HEAT TRANSFER MODEL FOR MENORRHAGIA

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By
Shabina Ashraf

Department of Biotechnology and Medical Engineering

National Institute of Technology

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ROURKELA

CERTIFICATE

This is to certify that the thesis entitled. ñ*Heat Transfer Model for Menorrhagia"* submitted by Ms. Shabina Ashraf in partial fulfillment of the requirements for the award of Bachelor of Technology Degree in Biotechnology Engineering at National Institute of Technology, Rourkela (Deemed University) is an authentic work carried out by her under my guidance.

To the best of my knowledge the matter embodied in the thesis has not been submitted to any University/Institute for the award of any Degree or Diploma.

Dr. Amitesh Kumar,
Dept. of Biotechnology and Medical Engg.,
National Institute of Technology,
Rourkela-769008.

Date:

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Submitted by:

Shabina Ashraf,
Roll No: 108BT019,
Dept. of Biotechnology and Medical Engg.,
National Institute of Technology,
Rourkela.

ABSTRACT

Thermal balloon ablation is a modern non surgical procedure for the treatment of menorrhagia. It works on the principle of ablating the endometrial layer beyond a point of regeneration thereby reducing blood loss. Mathematical modelling of this procedure helps in improving accuracy of the treatment which reduces adverse affects of the procedure thereby making the procedure safer. Pennes bio-heat equation is used to calculate transient temperature in the uterine cavity. Thermal injury integral is used to calculate the irreversible thermal destruction of the uterine tissue. When thermal injury integral equals to or is greater than 1, the tissue is destroyed which prevents regeneration of the endometrium. The presented mathematical model is verified with the published experimental findings to check the validity of the model. The effect of overall convective heat transfer coefficient and balloon fluid temperature on tissue damage is studied. For an overall convective heat transfer coefficient above 2000$Wm^{-2}K^{-1}$, maximum depth of ablation at 87°C was 3.77mm. For higher fluid temperature, depth of ablation is found to increase. At a fluid temperature of 93°C, depth of ablation is found to be 4.39mm for an overall convective heat transfer coefficient 1000$Wm^{-2}K^{-1}$. The temperature at the surface of endometrium is found to increase with the increase in fluid temperature and also with the increase in overall convective heat transfer coefficient. The obtained results are valid in the absence of any pathological condition. In case of existing pathological conditions, the effects caused by them are also to be included. Thus, mathematical modelling involving convective heat losses is an effective tool to make thermal balloon procedure more accurate.

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CHAPTER-1

INTRODUCTION

1.1 HISTORICAL REVIEW:

The fact that menstruation is a normal physiological process of female reproductive system is obvious, but in the earlier centuries it was considered to be an impure phase of every womanôs life. Pliny the elder, back in the first century AD, represented the way menstruation was viewed. It was then considered as an unpleasant event of a womenôs life. However, this thought has changed to a modernised one by nineteenth century AD. H.Beckwith white house described menstruation in academic context as- ñone of the sacrifices to be offered by woman at the altar of evolution and civilizationò [1].

There were very few medical textbooks that dealt with the disorders of menstruation process. It was Hippocrates who described abnormal uterine bleeding for the first time around 460 BC [1]. Until 1800ôs the description mostly reflected abnormal bleeding symptoms as excessive bleeding described as heavy evacuations of the menses, inordinate flowing, immoderate flux, an overflowing of courses, menstruation to be too profuse, excessive flooding, and uterine haemorrhage [2]. The medical text books of Hippocrates were later translated and quoted by Aristotle as- ñin quantity, bleeding is excessive saith Hippocrates, when they flow about eighteen ounce.ò But the fact that eighteen ounce is about 540ml. is quite shocking to know since it is about seven times the maximum limit. In the middle part of the seventeenth century, William Heberlen, a gynaecologist and successful physician provided earliest and best description of abnormal uterine bleeding available till then [1].

None of the early writers used terms like ómenorrhagiaô or ómetrorrhagiaô until the later parts of seventeenth century [2]. The term menorrhagia was used for the first time by William Cullen, professor at the university of Edinburg [1, 2]. According to Cullen, menorrhagia was a disease involving deviations from normal which are too high in degree and causes a state of disability [2]. To be particular, the term ñmenorrhagia rubraò was used for non puepperal women and ñmenorrhagia abortusò was used for pregnant women [1]. The term ñmenorrhagiaò was first found in treatise by a postgraduate student of Cullen which was attributed to him. Exact spelling used by Cullen was ñmaetrorrhagiaò [2]. Fleetwood Churchill, a specialist in gynaecology described the abnormalities associated with uterine bleeding as ñmetrorrhagiaò in his medical books which later came to be known as ñmenorrhagiaò [1]. However, the roots arise from Greek language which is from the merge of words ñmeneò and ñregnumiò as ñmenorrhagaò. ñmeneò is moon and the verb ñregnumiò is to burst forth [1-3]. Graves used the term ñdysfunctional uterine bleedingò for the first time which according to him meant ñimpairment of endocrine factorsò which is similar to regular or irregular menorrhagia or disturbances that were caused during ovulation state [1, 2].

To know the causes that lead to menorrhagia, firstly it is needed to know the menstrual cycle, formation and shedding of the endometrium, and the abnormalities associated with it. This primarily deals with the structure and biological characteristics of the uterus. Uterus can be described as a hollow organ, about the size of a medium pear and is the place where a foetus grows and develops when a woman is pregnant [4]. It has two main parts. The upper part is called the body of the uterus which is scientifically coined as corpus (meaning body in Latin) and the lower part which extends into the vagina called the cervix. The body of the uterus in turn comprises of two layers- the inner layer and the outer layer. The inner layer is termed as the endometrium and the outer layer of muscle is called the myometrium that pushes the baby out during birth. The tissue that coats the outer side of the uterus is known as the serosa. Hormonal changes during the menstrual cycle of a woman result in the change of the endometrium [4].

