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# IMPORTANCE OF *KSHETRA* IN *GARBHADHARANA* W.S.R TO ENDOMETRIAL RECEPTIVITY

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## ABSTRACT

Advancement in medical field in the modern medical sciences have detailed and recognized the factors which cause infertility that includes ovarian factor, tubal factor, uterine factors, pelvic and cervical factors. Out of which under uterine factors, endometrial abnormalities play an important role in the causation of infertility. As Fertility and implantation in human are completely dependent upon synchronous events that render the formation and development of blastocyst and receiving uterus competent for implantation. In *Ayurveda Ritu* (fertile period), *Kshetra* (Female Reproductive system), *Ambu* (Nutrient fluid), *Beeja* (High quality of spermatozoa and ovum) are considered as essential factors for conception. *Khsetra* is the most essential factor which can be correlated to endometrium, where the embryo is to get implanted. Hence, this review is focused on importance of kshetra in the process of *garbhadharana*.

## INTRODUCTION

Infertility and recurrent pregnancy losses are an enduring problem to women's physical and psychological wellbeing. According to recent statistical analysis one in every four couples in developing countries had been found to be affected by infertility. There are several possible factors for the causation of infertility. In *Ayurveda*, *Acharya susrutha* has detailed four essential factors for the conception thousands of years back. Those are *Ritu, kshetra, ambu* and *beeja*.[1] Any irregularity in the above mentioned factors can lead to vandhyatwa. Out of these factors, *kshetra* is considered as the normal functioning female reproductive system. In female reproductive system the common aetiological factors abnormalities of the ovaries, uterus, fallopian tubes and the endocrine system. Recent advancement in ART, especially at genetic level has helped to understand the cause of infertility in a better way. But some couple fail recurrently even after transferring good quality embryo without any recognizable reason and this becomes a major continuing problem in ART treatment. It can be speculated that in such cases insufficiency of endometrium might be the possible reason for infertility.

The evaluation of infertility has given prime focus on endometrial factor in the current treatment setup. The successful embryo implantation necessitates both synchronous development and collaboration between hatched blastocyst and endometrium.[2]

The review article summarized the importantance of *kshetra* in *garbhadharana* in correlation with endometrial receptivity.

### Concept of Kshetra in Ayurveda

The word *Kshetra* refers to our body in general. According to Vedic literature, the stree being the origin of children is considered as kshetra. In *charaka samhita*, the term *khsetra* is used in the context of *vajeekarana* denoting *praharshini stree* as *agrya* for *vajeekaranartha*.[3] *Chakrapani* comments *Kshetra* as a place where *beeja prarohana* occurs. In *manusmruth*i, *Kshetra* is considered as stree and beeja indicated to *purusha*. *Manu* has compared women to a field, where the seed sown and sprouts yielding *dhanya*. Similarly, *Shukra* implanted in *garbhashya* leads to a son.[4]

In relation to *garbha* formation, it can be taken as a normally functioning female reproductive system. *Acharya Dalhana* has explained *kshtera* is *garbhashaya*.[5] According to *sabdakalpadruma*, the word garbhashya refers to the place where *Garbha*/ *Bruna* formation takes place.[6] *Stree garbhashya* is the eighth *ashaya*.[7] which is present in between *pittashaya* and *pakwashaya*.[8] *Garbhashya* has the shape of *rohita matsya mukha*.[9] Hence *kshetra dushti* can be considered as any abnormalities of *garbhashaya* including congenital defects, fibroid uterus, polyps, chronic infections, pcod and inflammation of the fallopian tubes as well as tissue lining inside the uterus, and Hormone abnormalities.

**Kshetra Vs Endometrium**

The union of *Sudha sukra, Sonita* and *Athma* inside the *kukshi* forms the *garbha*.[10] Here the explanation of *kukshi* is "कुक्षिगते इति कुक्ष्येकदेशगतगर्भाशयगते". According to *Acharya Susrutha*'s definition, *garbhashaya* is situated in the third *avartha* and it is the place of "*garbhashayya*".[11] One of the synonyms of the word *garbhashaya* is *dhara*, which means to hold or accommodate the *garbha*.[12] *Acharya Susrutha* says that *parivrudhi* of *garbha* takes place by *rasa* provided by the mother and *purana* of *srothas* with the help of *vata*.[13] Uterus has got three layers, the perimetrium, myometrium and endometrium.[14]

Human endometrium is the complex, multicellular tissue that is regulated by steroid hormones and has different characteristics during each phases of menstrual cycle.[15] An endometrial thickness of 7 mm minimum was found necessary for implantation success. It consists of a single-layered prismatic epithelium and cell-rich connective tissue with blood vessels that surround the uterine glands. The single-layered prismatic epithelium consists of three types of cells: secretory cells, cells with cilia, and basal cells. Every month, cells in the functional layer of endometrium separates from the basal layer during menstruation. The basal layer attached to the myometrium and act as a base for further regeneration of endometrium. The endometrium consists of various cell types, including luminal and glandular epithelial cells, stroma with stromal fibroblastic cells, immuno competent cells and blood vessels. The endometrium is remodelled throughout the different phases of menstrual cycle and exhibits only a short period of receptivity known as window of implanation.[16] Progesterone and estrogen are the dominant hormones which modulate the formation of endometrium.[17] The epithelial and stromal compartments contain progesterone and estrogen receptors, which regulates the endometrial function.

