ESCO® ASTER

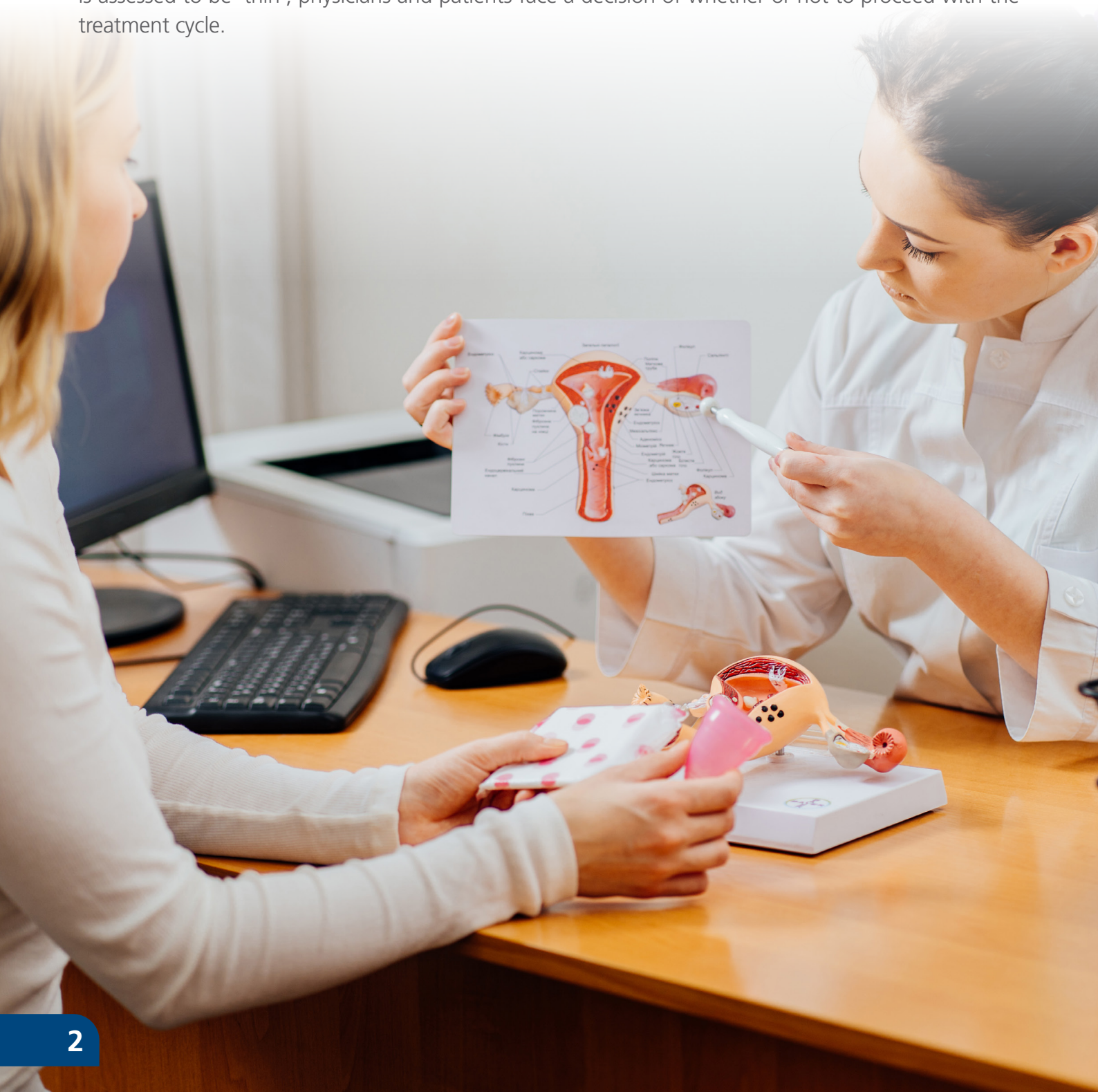
Thin Endometrium with Repeated Implantation Failure

Stem Cell Therapy using Tide Motion System

Introduction

During pregnancy, at least 9 mm of thickness is required to provide a site for proper implantation of the fetus. This thickness not only plays an important function in the implantation of the fetus to the uterine wall, but also assists the development of the baby in the later stages of pregnancy. If due to any cause, this lining becomes thin, it becomes unfavorable for the fertilized egg to get implanted to the wall. This can lead to infertility of a female uterus. Pregnancy cannot take place because a fertilized egg needs strong support for implantation and support for growing into an embryo.