In the early part of the menstrual cycle, that is before the ovaries release an egg (ovulation), they produce estrogens and this thickens the endometrium so that it could nourish the embryo if pregnancy occurs during that cycle. In the absence of pregnancy, estrogen is produced in lesser amounts and another hormone called the progesterone is produced in higher amounts after ovulation which causes the innermost layer of the lining to get prepared for shedding [4]. In general, normal shedding of the endometrial (menstruation) occurs as a result of stimulation of the endometrial lining by the physiologic levels of estrogen and progesterone which are maintained in a balanced state during the normal ovulatory cycle, followed by the rapid withdrawal of these two hormones [5]. The stimulation of these hormones causes the shedding of endometrium and by the end of the menstrual cycle, the endometrial lining is shed from the uterus which becomes the menstrual flow (period). This cycle repeats throughout a woman's life until menopause [4].

In the modern scientific approach, menorrhagia is defined as prolonged menstrual bleeding. During a normal period, the bleeding lasts for about 7 days to a maximum in a 21-35 day cycle with a volume flow measuring about 25-80 ml. So, menorrhagia can be described as loss of blood more than 80ml per cycle lasting more than 7 days [1, 6-12].

Until the eighteenth century reason for menorrhagia was guessed by Aristotle. It was thought that excessive uterine bleeding was due to heating of blood, trauma, or due to breaking of veins. Later, by the middle of eighteenth century several interesting hypothesis came into existence. Dewees, from his observations described the cause for heavy menstrual bleeding in women with some imbalance in daily activities like little or no exercise, intemperate nature, irregular dancing, having several child bearings, who were affected by some infections in the past, who were at their advancement of non menstrual period, who yielded to passions or emotions easily. In the book *The Married Woman's Private Medical Companion*, written by Mauriceau some other causes as per his observations were stated [1]. Women who had miscarriages in the past, weak women, women who underwent heavy exercise, highly obese women are prone to have fair chances of suffering from menorrhagia.

In nineteenth century, introduction of anaesthesia was a great boon to humanity. It paved a way to perform complicated surgeries effectively. Apart from that, the sample specimens could also be studied with greater efficiency. Advancement in science and technology helped in revealing the facts of physiological problems [1]. This lead to careful and close examination of uterus cavity and the thought of some surgical operation to be performed as a cure to menorrhagia paved its way.

By the earlier part of twentieth century, the causes for uterine fibroids were found which was a reason for heavy menstrual bleeding; but endometrium associated problems were not discovered until the later parts of the century. It was Samson, whose studies paved a major contribution in learning the causes of menorrhagia [1].

1.2. LITERATURE REVIEW:

The terms ñabnormal uterine bleedingò, ñdysfunctional uterine bleedingò, ñmenorrhagiaò though have similar meanings; there is a slight difference when keenly learnt. Dysfunctional uterine bleeding is a part of abnormal uterine bleeding and menorrhagia is the term used when the earlier stated definition holds true, i.e., loss of more than 80ml. of blood per menstrual cycle for more than 7 days [1, 6-12].

In general, causes of abnormal uterine bleeding can be classified into four categories. The first one being the organic causes- caused due to infection, endometrial polyps, pregnancy and malignancy; the second type being the systemic causes- as a result of imbalances of system such as thyroid, liver or renal diseases; the third kind called iatrogenic- holds the effects caused by glucocortico steroids, steroid hormones, intra uterine devices containing copper; the fourth category referred to as idiopathic- holds good for the cases where no definite cause could be identified and such an abnormal uterine bleeding can be termed as ódysfunctional uterine bleedingô (DUB)[7].

DUB is generally caused as a result of continuous stimulation of the endometrial layer with unopposed estrogen that occurs due to a dysfunction of the hypothalamic-pituitary-ovarian axis [5]. DUB can also be caused by uterine fibroids, inflammatory diseases of the pelvis, imbalances of hormones such as estrogen and progesterone, high levels of prostaglandins and endothelins which may lead to menorrhagia [8]. Sometimes, DUB may also be caused due to improper functioning of the endometrium causing erratic responses, insufficient progesterone and anvoulary cycles [7]. Disorders of thyroid, liver, and kidney might also turn up to be a cause of extensive uterine bleeding [8]. Menorrhagia causes are generally associated with pathologies like polypi of the endometrium and adenomyosis [6].

It is found that about 30% of pre menopausal women are suffering from menorrhagia during their child bearing years [8, 9]. Most of the people view menorrhagia as a common problem associated with women in recent years. As inferred from the records, 25% of the women undergo hysterectomy below the age of 60 [6]. Women suffering from menorrhagia have fair chances of experiencing pain in the lower part of the abdomen [3].

There are other problems caused by menorrhagia, as the personal life of an individual is observed. Anaemia is the mostly observed disorder caused due to menorrhagia [9]. Loss of blood beyond a presumable limit may cause a deficiency in the amount of blood and thereby related iron deficiency disorders. Moreover, it is related to social, economical and physiological well being of a woman [9]. A great deal of physical as well as mental stress, discomfort, embarrassment might also be caused [9]. Frequent mood swings, irritation, often frustration, which change the way of life, have a profound impact in the lives of women who suffer from menorrhagia disorder.

Before confirming menorrhagia, certain tests are to be done. Physiologically, though it is defined as loss of more than 80ml of blood, it is confirmed only after certain investigations are done, so as to rule out uterine pathology [13]. Endometrial biopsy eliminates the chances of endometrial cancer thereby providing scope for confirming menorrhagia [13]. Various tests that are carried out include blood tests, ultrasound testing, endometrial biopsy, and hysteroscopy (a visual examination of the uterus) [8].

The first line of approach for treatment of menorrhagia is drug based; which includes various drugs like oral contraceptives, inhibitors of prostaglandin synthesis, progestagens, anti fibrinolytics and hormone releasing intra uterine systems [10]. Apart from drugs, a traditional drug therapy might also be employed which involves medical therapy with hormones, non steroidal anti inflammatory drugs, anti prostaglandins. But their side effects in the long run might be unacceptable [11]. Sometimes, medical treatments for menorrhagia might be quite ineffective and there is a fair chance of side effects [14]. Hence, when a non surgical treatment is provided, future implications need to be kept under consideration.

