

## Menstrual Blood: A Valuable Source for Regenerative Medicine

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### Abstract

Menstrual blood is a rich source of stem cells, the endometrium-lining of the uterus regenerates every month. Research on stem cells provides knowledge about how healthy cells replace damaged ones in adults, leading to the possibility of cell-based therapy to treat diseases. Menstrual Stem Cells (MenSCs) show multipotency by directionally differentiating into chondrogenic, adipogenic, osteogenic, neurogenic, and cardiogenic cell lineages. These studies demonstrate the plasticity of MenSCs for potential research in regenerative medicine. Researchers seeking new and more abundant sources of stem cells for use in regenerative medicine have identified a potentially unlimited, noncontroversial, easily collectable, and inexpensive source- menstrual blood.

**Keywords:** Menstrual Blood, stem cell, MenSCs, Regenerative Medicine

### Reproductive development in woman

When a baby girl is born, she has all the eggs her body will ever use, and many more, perhaps as many as 450,000. They are stored in her **ovaries**, each inside its own sac called a **follicle**. As she matures into puberty, her body begins producing various hormones that cause the eggs to mature. This is the beginning of her first cycle; it's a cycle that will repeat throughout her life until the end of menopause<sup>1</sup>.

The hypothalamus is a gland in the brain responsible for regulating the body's thirst, hunger, sleep patterns, libido and endocrine functions. It releases the chemical messenger **Follicle Stimulating Hormone Releasing Factor (FSH-RF)** to tell the **pituitary**, another gland in the brain, to do its job. The pituitary then secretes **Follicle Stimulating Hormone (FSH)** and a little **Leutenizing Hormone (LH)** into the bloodstream which cause the follicles to begin to mature.

The maturing follicles then release another hormone, **estrogen**. As the follicles ripen over a period of about seven days, they secrete more and more estrogen into the bloodstream. Estrogen causes the lining of the uterus to thicken. It causes the cervical mucous to change. When the estrogen level reaches a certain point it causes the hypothalamus to release **Leutenizing Hormone Releasing Factor (LH-RF)** causing the pituitary to release a large amount of **Leutenizing Hormone (LH)**. This surge of LH triggers the one most mature follicle to burst open and release an egg. This is called ovulation

### Ovulation

As ovulation approaches, the blood supply to the ovary increases and the ligaments contract, pulling the ovary closer to the Fallopian tube, allowing the egg, once released, to find its way into the tube. Just before ovulation, a woman's cervix secretes an abundance of clear "fertile mucous" which is characteristically stretchy. Fertile mucous helps facilitate the sperm's movement toward the egg. Some women use daily mucous monitoring to determine when they are most likely to become pregnant. Mid cycle, some women also experience cramping or other sensations. Basal body temperature rises right after ovulation and stays higher by about 4 degrees F until a few days before the next period<sup>2</sup>.

### Uterine Changes

Between midcycle and menstruation, the follicle from which the egg burst becomes the corpus luteum (yellow body). As it heals, it produces the hormones oestrogen and, in larger amounts, progesterone which is necessary for the maintenance of a pregnancy. In the later stages of healing, if the uterus is not pregnant, the follicle turns white and is called the corpus albicans. Oestrogen and progesterone are sometimes called "female" hormones, but both men and women have them, just in different concentrations. Progesterone causes the surface of the uterine lining, the endometrium, to become covered with mucous, secreted from glands within the lining itself. If fertilization and implantation do not occur, the spiral arteries of the lining close off, stopping blood flow to the surface of the lining. The blood pools into "venous lakes" which, once full, burst and, with the endometrial lining, form the menstrual flow. Most periods last 4 to 8 days

## Menstruation

**Menstruation** is the shedding of the uterine lining (endometrium). It occurs on a regular basis in reproductive-age females of certain mammal species. The **menstrual cycle** is a cycle of physiological changes that occurs in fertile females. Overt menstruation (where there is bleeding from the uterus through the vagina) is found primarily in humans and close evolutionary relatives such as chimpanzees<sup>3</sup>. The females of other placental mammal species have estrous cycles, in which the endometrium is reabsorbed by the animal (covert menstruation) at the end of its reproductive cycle.

