterone in patients of Endometriosis.

10. In your clinical practice, what benefits do you observe with dydrogesterone/SR over micronized progesterone? [you may tick more than one options]

a. Increased efficacy
b. Less side effects
c. Better tolerability
d. Patient convenience
e. All of them



According to 32% of doctors, increased efficacy, less side effects, better tolerability, patient convenience are the benefits theyobserve with dydrogesterone/SR over micronized progesterone.

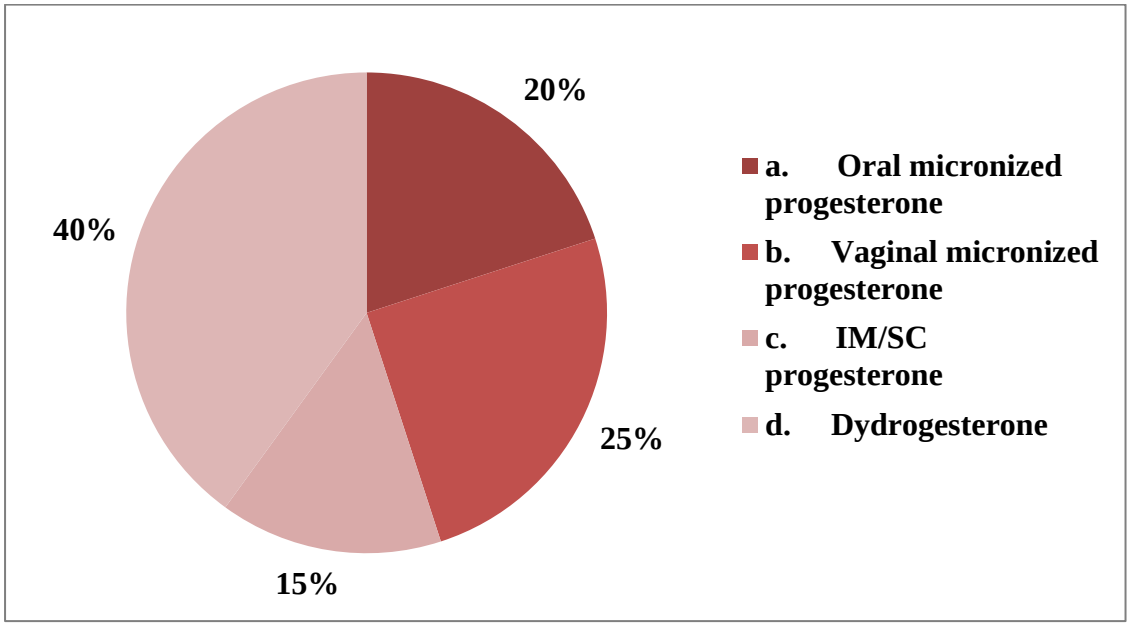
11. **Which of the following is your most preferred type of progestogen in recurrent pregnancy loss?**