After the drug or hormonal based treatment, the most preferred procedures are the surgical procedures termed as second line of approach for the treatment of menorrhagia [10]. Menorrhagia was treated in the past by hysterectomy, myomectomy, and dilation and cutterage [10, 15]. In United States, hysterectomy is one of the most common surgical procedures [6]. The widely available effective treatment procedure until recent past was hysterectomy in which a surgical operation is carried out to remove the uterus [8]. According to National centre for health statistics, hysterectomy is the second most performed surgical procedure after caesarean delivery [15]. Hysterectomy has been 100% successful proving out its effectiveness [8].

But the main drawbacks for hysterectomy are its high costs, morbidity, and complex surgical procedure [8, 14, 16]. Moreover, surgical treatment of hysterectomy requires a great deal of skill and experience of gynaecologist who performs it [19]. Removing the entire uterus was inevitable for some disorders while in others all that was needed was a reduction in blood outflow. In dysfunctional uterine bleeding the only problem was heavy bleeding and removing the entire uterus was not a choice to be preferred. This led to other procedures which are precise only to the problem of heavy bleeding. Thus, non-surgical procedures were developed. These non-surgical methods are improved further by employing mathematical models which are solved by Pennes bio heat equation to describe transient temperature in tissues. Parameters like temperature of ablation, depth of ablation, treatment time are studied by formulating mathematical equations. In a study by Baldwin et al., high temperatures for a short time period are analysed and cases of vaporisation and no vaporisation are considered [27]. In another study, transient temperatures across uterine cavity are determined by employing finite element analysis. It is found that temperature across uterus depends strongly on the perfusion coefficient and is affected by rate of decay of the fluid temperature [38]. Yet, another study is based on enthalpy method that accounts for liquid to vapour change at elevated temperatures. Phase change occurrence and complete suppression of perfusion have shown to be the factors effecting ablation depth [16].

1.3. METHODS OF ABLATION:

The concept that ablating the endometrial layer causes reduction in menstrual flow led to the development of new technologies [3]. Hence, the first generation techniques were designed. These included three suitable techniques to ablate the endometrium namely:

- Roller ball technique,
- Ndï YAG laser ablation, and
- Transcervical resection of endometrium (TCRE) [7,20].

All the three procedures had almost similar outcomes when post operative readings were taken [12]. But these first generation techniques were of less efficiency, longer duration, required skill and had life threatening complications which led to the further development of new techniques [14, 16].

These new methods were termed as the second generation ablation methods which were easy to perform, less time consuming and of good efficiency [16, 17]. These procedures were developed on the concept of ablating the endometrial layer beyond a point of regeneration selectively, which inhibits the endometrium formation and therefore causes a reduction in menstrual flow [8]. A less invasive treatment is thermal endometrial ablation, in which endometrium regeneration is inhibited by forming scar tissue on the wall of uterus [14, 22, 23]. Endometrial ablation has advantages as compared to the surgical procedures in the past that it can be an office-based procedure which does not require general anaesthesia or total removal of the uterus [14]. These technologies ablate the entire surface of endometrium hence are also called as global ablation techniques instead of ablating the selective regions as in rollerball elecctrosurgery or laser surgery [15].

However, thermal endometrial ablation has its own risks and complications which include thermal damage to the bowel, urinary bladder, cervix, uterus, and pelvic blood vessels [14]. There are quite a good number of second generation procedures and they are preferred for their simplicity in performance. They are easily performed in a clinical setting rather than in an operative surgical setting [20]. These include:

1. Balloon systems
2. Intrauterine laser devices
3. Multi-electrode radio-frequency ablation
4. Bipolar impedance controlled ablation
5. Hot saline instillation systems

6. Microwave energy
7. Cryo-ablation therapy
8. Chemical cautery of the endometrium
9. Photodynamic therapy

Food and Drug Administration (FDA) has approved use of five global endometrial methods namely thermal balloon ablation, circulating hot fluid, ablation using microwave energy, cryotherapy, and radio frequency ablation. All these five methods have recorded high satisfaction rates with lesser complications [15, 24]. The devices termed for each of the procedures, production details can be obtained from below.

FDA-Approved Endometrial Ablation Devices [7]:

1. ThermaChoice, Uterine Balloon Therapy System, GyneCare, Ethicon, A Johnson & Johnson Company, Menlo Park, California.
2. Hydro ThermAblator Endometrial Ablation System, BEI Medical Systems, Boston Scientific, Teterboro, New Jersy.
3. Her Option Uterine Cryoblation Therapy System, CryoGen, American Medical Systems, San Diego, California.
4. NovaSure Impedance Controlled Endometrial Ablation System, Novacept, Palo Alto, California.
5. Microwave endometrial ablation (MEA, Microsulis Medical, Hampshire, UK) [16]

The first four endometrial devices are available in the United States [7]. In the above devices microwave endometrial ablation is not included initially. Microwave ablating device has been introduced by the clinicians of National Institute of Clinical Excellence (NICE), United Kingdom [16].

However, there are certain contradictions when endometrial ablation is not preferred. In such cases ablating the endometrium should never be a choice to be opted. Some of such cases are [15]:

- Pregnancy or desire to be pregnant in the future
- Premalignant change in the endometrium
- Active pelvic inflammatory disease
- Carcinoma of the endometrium
- Classic caesarean delivery or transmural myomectomy in the past
- Uterine abnormalities such as separate uterus, bicornuate uterus, or unicornuate uterus
- Active urinary tract infection
- Refusal or intolerance to medical treatment.
- Endometrial hyperplasia or malignancy.

In exception to the above conditions, ablation of endometrium is a good choice to be opted. Discussing various methodologies numbered above in detail gives a good idea regarding the ablation of endometrium.

1. **Circulating hot fluid:**

This is approved by the FDA in 2001 [15]. When fluid is infused through the cervix at pressures below 70 mm Hg, it will not spill into the peritoneal cavity and this principle is used in hydrothermal ablation devices [20]. It is a software-controlled thermal ablation system designed in the form of a closed loop system that circulates hot saline at 90°C in the endometrial cavity [4, 9]. An external canister is the heating source for this saline [5]. A polycarbonate sheath having an outer diameter of 7.8 mm is fitted over a standard 3mm hysteroscope for fluid circulation [15, 20]. Saline with a concentration of 0.9% is infused through the inflow channel [16, 25].