**Endometrial Receptivity[18]**

Endometrial receptivity is a complex process which provides attachment, invasion, and development of embryo in the innermost lining of the uterus. The Endometrial receptivity will be more during the implantation window, which opens 6-7days post ovulation and extends to 3-6 days within the secretary phase of a menstrual cycle. The endometrium has got a unique ability to allow embryo implantation, only during the narrow receptive phase. In certain conditions, this window is narrowed or shifted to impede the normal implantation process, leading to infertility or pregnancy loss.

Initiation of the endometrial receptivity depends upon the down regulation of endometrial estrogen and progesterone receptor stimulated by progesterone. When the embryo reaches the endometrial cavity, a preprogramed sequence of events occur which includes the secretion of a myometrial factors by the endometrium and the embryo, leading to the formation of receptive endometrium.

The term implantation refers to the process for establishing pregnancy, requires molecular and cellular events resulting in healthy uterine growth and differentiation, blastocyst adhesion and invasion. This process begins at the end of first week after successful fertilization and the process is classified into three phases: apposition, attachment (adhesion) and penetration (invasion). During the process of implantation, many endocrine, paracrine and autocrine interactions take place between maternal−embryonic cells that facilitate an intricate dialogue between endometrium and the conceptus. These developmental events are mainly carried out by sex steroids, human chorionic gonadotrophin (HCG), growth factors, cytokines, adhesion molecules, the extracellular matrix proteins and prostaglandins (Dey et al., 2004).[19]

Endometrial receptivity is mainly organized by sex steroids, directly by their specific receptors, and indirectly by cytoplasmic or nuclear interactions. It is also controlled by growth factors, such as HBEGF, amphiregulin, and adhesion molecules, e.g. integrins, E-cadherin, laminin, fibronectin, which are necessary for embryo attachment. The receptive phase of endometrium is also highlighted by the continuous growth and development of the spiral arteries. In addition to that a large number of molecular mediators, including adhesion molecules, cytokines (LIF, Interleukin-1, and colony stimulatory factor -1), growth factors and lipids have been identified to take part in receptive endometrial formation. LIF is likely to influence the pre-impanation, implantation, embryo development, and placentation. Increased production of CSF -1 is expressed during the course of pre-implantation, implantation, decidual functions, and placental growth.

The Spiral arteries situated in the endometrial layer is originated from the radial arteries, which are the branches of arcuate and ultimately, uterine vessels. During endometrial growth, spiral arteries lengthen at a rate appreciably greater than the rate of endometrial tissue thickening. Spiral artery development reflects a marked induction of angiogenesis, consisting of widespread vessel sprouting and extension.

The concept of *navina rajasthapana* every month in *garbhashaya* can be understood as the regeneration of endometrial layer. During the early stage of pregnancy, there will be an enlargement of uterine glands and blood vessels in the endometrium which can be correlated with the statement of *susrutha*.[20]

All the *tridosha* are involved in this process when we analyse the formation of endometrium. *Samyoga* and *vibhaga karma* of *vata* help in the process of cell division and regeneration from the basal layer of endometrium. *Pitta* is responsible for all *paka karmas* in

the body Thus it is responsible for steroidogenesis and aromatization of hormones and with *asraya asrayibhava*, *pitta* influence *raktha* formation. So we can infer that *pitta* may plays a role in angiogenesis of spiral arteries. Similarly, Due to the *upachaya* function of *Kapha* we can figure out that it takes part in the priming of the endometrium during proliferative phase. Moreover *Acharya* have quoted without *vata*, *yoni* never gets vitiated, and here *yoni* can be taken as the whole reproductive system which includes endometrium.[21] And the *chala guna* of *Vata* and *sara guna* and *drava guna* helps in normal functioning of HPO axis (preethi agarwal et al.). Bringing the *pitta* and *kapha* to the endometrium to perform their respective functions is the duties of *vata*. So in the pathogenesis of defective endometrium also vata plays a crucial role. It can be understood as a vata predominant *tridosha* condition.

**Kshetra Dusti**

Even though *Acharyas* mentioned *kshetra* as an essential factor for conception, there is no direct reference of *kshetra dushti* available in *Ayurvedic* classics. But there are few diseases we can assume due to the implanation failure because of the defect in *kshetra*. These are *Vamini*, *Asruja* and *Vandya yoni vyapad.*

In ***vamini yoni vyapad***, it is explained that after sixth or seventh day the yoni vomits *beeja* with *raja* and *vata*. Blastocyst reaches uterine cavity after one week of fertilization. During this stage if the endometrium is not receptive for implanation the fertilized product expelled out of the uterine cavity.[21]

In ***Asruja Yoni vyapad,***[22] due to excessive shedding of endometrium, it cannot support the product of conception. *Chakrapani* says it as "*APRAJA*" means after conception the product cannot remain in uterine cavity for further development in this way infertility occurs.