    a. Oral micronized progesterone

    b. Vaginal micronized progesterone

    a. IM/SC progesterone

    b. Dydrogesterone

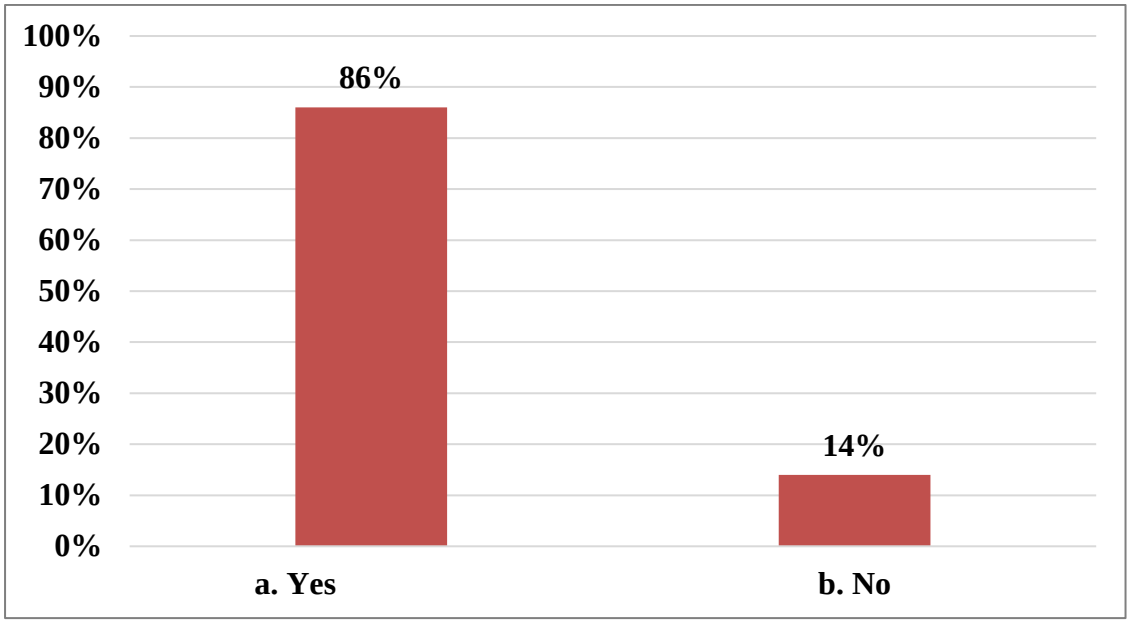


As per 40% of doctors, Dydrogesterone is the most preferred type of progestogen in recurrent pregnancy loss.

12. Do you use dydrogesterone in Recurrent Pregnancy Loss (RPL)?

a. Yes

b. No



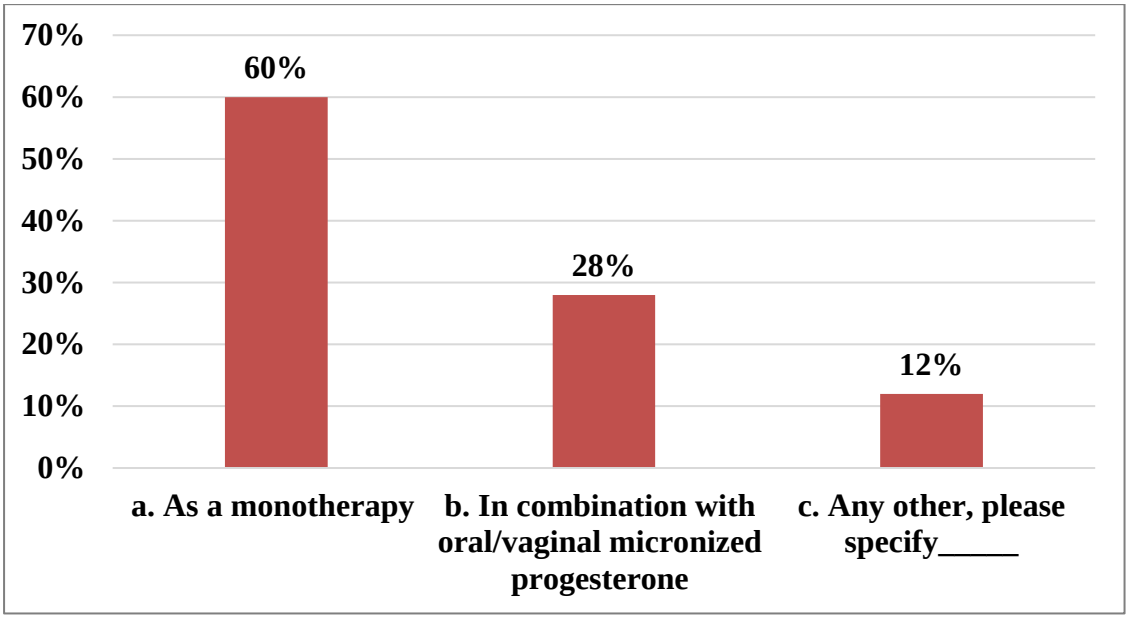
According to 86% of doctors, they do use dydrogesterone in Recurrent Pregnancy Loss.

13. How do you use dydrogesterone in your patients with RPL?

a. As a monotherapy

b. In combination with oral/vaginal micronized progesterone

c. Any other, please specify_____



According to 60% of doctors, they use dydrogesterone in their patients with RPL as a monotherapy.