Before circulating the heated fluid, a priming phase is carried out for inspecting the endometrial cavity during which room temperature saline is circulated within the endometrial cavity at a flow rate of about 300 ml/min, for 2 min [15]. The next phase called the active treatment phase causes the heating element to gradually heat the fluid under low pressure of about 55mm Hg, which is a pressure below the fallopian tube opening pressures [15].

2. Cryo ablation therapy:

Her Option is approved by the FDA in 2001. This device uses cryotherapy in the form of a cryoprobe which is cooled by pressurized gas to create temperatures of -100°C to -120°C at the tip of the probe [15]. The device consists of a cryoprobe which is about 5-5.5 mm in diameter and is disposable [7, 20]. When the cryoprobe is placed within the endometrial cavity, an ice ball is produced as a result of such low temperatures [15]. Transabdominal ultrasonography is used in monitoring the placing of cryoprobe and formation of ice ball. It is inserted into the uterus for two freezeï thaw cycles to complete total treatment [20]. In the FDA trial, two freeze cycles of 4 and 6 min were used [15]. The probe is placed into each cornu which develops a cytotoxic freeze zone that resurrects the endometrial layer [7]. The duration of treatment is about 10-15min [7].

3. Radiofrequency Thermal Ablation:

The NovaSure endometrial ablation system gained FDA approval in the year 2001 and is based upon the principle of using energy from bipolar radiofrequency to vaporise the endometrial lining [15]. A cavity perforation test is performed prior to the initiation of ablation where carbon dioxide is diffused into the uterine cavity. It ensures that pressure is maintained and vacuum is produced which keeps the array intact with the endometrium [15, 20]. Once the device is set into function and tissue destruction is initiated, the electrical impedance of the tissue increases with the depth of ablation [15]. When the impedance between the tissue and electrode reaches about 50 ohms or when the total treatment time is 1.5-2 min, the procedure is stopped [7, 15].

4. Microwave Thermal Ablation:

In 2003, FDA approved microwave endometrial ablation device, which uses microwave energy to destroy the endometrium [15]. It is based on the principle of using electromagnetic energy to ablate the endometrium [20]. It consists of a hand-held applicator which applies microwaves at a frequency of 9.2GHz through the cervix to the endometrial lining, and a temperature level between 75℃ and 85°C [15, 20]. A maximum depth of 6mm can be ablated [15, 20]. The treatment time varies between 3-5min for a normal sized uterus [15, 20]. There is a control unit that records treatment profiles when each probe is used, thereby facilitating the collection of data [20].

5. Uterine Balloon Therapy:

It is the first approved treatment by FDA [15]. It consists of a balloon that is disposable (made of silicone or latex) which is placed into the uterine cavity and is filled with fluid made of 5% dextrose and water that maintains its temperature from a central heating element [7, 15, 17, 18, 20]. Initially the balloon is inserted into the endometrial cavity and is inflated by introducing the fluid [15]. The inflation of the balloon causes a pressure in the uterine cavity which ensures a good contact of balloon with the uterine cavity [20]. Usually the pressure is between 160-180 mm Hg [7, 15]. Treatment time is about 8 min, and the usual fluid temperature maintained in the balloon is 87°C [7, 15].

The system used for uterine balloon ablation is called Thermachoice system. There are three kinds of Thermachoice systems available. Thermachoice I was approved initially which is used for patients with greater thickness of the endometrium. It is featured with a dip-moulded latex device filled with non-circulating saline solution [26]. It ablates to a depth of 6.3mm and ablating to such greater depths could cause perforation of the organs nearer to the uterus [24]. Then a modified form of uterine balloon ablation was introduced known as Thermachoice II which is used for patients with lower thickness of endometrium as it ablates to a depth of 4.77mm [24]. It has a silicone balloon which is introduced in the uterine cavity along with a circulation mechanism, thus providing more even ablation of the endometrium [26]. Further improvement in Thermachoice systems lead to the development of Thermachoice III which ablated endometrium to a thickness of 3.52mm [24]. This model had a stronger and more flexible silastic balloon and it confirms better to the contours of the uterine cavity and thus increases coverage of cornua and lower uterine segment causing effective ablation [26].

Mostly 5% dextrose and water is used as the circulating fluid [15]. But there are certain other fluids that are used by heating separately and then are induced in the balloon. This ablation device is termed as Cavaterm [20, 22]. The most recent balloon ablation system is Thermablate, which has a biocompatible liquid within a disposable catheter-balloon and the unit is heated to an initial temperature of 173 °C. It is forced into an intra-uterine balloon through a series of cycles of pressurisation and depressurisation for a treatment period of 2 min thus causing ablation in a very short period of time [20].

Thermachoice gained FDA approval in 2001 and since then it has been widely used in comparison to other procedures [15]. The average list prices for different disposable units of thermal ablation procedures are $650.00 for the ThermaChoice and Hydro ThermAblator; $850.00 for the NovaSure; and $1,200.00 for the Her Option treatment [7]. From the prices it could clearly be differentiated why Thermachoice is the most widely used practice for thermal ablation. Its affordable cost and being the first procedure to be approved by the FDA, most of the patients prefer Thermachoice. Although HydroThermAblator has the same price, the procedural risks involved might be high in comparison to Thermachoice. Hence, we have chosen uterine balloon therapy.

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1.4 FACTORS UNDER CONSIDERATION:

There are certain conditions under which uterine balloon therapy is not preferred [13, 28]:

- A patient who is already pregnant or who wishes to become pregnant in the future.
- History of urinary allergy.
- A patient suffering with uterine cancer or is suspected to have endometrial cancer.
- A patient with a condition in which the myometrium could be weak like those who might have undergone previous caesarean section or transmural myomectomy.
- Active genital tract or urinary infection at the time of procedure.