Menstruation is the most visible phase of the menstrual cycle. Menstrual cycles are counted from the first day of menstrual bleeding, because the onset of menstruation corresponds closely with the hormonal cycle.

During pregnancy and for some time after childbirth, menstruation is normally suspended; this state is known as amenorrhoea, i.e. absence of the menstrual cycle. If menstruation has not resumed, fertility is low during lactation. The average length of postpartum amenorrhoea is longer when certain breastfeeding practices are followed; this may be done intentionally as birth control (lactational amenorrhoea method).

The menstrual cycle, under the control of the endocrine system, is necessary for reproduction. It is commonly divided into three phases: the follicular phase, ovulation, and the luteal phase; although some sources use a different set of phases: menstruation, proliferative phase, and secretory phase<sup>4</sup>. The length of each phase varies from woman to woman and cycle to cycle, though the average menstrual cycle is 28 days<sup>5</sup>. Hormonal contraception interferes with the normal hormonal changes with the aim of preventing reproduction.

Stimulated by gradually increasing amounts of estrogen in the follicular phase, menses slow then stop, and the lining of the uterus thickens. Follicles in the ovary begin developing under the influence of a complex interplay of hormones, and after several days one or occasionally two become dominant (non-dominant follicles atrophy and die). Approximately mid-cycle, 24–36 hours after the Luteinizing Hormone (LH) surges, the dominant follicle releases an ovum, or egg in an event called ovulation. After ovulation, the egg only lives for 24 hours or less without fertilization while the remains of the dominant follicle in the ovary become a corpus luteum; this body

has a primary function of producing large amounts of progesterone. Under the influence of progesterone, the endometrium (uterine lining) changes to prepare for potential implantation of an embryo to establish a pregnancy. If implantation does not occur within approximately two weeks, the corpus luteum will involute, causing sharp drops in levels of both progesterone and estrogen. These hormone drops cause the uterus to shed its lining in a process termed menstruation.

The menstrual cycle can be divided into several different phases. The average length of each phase is shown below **assuming a 28-day cycle**:

Name of phase	Average start day	Average end day
Menstrual phase (menstruation)	1	4
Proliferative phase (some sources include menstruation in this phase)	5	13
Follicular phase	1	13
Ovulatory phase (ovulation)	14	14
Luteal phase (also known as secretory phase)	15	28
Ischemic phase	27	28

In the menstrual cycle, changes occur in the female reproductive system as well as other systems (which lead to breast tenderness or mood changes, for example). A woman's first menstruation is termed menarche, and occurs typically around age 12. The end of a woman's reproductive phase is called the menopause, which commonly occurs somewhere between the ages of 45 and 55.

Menstruation is also called **menstrual bleeding**, **menses**, **catamenia** or a **period**. The flow of menses normally serves as a sign that a woman has not become pregnant. (However, this cannot be taken as certainty, as a number of factors can cause bleeding during pregnancy; some factors are specific to early pregnancy, and some can cause heavy flow)<sup>6,7,8</sup>. During the reproductive years, failure to menstruate may provide the first indication to a woman that she may have become pregnant.

### Bleeding - A New Theory

Some researchers view menses as the natural monthly cleansing of the uterus and vagina of sperm and bacteria they carried.

### **Ingesting Menstrual Blood**

In the African-American hoodoo tradition, as well as in Sicilian folk-magic, menstrual blood served to a man in his coffee or tea is a sovereign recipe for capturing his sexual attention. No ritual, prayer, or invocation is necessary; simply adding some menstrual blood to the man's coffee or tea. The idea is to get her scent into the beloved's sphere of consciousness. This is nothing more or less than pheromone-magic, and as such it partakes of biology as much as it does of occultism<sup>9</sup>.

### **Menstrual Extraction**

Menstrual extraction is a simple suction technique used to remove the menstrual blood from the uterus on the first day of menstruation. It can remove a fertilized egg from the uterus. A menstrual extraction can be performed by removing the rest of the retained tissue and the uterus can be able to clamp down and slow the bleeding to an acceptable level. It is usually done by an experienced group of women, as a home-care procedure in order to gain knowledge about their bodies and menstrual cycles and to exert more direct control over their reproductive cycles. The procedure is very safe; in reality it can be safer than a clinical abortion, when done correctly by a group with experience. There is no waiting for weeks as in a clinical abortion. Due to the early timing the cervix does not need to be dilated (forced open) because the smallest size canula can be used. The contents of the uterus are gently sucked out; there is no cutting or scraping of the uterine wall necessary. The contents consist of mostly blood, chorionic villi and some tissue, the amount of tissue depends on how far along the pregnancy is, the rapidly dividing cell structure is still too small to be seen.