14. What is the preferred dose of dydrogesterone in RPL?

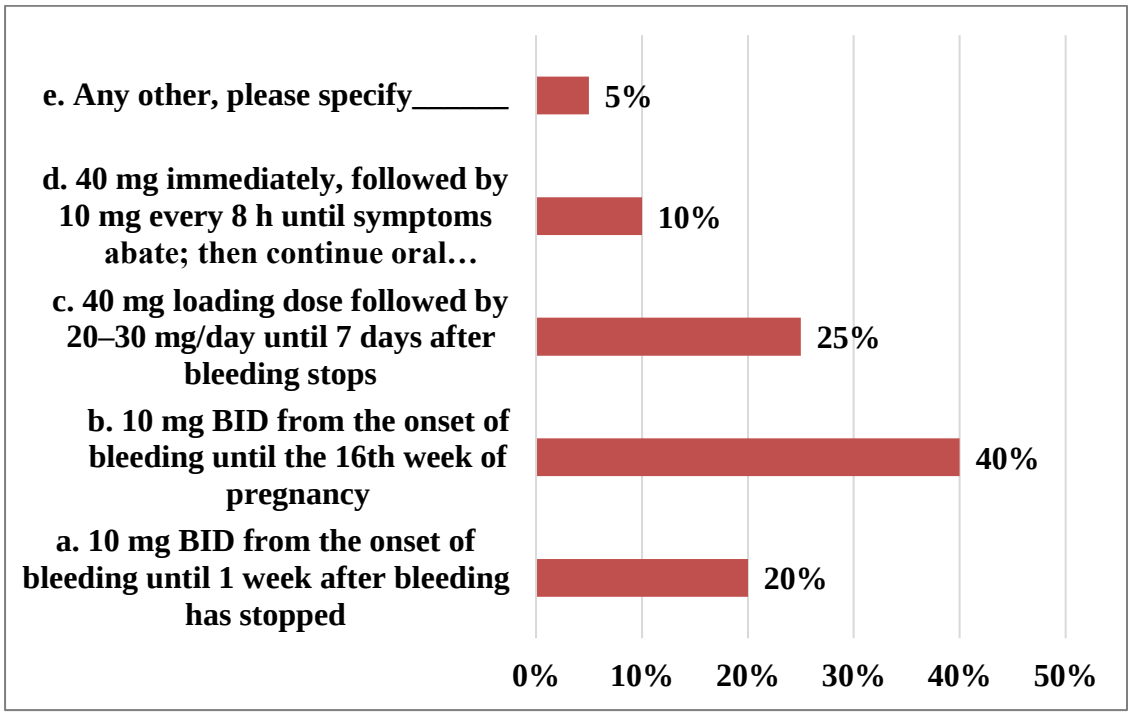
a. 10 mg BID from the onset of bleeding until 1 week after bleeding has stopped

b. 10 mg BID from the onset of bleeding until the 16th week of pregnancy

c. 40 mg loading dose followed by 20–30 mg/day until 7 days after bleeding stops

d. 40 mg immediately, followed by 10 mg every 8 h until symptoms abate; then continue oral dydrogesterone for 1 to 2 weeks

e. Any other, please specify_____



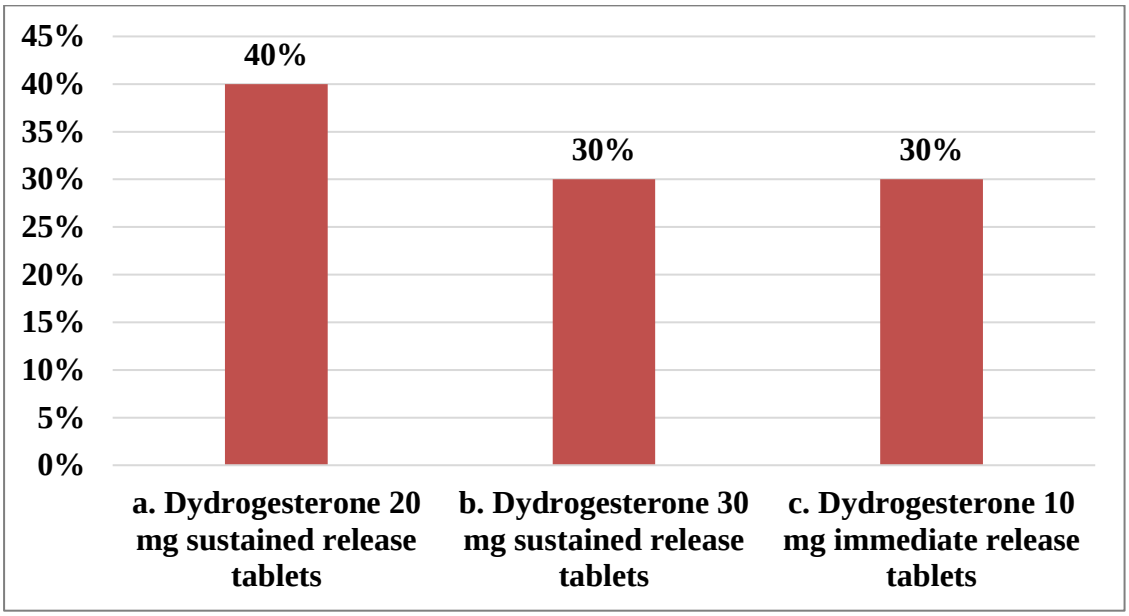
According to 40% of doctors, 10 mg BID from the onset of bleeding until the 16th week of pregnancy is the preferred dose of dydrogesterone in RPL.