One in nine couples in Europe and USA is affected by implantation disorders, and it is estimated that repeated implantation failure (RIF) has a prevalence of 15-20% *in vitro* fertilization (IVF). Consequently, endometrium assessment is an essential component in assisted reproduction. When the endometrium is assessed to be 'thin', physicians and patients face a decision of whether or not to proceed with the treatment cycle.

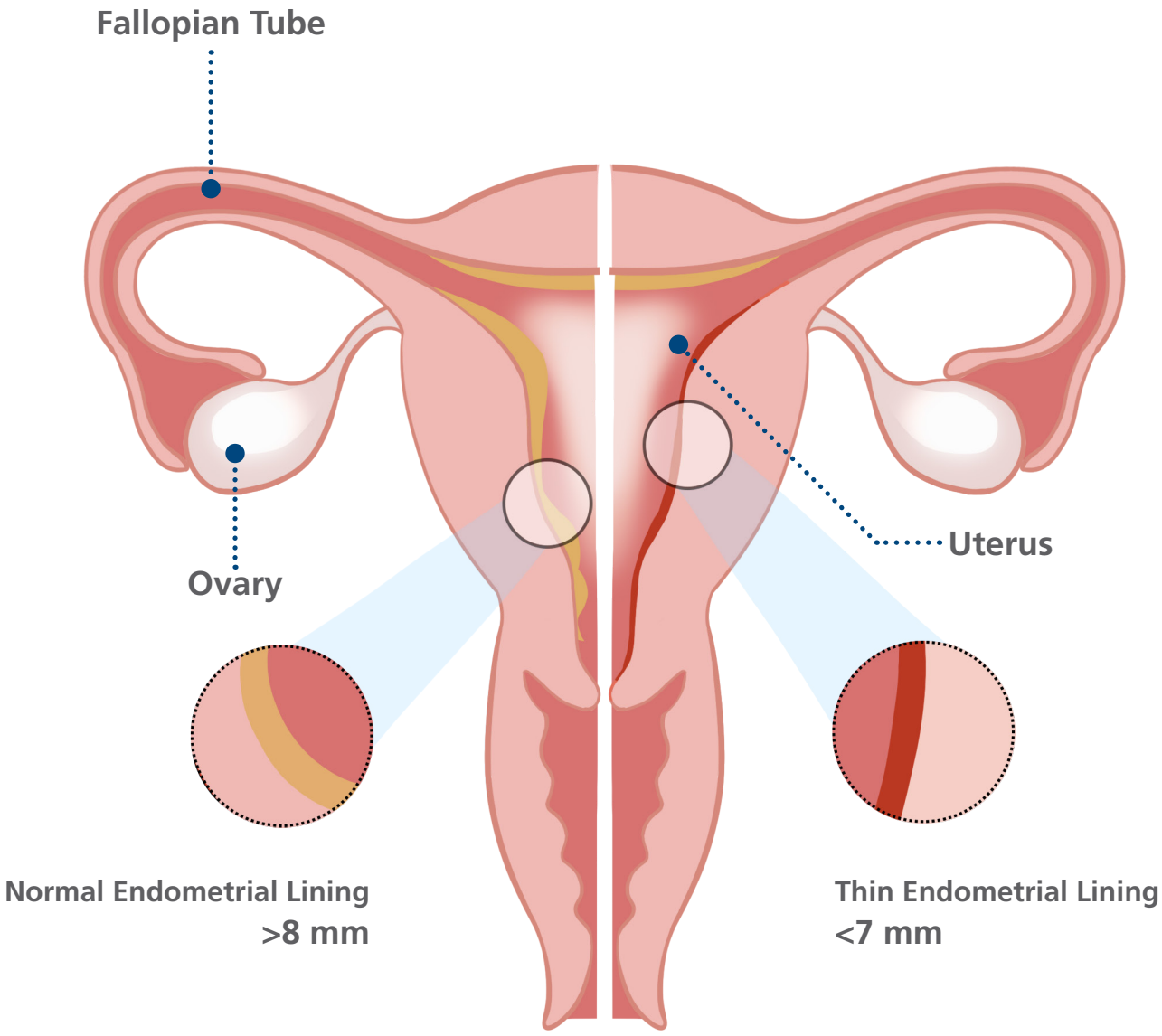


What is Thin Endometrium?

The definition and cut-off for thin endometrium differ between studies, although most studies use the endometrial thickness of <7 mm or <8 mm as a basis. It is a condition that arises mainly due to inadequate estrogen levels in the female body.

According to Miwa et al., a thin endometrium is characterized by poor growth of glandular epithelium, high uterine blood flow impedance, decreased vascular endothelial growth factor (VEGF) expression, and poor vascular development.

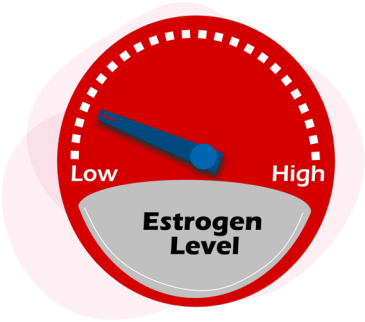
Thin endometrium results in affecting the implantation of fertilized eggs inside the uterus and thus affects pregnancy.