To ensure proper blood supply to keep Endometrium productive and thick, estrogen hormone plays a very important role. Inadequate level of estrogen results in thin Endometrium. In ***Vandya yoni vyapad*** the *artava nasha* can be consider as *beeja roopa artava*. The distortion of menstruation may be due to endometrium functional layer could not proliferate.

The causes of defective endometrial receptivity includesaltered E2 to progesterone ratio, Disturbed LH levels, Corpus luteum deficiency, endometrial asynchrony and earlier expression of pinopodes, Infectious or inflammatory progressions such as endometritis, thin endometrium without adequate thickness for embryo implantation.[23] Changes in the coagulation system (thrombophilias), Shift of the implantation window, Chromosomal Modification, Systemic immunological diseases and Microbiota alterations such as bacteria, fungi, and/or viruses that establish a "biofilm" inside the uterus.

**Investigations to Assess Endometrial Receptivity**

Implantation involves a complex sequence of signalling events that are crucial to the establishment of pregnancy. The recent discovery of molecules vital for successful implanation has offered researchers an insight to this field. These various molecular markers are collectively called "OMICS" and include study of genomics, epigenomics, transcriptomics, Proteomics, metabolomics and lipidomics. Currently transcriptomics is considered the most established technology available for evalaulation of ER.[24]

A number of bio chemical markers have been associated with the process of implanation. The one which shown significance during WOI are the integrins, Leukemia inhibitory factor, Homeobox A10, mucin 1, Calcitonin, and cyclo-oxygenase 2 . Many more are being investigated.[25]

Ultrasound Assessment of the endometrium is a standard non-invasive procedure during the diagnostic workup and treatment of infertility. The effects of varying concentrations of oestrogen and progesterone throughout the course of the menstrual cycle have characteristic effects on the endometrium. The endometrial changes that occur can be visualized with sonography is often used to examine various parameters of endometrium like endometrial thickness, morphology and blood flow status to predict uterine receptivity. Endometrium pattern, endometrium thickness and end-diastolic blood flow were shown to be the most effective combination for evaluation of uterine receptivity.

It has been found that endometrial receptivity disorder is the leading cause for implanation failure. The improvement of endometrial receptivity will give more advancement in the ART technology.

**Treatment for reduced endometrial receptivity**

The human endometrium is a fluctuating and multicellular complex tissue and it is depended upon the ovarian-derived steroid hormones. In the reduced level of ER caused by Low estrogen levels in the body and intra uterine adhesions, high doses of estrogen is injected to improve the ER.

In recent years, studies indicate that aspirin increases the blood flow of the uterine artery by inhibiting platelet aggregation. Asprin can regulate the expression of certain cytokines and growth factor in the endometrium.

Vitamin E is also using to increase the ER as it is one of the most important anti-oxidants and have the property of dilating vessels.

In addition to this Platelet Rich therapy (PRP) and Acupuncture is also using to increase the ER.

**Ayurvedic Management of Ksetra Dushti**

*Ayurveda* being the ancient system of medicines offers several therapies for the management of *vandhytwa*. *Panchakarma* is the main line of treatment of *vandhyatwa* as it removes *srothorodha* and maintains *tridosha Sathmyata*. *Basti* is principally advised in *Vata* predominant diseases. It is classified as *niruha* and *anuvasana basthi*. *Anuvasana basthi* is highly beneficial for women those who are infertile.[26] Action of *basti* is predominantly on *vatadosha* and *pakvashaya*. *Vasthi karma* indicated in *alparaja* and *anarthava* condition. It does the *dhathu pushti* by eliminating *dhushitha apana* and there by achieve *avyapanna garbhsambhava samagri.*

***Uttarabasti*** is a unique procedeure in *Ayurveda* where the medicated oil/ghee is injected ito the uterine cavity. *Uttarabasthi w*ith *Ayurvedic* formulations possesseing phytoestrogenic property helps in proliferation of endometrium. It rejuvenates the local tissue and potentiates the endometrial receptors.

***Yoni pichu*** majorly have a localised action. Vaginal wall is highly vascularized which also increases the drug absorption. *Yoni pichu* with drug having phytoestrogenic property will help increasing the endometrial receptivity.

## CONCLUSION

Analysing the *garbhasambhava samagris* mentioned in the *samhitas*, the concept of *kshetra* can be interrelated with endometrium of the uterus. By understanding endometrium with its anatomy, physiological, vascular and biochemical changes that observed in the menstrual phases and in the pregnancy helps to devolpe a well result oriented approach towards *Ayurvedic* infertility management. Drugs having *rasayana*, *vatahara* and *jeevniya* properties can be used in the multiple formulations with different route of administration. This helps to reduce the incidence of early pregnancy loss due to implanation failure. This opens the window to an integrated Artificial reproductive techniques with a better success rate that helps to reduce the psychological and economic burden millions of infertility couple worldwide.

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