15. Which of the following dydrogesterone formulation would you prefer in patients of RPL?

a. Dydrogesterone 20 mg sustained release tablets

b. Dydrogesterone 30 mg sustained release tablets

c. Dydrogesterone 10 mg immediate release tablets



As per 40% of doctors, Dydrogesterone 20 mg sustained release tablets is preferred in patients of RPL.

Summary

- According to 41% of doctors, they encounter of 5 - 20% cases of Endometriosis in patients visiting to their clinic every month.
- As per 66% of doctors, in 41-60% of their patients they prefer progestins.
- According to 55% of doctors, they prefer oral progesterone and its derivative the most.
- According to 29% of doctors, in 41-50% of patients with endometriosis they prescribe Dydrogesterone.
- As per 52% of doctors, 10 mg BID is the preferred dose of dydrogesterone in patients with endometriosis.
- As per 56% of doctors, frequent dosing (TID) could be the possible reasons of non-adherence to dydrogesterone in patients of Endometriosis.
- According to 72% of doctors, they prefer sustained release formulation of dydrogesterone in patients with Endometriosis, with 20 mg Dydrogesterone SR (BID) being the preferred dose.
- As per 41% of doctors, the patient profiles most suitable for Dydrogesterone SR therapy is endometriosis.
- According to 35% of doctors, 3-6 months is the average duration of the treatment with dydrogesterone in patients of Endometriosis.
- According to 32% of doctors, increased efficacy, less side effects, better tolerability, patient convenience are the benefits theyobserve with dydrogesterone/SR over micronized progesterone.
- As per 40% of doctors, Dydrogesterone is the most preferred type of progestogen in recurrent pregnancy loss.
- According to 86% of doctors, they do use dydrogesterone in Recurrent Pregnancy Loss.
- According to 60% of doctors, they use dydrogesterone in their patients with RPL as a monotherapy.
- According to 40% of doctors, 10 mg BID from the onset of bleeding until the 16th week of pregnancy is the preferred dose of dydrogesterone in RPL.
- As per 40% of doctors, Dydrogesterone 20 mg sustained release tablets is preferred in patients of RPL.

Consultant Opinion

Market Opportunities:

With 55% of doctors often prescribing Tenecteplase for ACS, there is a significant market opportunity for pharmaceutical companies to meet the growing demand for this thrombolytic agent.

STEMI accounts for 70% of the primary indications for Tenecteplase. There is potential to explore and expand its usage for other ACS conditions, such as non-ST-elevation myocardial infarction (NSTEMI), to capture a broader market share.

Value for Healthcare Professionals:

Given that 52% of doctors consider ECG as the most reliable diagnostic tool for assessing Tenecteplase therapy's success, there is an opportunity for pharma companies to invest in developing advanced diagnostic technologies or tools that complement ECG assessments, providing more comprehensive insights into treatment efficacy.

Healthcare professionals value comprehensive training and education on Tenecteplase administration, monitoring, and management of complications. Pharma companies can provide valuable educational resources, including online courses, workshops, and webinars, to enhance healthcare professionals' knowledge and skills.

Adverse Effect Management:

Since 54% of doctors occasionally encounter bleeding complications with Tenecteplase therapy, there is a need for improved strategies and resources for managing these adverse effects. Pharma companies can develop educational materials, guidelines, and support programs to assist healthcare professionals in promptly identifying and managing bleeding complications.

Withdrawal Management:

Pharma companies can collaborate with healthcare professionals to develop standardized protocols and guidelines for safely discontinuing Tenecteplase therapy when necessary. This includes strategies for gradual withdrawal and alternative treatment options to minimize risks and ensure patient safety.

Market Positioning:

Pharma companies should emphasize the unique advantages of Tenecteplase, such as its single-bolus administration and rapid reperfusion capabilities, in their marketing efforts. Positioning Tenecteplase as a convenient and effective treatment option can differentiate it from other thrombolytics in the market.

Personalized Treatment Decisions:

Develop and promote risk assessment tools or algorithms that aid healthcare professionals in personalized treatment decisions for ACS patients. These tools can integrate patient-specific factors, clinical stability, and availability of PCI facilities to guide treatment selection between Tenecteplase and PCI.

Improving Patient Outcomes:

Encourage regular follow-up and monitoring of patients treated with Tenecteplase through ECGs, biomarker measurements, and echocardiograms, as recommended by 65% of doctors. Pharma companies can provide support in implementing these monitoring practices to improve patient outcomes and long-term prognosis.

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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