What Causes Endometrium Thinning?

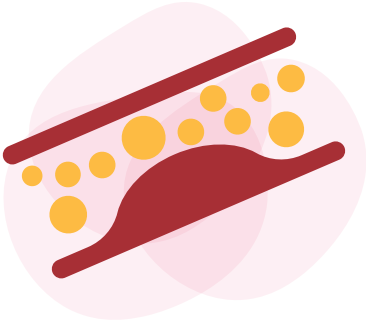
A healthy endometrium is crucial for normal menstrual cycle and trouble-free pregnancy. It also goes a long way in ensuring effective implantation of fertilized eggs inside the uterus.

Numerous medical studies have found that persistently thin uterine lining is an indication of serious problems from gynecological point of view including lower chances of successful pregnancy. Some of the causes are listed below:



Low Estrogen Levels

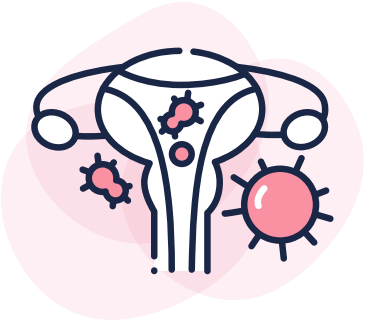
The primary reason for a thin endometrial lining is lack of adequate estrogen. Since this hormone thickens and prepares the endometrium for implantation, low levels might indicate lesser chances of pregnancy.



Insufficient Blood Flow

Reasons of inadequate blood flow in the endometrium includes:

- Sedentary lifestyle
- Tilted uterus
- Uterine fibroids
- Uterine fibroid embolization
- Uterine arterial constriction



Genital Tuberculosis

The fallopian tubes are affected in almost all cases of genital TB, and along with endometrial involvement, it causes infertility among women.