Precautions in using a Thermachoice system are [13, 28]:

- To be used in women who have completed childbearing.
- It is not a sterilised procedure. Therefore, pregnancies after ablation can be dangerous for both mother and foetus.
- Thermal endometrial ablation does not eliminate the risk for endometrial hyperplasia or cancer thereby masking a physicianôs ability to diagnose such pathology.
- In a treatment cycle, the patients are to be treated only once.
- Caution is to be taken so as not to perforate the uterine cavity while performing the procedure or ultrasound. If any perforation is present, the procedure needs to be abandoned immediately.

Before performing uterine balloon ablation therapy, certain investigations are to be made such as:

- Good history and examination of the uterine cavity
- Sonography so as to rule out any uterine pathology.
- Tests so as to rule out endometrial cancer such as PAP smear and endometrial biopsy.

As this procedure involves ablation in the uterine cavity itself, local anaesthesia serves the purpose. It helps in reducing pain to the patient, thus making the procedure more comfortable. Moreover, there is no dilation performed prior to ablation; hence there is no requirement of general anesthesia. Local anaesthetic drugs like 1% Lidocaine or bupivacaine with or without rapid acting drugs like fentanyl and a benzodiazepine such as midazolam gives sufficient pain relief [13].

The thermal balloon endometrial ablation process is safer and does not require much expertise [22, 23, 29]. The results obtained are comparable to major surgical procedures [22]. Outcomes include amenorrhea, hypomenorrhea in most of the cases and bleeding is greatly reduced after thermal balloon endometrial ablation [20, 29]. Therefore, using thermal balloon procedure for endometrial ablation is preferred in recent days.

Endometrial ablation by thermal balloon procedure involves heat transfer through uterine cavity which can be presented as a mathematical model. This model involves various parameters such as overall heat transfer coefficient, temperature, and thermal injury integral that contribute to the depth of ablation. Varying these parameters and studying their effect on uterine cavity helps in the betterment of the procedure.

While performing thermal balloon ablation, as the heat diffuses across the uterine cavity, a convective heat loss is associated with it. Calculating the reduction in temperature due to the convective heat loss helps in optimizing the process and gives more exact result regarding the fluid temperature that should be used. Studying the effect of fluid temperature and overall convective heat transfer coefficient on ablation depth is the objective of this study.

CHAPTER-2

MATHEMATICAL MODELING

2.1. MODEL DESCRIPTION:

Endometrial ablation of uterine cavity as a treatment for menorrhagia can be considered as a simple model in which the heat from the silicone balloon traverses in one dimension throughout the cavity along the endometrium, myometrium and the serosa. Endometrium varies in thickness from 1mm to 4mm in most of the normal women. For a thickness of less than 4mm, abnormalities are rarely observed [31, 32]. There are cases where women with endometrial thickness greater than 4mm do not suffer from menorrhagia necessarily but greater the thickness, greater the liability of the disorder as it is observed in women. In a research on post menopausal women, endometrial thickness up to 5mm was considered to be normal [33, 34, 40]. In another case study on women suffering from abnormal bleeding, the correlation of endometrial thickness and abnormality was found to be up to 4mm for post menopausal women and up to 5mm for pre menopausal women [34]. An overall thickness greater than 4mm to 5mm could be treated as abnormal.

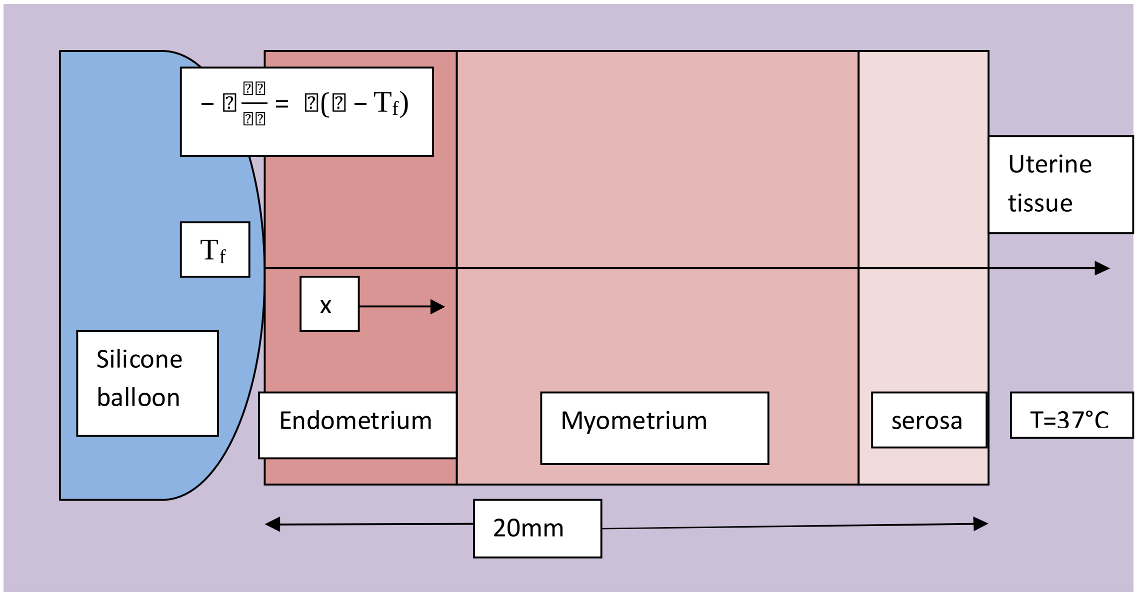

Figure 1: One dimensional model of heat flow in the uterine cavity.

In our model as shown in figure 1, we consider heat transfer in one dimension throughout the uterine tissue. The conductivities of endometrium and myometrium are 0.542 +/- 0.008 W m(-1) K(-1) (mean +/- 1 SD) and 0.536 +/- 0.012 W m(-1) K(-1) (mean +/- 1 SD) repectively in an in vitro analysis by Olsrud J et al. [35]. It could be well observed that there is very little difference in thermal conductivities of endometrium and myometrium. The endometrium, myometrium and serosa are homogeneous throughout the uterine cavity; hence they could be treated as a single cavity, collectively called as the uterine cavity. Heat from the 5% dextrose water transfers through the silicone balloon into the endometrium initially followed by the myometrium and the serosa as indicated in the figure 1.