Because the cervix is not dilated this means technically it is safe (but not advisable) to take a bath, to make love or to use a tampon. After a clinical abortion, if you do any of these things it could give you a nasty uterine infection, which is why they give women antibiotics after a clinical abortion. When the cervix is dilated the trap door of the cervix is unable to close to protect the uterus from the outside world<sup>10</sup>.

There are no drugs given. Allowing the woman to stay in touch with what is happening to her body. She is in control. She can stop at any time to take a break. The whole process could take an hour, or up to 3 hours. For every woman it is different. For some women it is mildly uncomfortable and other women experience more severe cramping, nausea, or dizziness, the experience is different for each woman.

Menstrual extractions can be done safely up to 8-9 weeks from the last menstrual period. The sooner it is done the less intense it is physically, it can be done when menstruation is due, up until 8-9 weeks from the last menstrual period. After 9 weeks the tissue is too large for the canulas used in the menstrual extraction kits. The risk of incomplete extraction can occur thus increasing the risk for possible hemorrhage or infection<sup>11</sup>.

### **Cell Procurement and Processing**

An endometrial/menstrual cell sample was procured during the first few days of a menstrual cycle. The cells were harvested with the informed consent of the donor as approved by institutional review board. The cells were transferred in phosphate-buffered saline (PBS) with penicillin/streptomycin and heparin. The sample was shipped at 4°C until it reached the processing laboratory within 24–48 h after procurement. The sample was centrifuged and supernatant was evaluated for bacteria and the cells were then cultured<sup>12</sup>.

### **Stem Cells in Menstrual Blood**

The feasibility of using stem cells for regenerative therapies is limited by two factors: obtaining a significant number of cells and doing so in a relatively noninvasive manner. Because our bodies freely shed a limited and select number of cells, many stem cell types must be obtained using a rather invasive procedure. Stem cell research is undoubtedly a hot and controversial topic with people nation-wide as well as internationally. The topic only grew more heated when a ban on federal funding human embryonic stem cell research and promised to remove all ideology from scientific studies. However, no matter what your position on stem cell research is, it can undoubtedly mean great things for the health industry and go on to cure many illnesses and diseases, such as diabetes, cardiac, stroke, vascular regeneration, and many cancers.

It has been hypothesized that menstrual blood contains a viable source of stem cells to be utilized or preserved for future use, providing an ideal source for a vast range of stem cell research and therapies. However, two laboratories independently reported the discovery of a new type of stem cell that may overcome both obstacles; stem cells were found to reside in menstrual blood<sup>13,14</sup>. Researchers suspected stem cells to be present in menstrual blood because stem cells were previously found to be present in the lining of the uterus. The wall of the uterus is lined by a layer of cells called the endometrium (Fig. 1). To create ideal conditions for the uterus to accept and nurture an embryo, the endometrium

lining becomes thicker and increases the number of blood vessels and glands within it. However, if implantation does not occur, the endometrium lining is broken down and shed. Overall, the endometrium is quite a hyperproliferative tissue, continuously being broken down and rebuilt; it is an ideal tissue to investigate for the presence of stem cells. In the menstrual cycle, the shedding is known as menstruation, or menstrual bleeding; the excreted menstrual blood is made up of blood as well as cells from the endometrium layer. Researchers previously reported the presence of stem cells in the intact endometrium lining of the uterus<sup>15, 16, 17</sup>. Because stem cells were found in the endometrium, researchers thought it likely that stem cells could also be found in the shed endometrium in the form of menstrual blood, which can be obtained in relatively large quantities in a much less invasive manner. However, the stem cells discovered in menstrual blood, MenSCs, appear to be rather different from stem cells derived from the intact endometrium.