Induced Medical Abortion

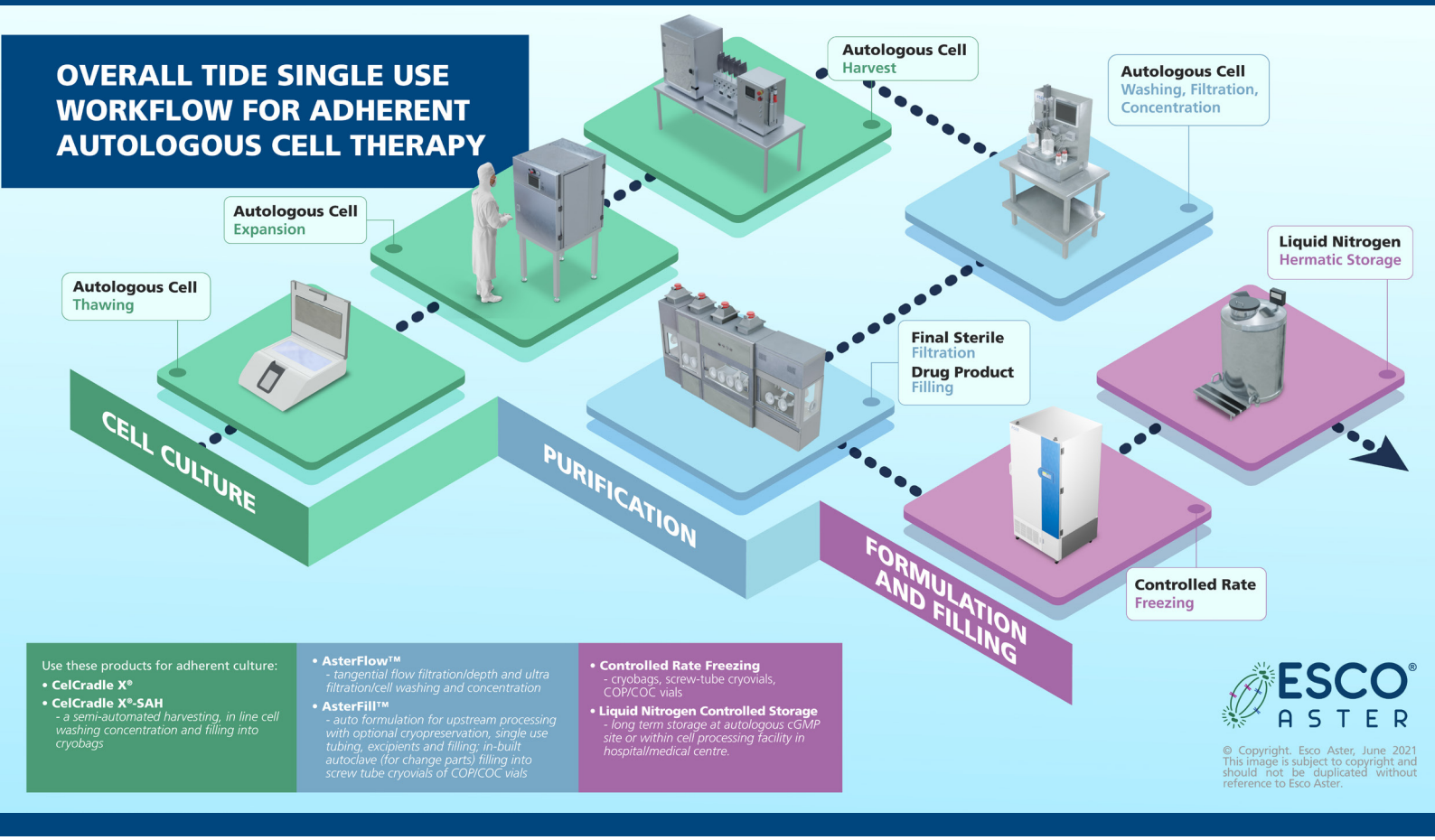
Induced medical abortion causes endometrium thinning thus, preventing the embryo from staying implanted and growing.

Prolonged Use of Birth Control Pills

Overuse of birth control pills, especially progestin, throws the normal balance of body hormones out of order and results in altered estrogen level and endometrial thinning.

Excessive Use of Clomid

Clomid is a medication used to stimulate ovulation. This medication can cause thinning of endometrial lining because this is “antiestrogen” (opposes estrogen production) in nature.



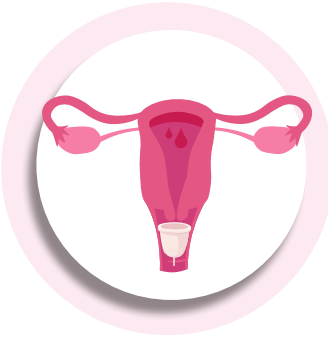
Endometrial Mesenchymal Stem Cell Therapy

Thin endometrium is characterized by the slow growth of the glandular epithelium causing embryos not to grow, thereby leading to infertility.