An overall thickness of 20mm of uterine cavity has been considered in the model. The temperature at the endometrial surface is not the temperature of the fluid inside the balloon (T_f) but varies and is less than the fluid temperature. This variation is in accordance with Robinôs boundary condition and the temperature at the surface of the endometrium is calculated by the equation

$$-k\frac{dT}{dx} = h(T - T_f)$$

Where k is the thermal conductivity of the tissue ($Wm^{-1}K^{-1}$), h is the overall convective heat transfer coefficient ($Wm^{-2}K^{-1}$), T is the temperature of the uterine cavity (°C), and T_f is the temperature of the fluid inside the silicone balloon (°C).

2.2. PENNES BIO HEAT EQUATION:

To deal with variation of temperature across the uterine cavity, the famous bio-heat equation is used. This equation is commonly used to describe transient temperature in tissues [36]. The Pennes bio-heat equation is:

$$\rho_t c_t \frac{\partial T}{\partial t} = \nabla(k_t \nabla T) + \rho_b c_b \omega_b (T_b - T) + q_m$$

where ɟ is the density (kg m^{-3}), c is the specific heat capacity (J kg^{-1} K^{-1}), T is the temperature of the tissue (°C), Ű is the time (s), k is thermal conductivity ($Wm^{-1}K^{-1}$), ɣ $_b$ is blood perfusion rate (m_b^3 m_t^{-3} s^{-1}), q_m is the rate of metabolic heat generation by the tissue (W m^{-3}). The suffixes b and t indicate blood and tissue respectively.

The left hand side indicates the rate of sensible heat that could be stored in a tissue which is equated to the right hand side involving the sum of three terms; conduction of heat by local temperature gradient in the tissue of our concern, the heat transport due to convection between the blood and the tissue, and the rate of heat that is generated as a result of metabolism.

The boundary conditions that are considered in this equation are:

At Ű=0, T=37 °C for all x,

x=0, $T<T_f$ for all Ű,

x=Ð, T=37 °C for all Ű.

where Ű is time (s).

2.3. THERMAL INJURY INTEGRAL:

While the above bio-heat equation describes the transient heat transfer in tissues, there is another expression that describes the degree of tissue injury computed by means of a cumulative damage integral which is [36]:

$$\Omega(x,\tau) = A\int_{0}^{\tau} \exp\left(-\frac{\Delta E}{RT(x,\tau)}\right) d\tau$$

where $\Omega(x,\tau)$ is the degree to which the tissue is injured, A is the kinetic expression frequency factor (s^{-1}), ΔE is the activation energy required for the burn reaction (J mol^{-1}), R is the universal gas constant (8.314 J mol^{-1} K^{-1}), and $T(x,\tau)$ is the temperature of the tissue as a function of position and time (°C).

The parameters A and ΔE depend on the type of tissue under consideration [14]. For human arterial samples the values of A and ΔE were found to be 5.6 x 10^{63} (± 8 x 10^{12}) s^{-1} and 4, 30,000 (± 85,000) J $mole^{-1}$ respectively [8, 14]. Most of the properties of uterine cavity and arterial samples were found to be the same; hence the values for arterial tissues could be considered in the study [14]. By means of these constants, when the damage integral (Ω) is equal to or exceeds 1, about 63% of the protein in the tissue is denatured [37]. Both the arterial and uterine tissues are composed of collagen fibrils and smooth muscle tissue which have some similar compositional characteristics. Hence a similar response to thermal injury could be expected and hence the parameters used in the model are valid [14].

The parameters used in our current model of heat transfer are tabulated as follows:

Table 1. Parameter values used in model. [2, 7, 27, 39]

Parameter	Denotion	Value	Units
Density of tissue	Ɉ $_t$	1060	kg m^{-3}
Density of blood	Ɉ $_b$	1080	kg m^{-3}
Specific heat capacity of tissue	c_t	3600	J kg^{-1} K^{-1}
Specific heat capacity of blood	c_b	3500	J kg^{-1} K^{-1}
Thermal conductivity of tissue	k_t	0.56	W $m^{-1}K^{-1}$
Blood perfusion rate	ɤ $_b$	0.0028	m_b^3 m_t^{-3} s^{-1}
Temperature of blood supply	T_b	37	°C
Rate of metabolic heat generated by the tissue	q_m	170	W m^{-3}
Frequency factor of kinetic expression	A	5.6x10^{63}	s^{-1}
Activation energy for burn reaction	E	4,30,000	J mol^{-1}
Universal gas constant	R	8.314	J mol^{-1} K^{-1}

The temperature at the surface of the endometrium would be the highest temperature of the cavity during the treatment time and is gradually cooled to body temperature (37°C) later on during the cooling period. When 63% of the protein is denatured, it results in coagulation of blood [41].

2.4. ASSUMPTIONS:

Certain assumptions are made to simplify the model. They are:

- The uterine wall can be considered as a one-dimensional structure, since the heat transfer takes place in one dimension from the heated fluid in the balloon along the thickness of the uterine cavity. Moreover, the length of the tissue is far larger when compared to its thickness; therefore one dimensional geometry could be justified.
- The uterine cavity is assumed to be a homogeneous cavity and hence the tissue properties like $k_{t,}$ Ɉ$_t$, c_t remain constant, and are independent of temperature.
- Blood perfusion rate though independent of temperature, is assumed to stop when the thermal injury integral equals to or is greater than 1 as a result of blood coagulation.
- Initial temperature of the uterine cavity was assumed to be the temperature of the body (37°C).
- The temperature of blood perfusion at the tissue was assumed to be that at normal body temperature that is at 37 °C.

2.5 SOLUTION APPROACH:

A 20mm domain is considered in this study. The heat transfer along the thickness is studied using Pennes bio-heat equation in Cartesian coordinate system. Fine grids are laid near the endometrium lining while coarse grids are used near the serosa. Central difference method is used to discretise the diffusion term while implicit three time level scheme is used for time marching which results in second order accuracy in spatial and temporal dimensions. Tissue damage integral is calculated using trapezoidal rule.