Menstrual blood contains millions of adult stem cells that demonstrate properties similar to bone marrow and embryonic stem cells. The stem cells found in menstrual blood rapidly multiply, turning into possibly every cell type in the human body. Whether you agree with stem cell research or not, everyone supports the research to cure many illnesses and diseases and retrieving stem cells from menstrual blood would not infringe upon anyone's moral code, considering that menstrual blood is something that arrives monthly for all women. These stem cells, termed menstrual stem cells (MenSCs), are not only harvested in a noninvasive manner and relatively readily available in large quantities, but they potentially overcome the problem of immune rejection in many female patients as well.

Compared with the stem cells from other sources, such as bone marrow and cord blood, menstrual stem cells are easier to collect, do not cause any harm or pain to the donor and can be collected for more than 35 years, from 12 years old to 47 years.

Experiments in lab dishes under the right conditions showed that, menstrual stem cells could turn into more different tissue types including bone, blood vessel, fat, brain, lung, liver, pancreas and heart than other adult stem cells. The new stem cells also grow readily and rapidly, which is an important advantage because it is difficult to get some types of adult stem cells to give rise to enough cells to be of any medical value.

While stem cells from the intact endometrium appear to

be mesenchymal stem cells (MSCs), MenSCs do not; they are distinctly different not only in their undifferentiated state, but in the cells they can differentiate into as well. Researchers categorize stem cells into certain groups based off of, among other factors, their cell morphology and the proteins they express. An established stem cell group usually expresses a distinct set of proteins. MenSCs, though morphologically appearing mesenchymal, were found to express only some, but not all, proteins characteristic of MSCs. Additionally, MenSCs were reported to be able to differentiate into, or become, cells from the three different germ layers: mesoderm (muscle, bone, fat, cartilage, and endothelial cells), ectoderm (neurons) and endoderm (liver, pancreas, and lung cells)<sup>13, 14</sup>. However, the mesenchymal stem cells from the intact endometrium cannot generate cells from all three germ layers. Overall, MenSCs were determined to be functionally distinct from endometrium MSCs<sup>13, 18</sup>.

The MenSCs expanded rapidly and maintained greater than 50 percent of their telomerase activity when compared to human embryonic stem cells and better than bone marrow-derived stem cells. Studies have demonstrated that MenSCs are easily expandable to clinical relevance and express multipotent markers at both the molecular and cellular level. Researchers emphasized the importance of the abundance and plasticity of MenSCs. Based on the results of their studies, they noted the potential for MenSCs in regenerative transplantation therapies for many different organs and tissues. The need for regenerative therapies using cells with the ability to engraft and differentiate is vast. The ideal cell would also have the ability to be used in an allogenic manner from donors for optimal immunogenic compatibility. Due to their ease of collection and isolation, MenSCs would be a great source of multipotent cells if they exhibit this property along with their ability to differentiate<sup>12</sup>.

Though MenSCs do not appear to be MSCs, the stem cell category MenSCs best fall into still remains unclear, along with several other basic answers concerning their stem cell identity. In addition to MSC proteins, MenSCs were also negative for proteins characteristic of hematopoietic stem cells, which are cells that give rise to the hematopoietic system. However, MenSCs were, surprisingly, positive for some proteins distinctive of embryonic stem cells<sup>13, 14</sup>. The expression of these embryonic stem cell proteins is quite unusual in adult stem cells, or stem cells derived from adult tissues, such



as MenSCs<sup>14</sup>. The presence of embryonic stem cell proteins in MenSCs, combined with ability of MenSCs to differentiate into the three germ layers, led one research group to label them pluripotent<sup>13</sup>, though others only refer to them as multipotent<sup>14</sup>. A pluripotent stem cell is generally one that is able to differentiate into cells from any of the three germ layers, while multipotent stem cells can only differentiate into cells from one or two of the germ layers. Most adult stem cells are only multipotent. If the MenSCs are indeed pluripotent, they may have a greater potential for cell-based therapies than if only multipotent.