Treatment of thin endometrium mainly involves drug therapy, stimulation scrape therapy, and intrauterine injection of granulocyte colony-stimulating factor (G-CSF). Although these multiple treatment approaches are accessible, the general curative result is low, making this condition in reproductive medicine challenging.

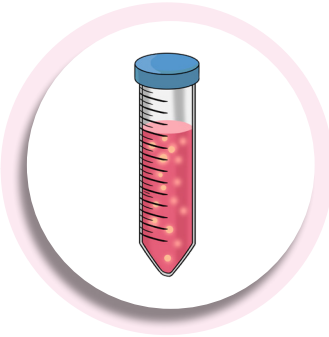
Endometrial Mesenchymal Stem Cells (EnMSCs), with their advantage of high clonality, significant proliferation and differentiation potential, regenerative capacity, immunomodulatory, angiogenic ability, low immunogenicity, non-invasive collection methods, and no ethical controversy are proposed as an alternative and appear to offer promising results in endometrial thinning which is one of the major cause of infertility among women.

Menstrual-Derived Endometrial Stem Cell Therapy Workflow



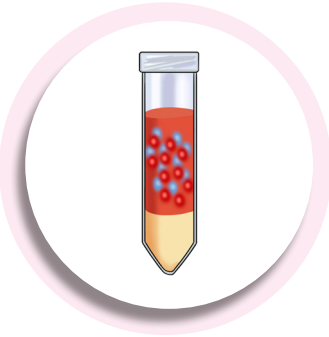
COLLECTION AND SAMPLING

5 ml of menstrual blood (MB) is collected using menstrual cup.



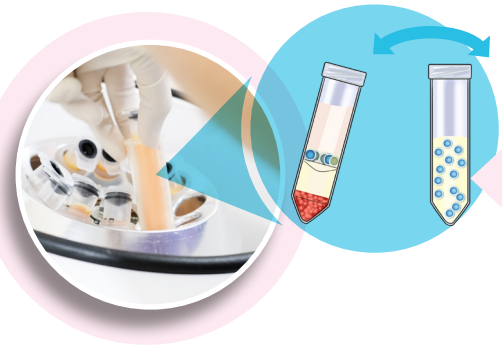
DECANTATION INTO ISOLATION MEDIA

Decant the collected MB sample into the falcon tube containing isolation media.



CELL ISOLATION USING DENSITY GRADIENT MEDIA

Slowly add the menstrual blood sample to the Ficoll-paque density gradient media.



CELL PROCESSING

After centrifugation, stem cells are then isolated and processed for expansion in the lab.

EXPANSION

enMSCs are then expanded using the proprietary Tide Motion bioreactor systems.

CRYOPRESERVATION

After expansion, enMSCs are then cryopreserved in a suspension solution.

THAWING

enMSCs are thawed at 37°C.

TRANSPLANTATION

Once thawed, the enMSCs will be transplanted with the use of an Embryo Transfer Transmyometrial Catheter.

Disclaimer:

These are potential applications of the Tide Motion system for Autologous Cell Therapy. Esco Aster under an investigator-initiated clinical trial can perform endometrial mesenchymal stem cells (EnMSCs) isolation, banking, and expansion to the filled product within our cGMP compliant facility in Singapore. Esco Aster does not make claims and warrants that the treatment is medically effective and such complementary and alternative medicine are to be performed under strict clinical advice from the patient's clinician/physician.