CHAPTER-3

RESULTS AND DISCUSSION

When the uterine cavity is exposed to the fluid temperature, the heat transfer takes place across the uterine cavity and in the process it ablates the tissue to a certain depth which is dependent on fluid temperature and overall convective heat transfer coefficient. The effect of overall heat transfer coefficient and the fluid temperature on the tissue damage is studied by the proposed mathematical model. In the present study, different overall convective heat transfer coefficient values 125 $Wm^{-2}K^{-1}$, 250 $Wm^{-2}K^{-1}$, 500 $Wm^{-2}K^{-1}$, 1000 $Wm^{-2}K^{-1}$, 2000 $Wm^{-2}K^{-1}$, and 4000 Wm-2 K^{-1} are employed and the variation of tissue damage is studied for each of the values. A similar study is done by employing different fluid temperatures 87°C, 90°C, and 93°C which are usually used in uterine balloon therapy. Moreover, thermal injury integral plays an important role in determining the depth of necrosis.

3.1. VALIDATION OF MODEL:

Mathematical model formulated in this study is validated by comparing the mathematical results with the published experimental results from the literature. Endometrial ablation by means of a thermal balloon was carried out in four patients in London in an initial study on thermal ablation. After the ablation, hysterectomy was carried out to study the potential for uterine cavity perforation, rupture, and thermal effects. The fluid temperature inside the balloon was 92 ℃ and the treatment time was 6 min [36]. For each case, the maximum temperature of the tissue at a thickness of 0.5mm is analysed. The thickness up to which the tissue has undergone necrosis was examined and the results were tabulated.

Table 2: Validation of mathematical model with experimental values

Case no:	Maximum temperature at 0.5mm depth	Zone of destruction
1	87.7	5.1
2	89.4	3.3
3	89.7	4.2
4	89.4	4.3
Average of experimental outcomes	**89.0±0.7**	**4.2±0.6**
mathematical model outcomes	**89.32**	**4.18**

From the Table 1, it is observed that the outcomes of the model lie within the range of experimental outcomes from published literature. This proves the validity of the model.

3.2 EFFECT OF DIFFERENT OVERALL CONVECTIVE HEAT TRANSFER COEFFICIENTS ON THERMAL INJURY:

In this section, different values of overall convective heat transfer coefficient are considered and its effect on the depth of ablation is analyzed. Overall convective heat transfer coefficients for the thermal balloon ablation system may vary and a set of possible values are chosen in this study. A graph is drawn for thermal injury integral versus the thickness of uterine cavity for different overall heat transfer coefficients at a temperature of 87°C.

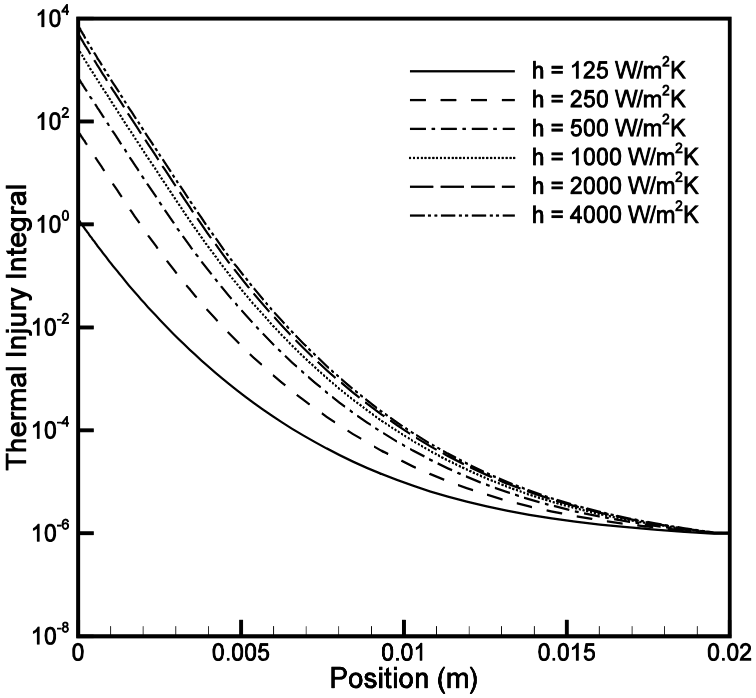

Figure 2: Variation of ablation depth for different overall convective heat transfer coefficients.

From Figure 2, it is observed that the ablation depths increase with increase in the overall convective heat transfer coefficient. But this increase is desirable only till the ablation depth is considerable. However, the variation of thermal injury integral shows no significant increase when the overall convective heat transfer coefficient is increased from 2000 $Wm^{-2}K^{-1}$ to 4000 $Wm^{-2}K^{-1}$. When the lower values of overall convective heat transfer coefficient are considered, there is a remarkable increase in the depths of ablation with increase in overall heat transfer coefficient. So, a fluid with an overall convective heat coefficient should be chosen such that the depth of ablation is sufficient enough to destroy the excessive uterine tissue.

Table 3: Ablation depths for different overall convective heat transfer coefficients.

Overall convective heat transfer coefficient(h) in $Wm^{-2}K^{-1}$	**Ablated depth (x) in mm.**
125	0.10
250	1.83
500	2.92
1000	3.41
2000	3.77
4000	3.77

The ablation depth that has occurred with fluids of varying overall convective heat transfer coefficient are represented in the Table 3 which gives us an insight in choosing a better fluid that gives reliable ablation depths. As discussed above, the difference in the depths of ablation is very little at very high convective heat transfer coefficient; and the same is observed from the table. Moreover, abnormality of the endometrium is associated when the thickness of the endometrium is above 4-5mm. In this regard 4mm may be chosen as the minimal thickness above which abnormality may occur. From the Table 3 it is observed that the ablation is below 4mm even for very high values of convective heat transfer coefficient at a temperature of 87°C. Fluids with higher temperature ablate the tissue to greater depths and the choice of fluid temperature is done on the basis of patient consideration. For patients who require a greater depth of ablation, temperatures above 87°C should be used.