Some reported characterization discrepancies of the MenSCs have led researchers to suspect that there may be a bit of variability in the quality of MenSCs isolated, possibly depending on many suspected factors, though none have been fully investigated yet. Since there was not a standard method of isolation in place for these cells, there could be great variability in the actual cells isolated depending on the specifics of the isolation method used. Additionally, the quality and potency of MenSCs isolated could depend on the individual donors, possibly being related to age or other factors, though this is currently untested<sup>19</sup>. In the menstrual blood, MenSCs make up a portion of the total cells present and are mainly selected for from this collection of cells by their ability to grow on tissue culture-treated plastic. Other cell populations within this fluid have not been fully investigated; it is quite possible that the subpopulations of cells in this fluid, including the MenSCs, may also vary significantly between donors<sup>19</sup>. To complicate the identity of these stem cells even further, it has been suggested that there may be multiple different stem cell populations in the menstrual blood, as researchers have had some conflicting protein expression results<sup>19</sup>. Lastly, the origin of these stem cells is still much up for debate. Some researchers theorize that the MenSCs are shed endometrium stem cells<sup>14</sup>, though, as discussed above, they are rather distinct from these cells, while other researchers hypothesize the MenSCs originate in the endometrial glands, as many glands are observed in menstrual blood<sup>18</sup>. With a better understanding of the origins of these cells in the body, and potential variability between donors, it will be easier to properly isolate the MenSCs for use in down-stream applications.

Though many questions remain to be answered to accurately characterize these newly discovered stem cells, a great amount of interest in using these cells for

regenerative therapies has already materialized. Researchers are currently looking into using MenSCs for treating neurodegenerative and cardiovascular diseases<sup>18,19</sup> and salvaging limbs<sup>20, 21</sup> among several other applications<sup>22</sup>. Preliminary clinical trials for treating multiple sclerosis in humans using MenSCs have already yielded some promising results<sup>23</sup>. With additional studies of the cells in a variety of categories, the use of these cells may lead to treatments for a number of serious diseases, such as osteoporosis, stroke, Alzheimer's and Parkinson's disease. The cells may even one day be used for customized anti-aging or sports medicine treatments. Overall, MenSCs hold great promise as a significant reservoir of stem cells obtained in a noninvasive manner that can often be patient-specific, with some evidence even suggesting them to be immune privileged, or less likely to cause an immune reaction than other stem cells.<sup>19,23</sup>

#### **Advantages of Menstrual Stem Cells**

- Stem cells from menstrual blood are easier to collect through a harmless procedure. An inexpensive source, it is not painful to the donor women and can be collected for about 35 years of a woman's menstruating age. However, younger women yield better quality of endometrial progenitor cells.
- Moreover, it takes care of ethical concerns as linked to the embryonic source and there is no fear of tissue rejection too. With multitude of benefits associated with these newly discovered stem cells, potential treatments could be devised for several medical conditions.
- The MenSCs can be processed and preserved effortlessly for future implementation. Researchers say that these cells have a higher reproduction rate, doubling every 19.4 hours, compared to the elemental cells from other sources. Compared to bone marrow, menstrual blood yields almost 30 times more stem cells.
- These "pluripotent" cells can develop into cardiac, hepatic, pleural, respiratory epithelial, adipocytic, osteogenic, pancreatic, and neurocytic cells, i.e. roughly nine cell categories, so far the highest known for any stem cell source.
- This implies that many medical conditions that have no cure till date, may find a new therapy through this regenerative medium. Host rejection is not a trouble with the MenSCs because they possess an immune system suppressing effect, enabling many patients other than the donor to accept curative therapies.

## CONCLUSION

Many refer menstruation as 'nature's curse on women'. It's commonly thought of as unclean. In some cultures, women are not even allowed to cook during those days of month. But, path-breaking new research could change the way people view the menstrual cycle and its here in India, for the first time ever. The blood that uselessly leaks away from a woman's body every month until she reaches menopause is a good source of stem cells, which are still at an early stage of development and retain the potential to turn into many different types of cell. Women create life; but now they will contribute medically to save lives through the Menstrual Stem Cells (MenSCs) or stem cells harvested from discarded menstrual fluid - known to be the most disgusting phase of woman's life. Menstrual blood, as researchers say, is found to be the most potent source of stem cells so far. Discovering curative power of stem cells has been a revolutionary breakthrough in the field of surgery and medicine till date, which has actually given many - the precious gift of life.

It is not hard to bank menstrual blood. The procedure is almost the same as giving a urine sample. It may be easier to harvest stem cells from menstrual blood than bone marrow or skin because it is a painless and non-invasive procedure. Preliminary research suggests that menstrual stem cells could be used to cure a woman's genetic family, such as parents, sibling or child.

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