Scientific Evidences

Tersoglio AE et al., evaluated the endometrial changes before and after the transfer of endometrial mesenchymal stem cells (enMSCs) in a population of thinned endometrium women, with absence or hypo-responsiveness to estrogen and repeated implantation failure (RIF). They've also evaluated the clinical outcomes of the intervention in terms of clinical pregnancy (CP), early abortions, ongoing pregnancy and live birth delivery rate (LBDR) per in vitro fertilization (IVF) cycle. Research results showed that there was a highly significant increase in endometrial thickness after the inoculation of enMSCs, expressing the high regenerative capacity of the intervention. In 8/29 (27.5%) cases, they presented pretreatment values with critical values of <4 mm, despite having been subjected to estrogen therapy for over 20 days. With these, they have concluded that subendometrial enMSCs inoculation produce a significant increase in endometrial thickness; normalize the enHP, enIHQ and enFC. As a result, IVF after treatment with enMSCs yields a higher rate of CP and LBDR.

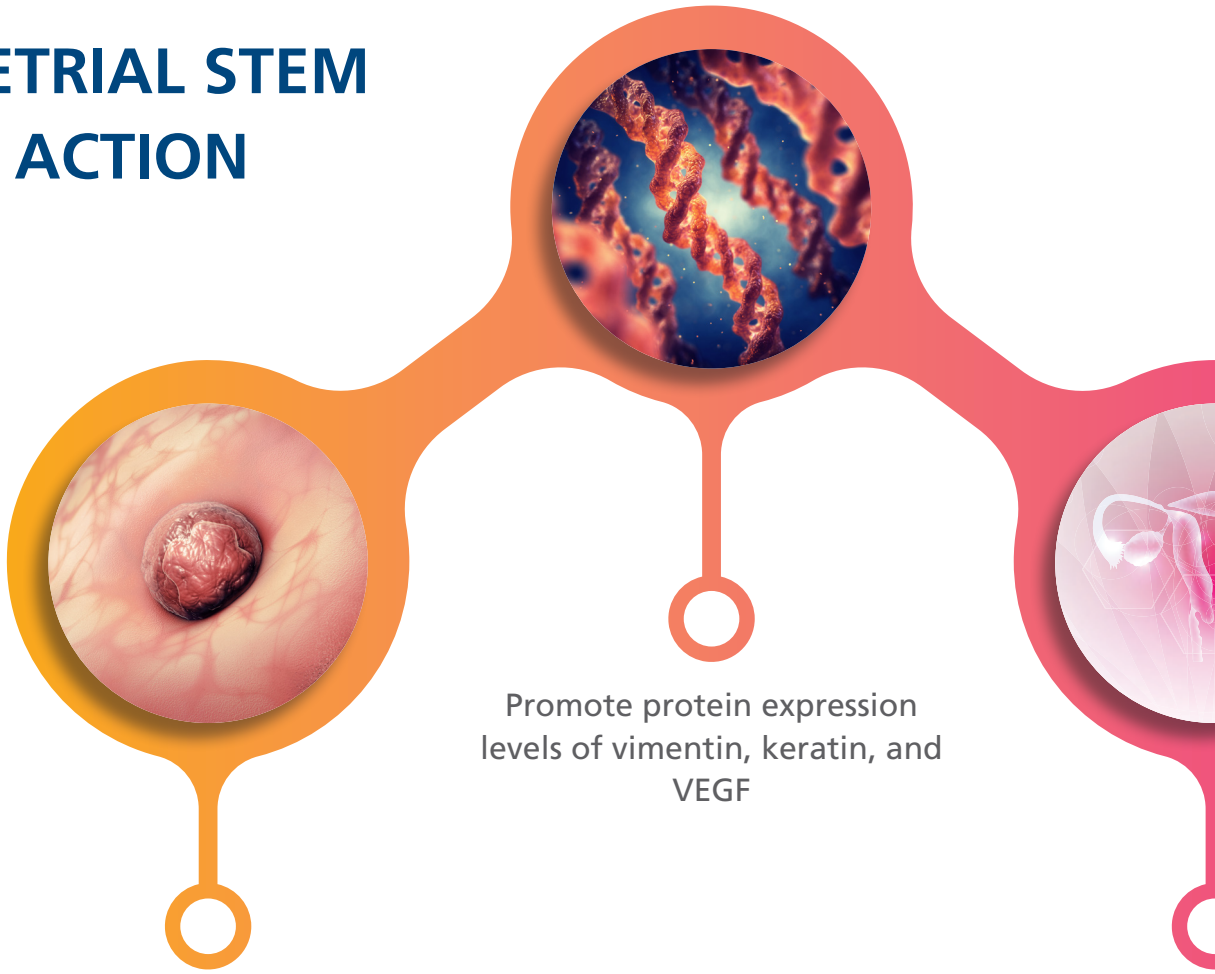
In a research led by Zhang Y. et al., they have established mouse endometrial injury model and examined the benefit of human endometrial mesenchymal stem cells derived from menstrual blood (MenSCs) in restoration of injured endometrium. Injured endometrium exhibited significantly accelerated restoration at Day 7 after MenSCs transplantation, with increased endometrial thickness and microvessel density. Moreover, the fertility of mice with injured endometrium was improved, with higher conception rate (53.57% vs 14.29%, P = 0.014) and larger embryo number (3.1 ± 0.6 vs 0.9 ± 0.7, P = 0.030) in MenSCs group than control group, while no difference was found in undamaged horns between two groups.

Another study by Zhu et al., evaluated the protective effects of MenSCs on impaired endometrial stromal cells (ESCs), as well as the signaling pathways involved in this process. Mifepristone was used to damage human ESCs, which were subsequently cocultured with MenSCs. The proliferation, apoptosis, and migration of ESCs were assessed, together with the expression of related signaling proteins including total p38 mitogen-activated protein kinase, P-p38, total protein kinase B (AKT), P-AKT, ß-catenin, and vascular endothelial growth factor (VEGF). MenSCs significantly recovered the proliferation and migration ability of impaired ESCs, inhibited ESC apoptosis, and upregulated protein expression of P-AKT, P-p38, VEGF, and ß-catenin. Their findings suggested that MenSC-based therapies could be promising strategies for the treatment of endometrial injury, and that AKT and p38 signaling pathways may be involved in this process.

References:

1. *Tersoglio AE, Tersoglio S, Salatino DR, et al. Regenerative therapy by endometrial mesenchymal stem cells in thin endometrium with repeated implantation failure. A novel strategy. JBRA Assisted Reproduction. 2020 May;24(2):118-127. DOI: 10.5935/1518-0557.20190061. PMID: 31589391; PMCID: PMC7169908.*
2. *Zhang Y, Lin X, Dai Y, et al. . Endometrial stem cells repair injured endometrium and induce angiogenesis via AKT and ERK pathways. Reproduction 2016;152:389–402.*
3. *Zhu H, Jiang Y, Pan Y, Shi L and Zhang S: Human menstrual blood-derived stem cells promote the repair of impaired endometrial stromal cells by activating the p38 MAPK and AKT signaling pathways. Reprod Biol. 18:274–281. 2018.*

ENDOMETRIAL STEM CELLS IN ACTION

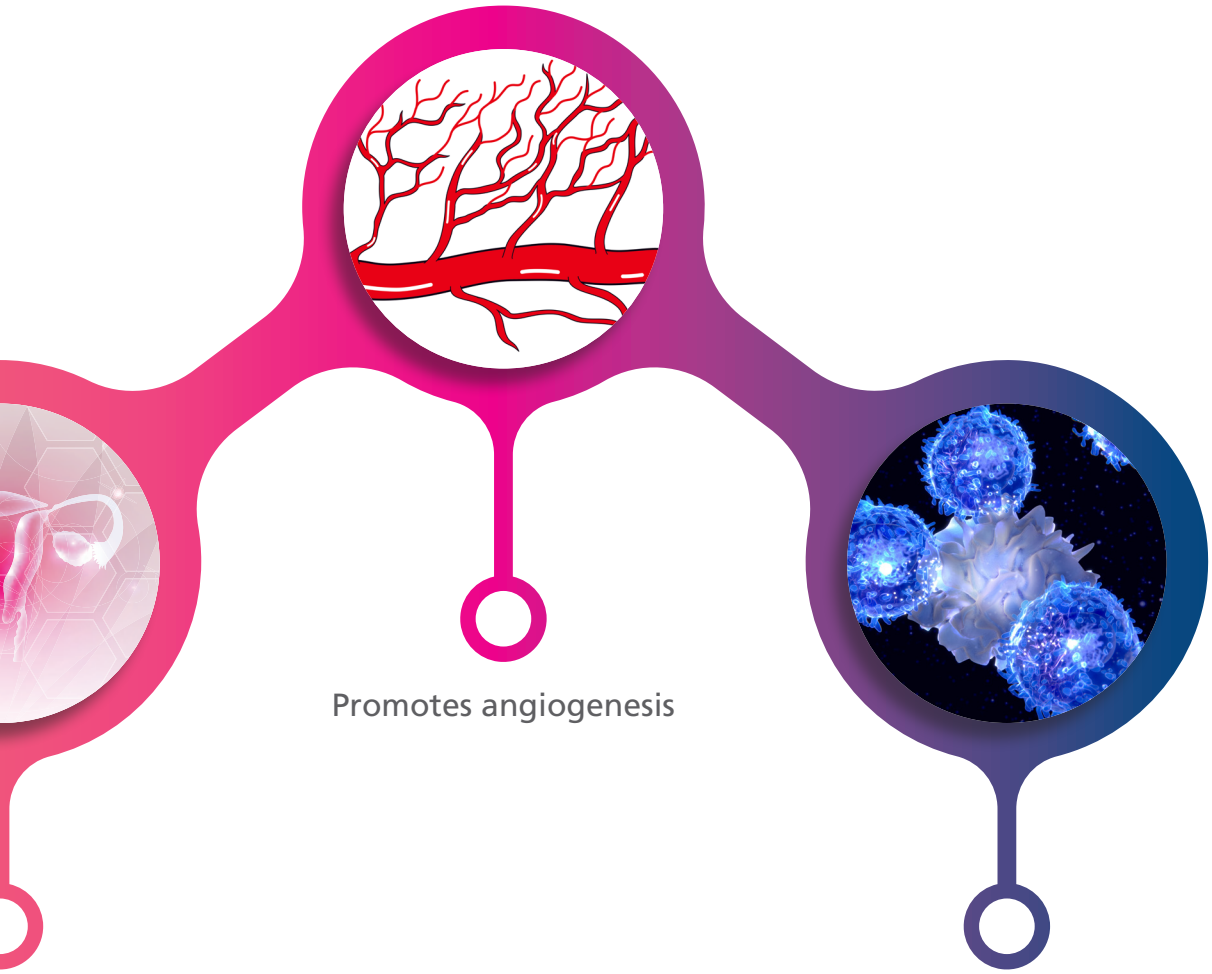


Promote protein expression levels of vimentin, keratin, and VEGF

Improve embryo implantation rate

Enhance endom and microve

The future of stem cell therapy demands high quantities of mesenchymal stem cells (MSCs) ranging from 10 million to more than 200 million cells per dosage. Conventional expansion of MSCs on plasticwares (2D culture systems) become impractical when large dosages of more than 50 million cells are required. The use of bioreactors which combines scaling-up ability, process control, and automation is the primary solution for this need. Many bioreactors are facing issues in supporting MSC cultures due to complications in balancing the need for proper mixing of media with the need to extremely low shear stress as well as the inability to separate cells from micro/macrocarriers with high cell yield and viability.



Promotes angiogenesis

etrial thickness
essel density

Enhance
immunomodulation

ESCO ASTER has leveraged on the use of Esco VacciXcell's Tide Motion bioreactors to establish a robust and scalable platform using macrocarriers to meet the demands for future clinical therapies. MSCs isolated from different tissues sources were seeded and allowed to expand within PET macroporous carriers. Throughout culture periods, cell culture conditions were monitored, with bioprocess parameters such as glucose consumption and pH levels measured to ensure proper scale-up. Key issues such as cell seeding densities, media culturing condition and improved bioprocess parameters needed for optimal stem cell systems were studied in our system. Overall, Esco Aster present a process optimization with quality controls and release criteria of functional and phenotypic characteristics for the translation of academic/industrial R&D into bench scale for future clinical trials and commercialization process.

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