3.3 EFFECT OF FLUID TEMPERATURE ON THERMAL INJURY:

The temperatures used for endometrial ablation by thermal balloon procedure vary from 87° to 93°C usually. The variation in temperature caused across the uterine cavity by this range of temperatures is studied in this section. From the calculated depths of ablation, the temperature dependent variation of ablation is obtained.

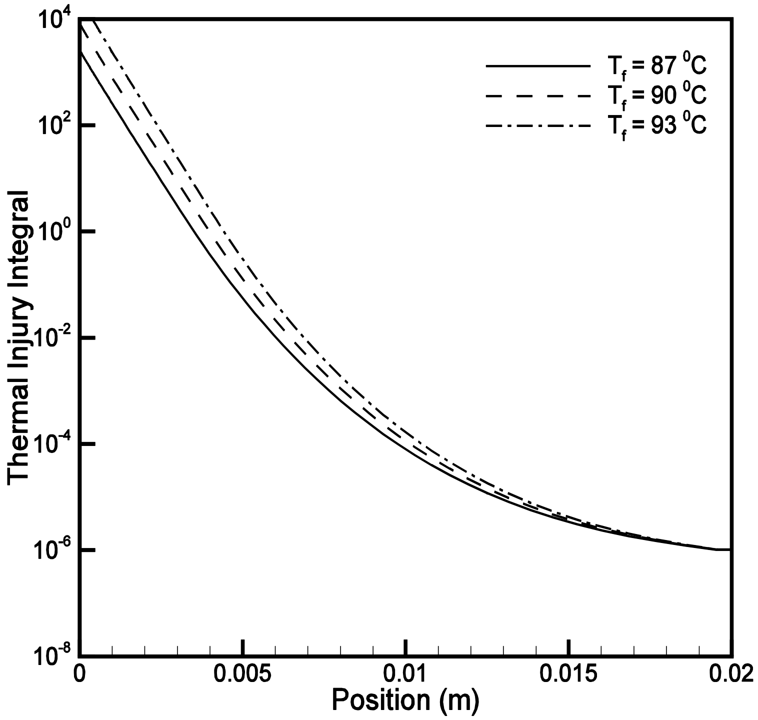

Figure 3: Variation of ablation depths for different fluid temperatures.

Thermal injury integral is plotted against the thickness of uterine tissue for different temperature values that are usually used in thermal balloon ablation as shown in Figure 3. Three temperature values 87°C, 90°C, and 93°C are chosen. As the temperature increases, irreversible damage that is induced into the tissue also increases. In this figure the overall convective heat transfer coefficient has been considered to be 1000 $Wm^{-2}K^{-1}$. At this value of overall convective heat transfer coefficient, the tissue damage is sufficient enough to destroy the undesired tissue. The following table indicates the thickness of ablated tissue at different temperatures.

Table4: Ablation depths for different fluid temperatures

Temperature of fluid (T_f) in °C	Ablation depth (x) in mm.
87	3.41
90	3.77
93	4.39

As indicated in Table 4 the variation of the ablation depth is considerable. Since, a minimal thickness of about 4mm is present in the endometrial lining; the depth up to which necrosis is needed could be determined by this study. A temperature of 93°C has a very high ablation depth in consideration to the other two values which is 4.39mm and is preferred for a thicker endometrium. The other two values have an ablation depth less than 4mm indicating that they are safer to be used when the minimal endometrium thickness for abnormality is considered to be 4mm.

3.4. EFFECT OF OVERALL CONVECTIVE HEAT TRANSFER COEFFICIENT ON THE ENDOMETRIAL SURFACE TEMPERATURE:

As the overall convective heat transfer coefficient varies, the rise in temperature at different distances from the surface of the endometrium also varies. This study is helpful in deciding the convective heat transfer coefficient of the fluid to be used in the balloon. If the convective heat transfer coefficient is too high, the rise in temperature due to convection also increases which may result in damage of the tissues nearer to the uterus. However, such an adverse effect is rare and can be attributed as a procedural risk. But, to know the transfer of heat by convection and the temperature rise caused as a result of this, it is necessary to study the dependence of overall heat transfer coefficient on the rise in temperature. The graph below indicates the temperature across uterine cavity for different values of convective heat transfer coefficient.

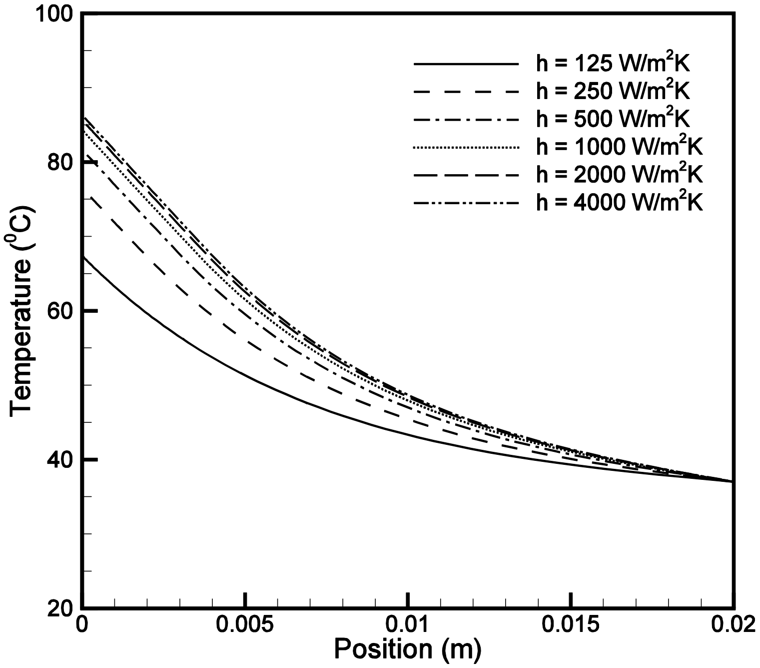

Figure4: Variation of temperatures at endometrial surface for different overall convective heat transfer coefficients

As observed from Figure 4, there is a sharp rise in temperature as overall heat transfer coefficient increases from lower values to higher values. However, this increase is very slight when the overall heat transfer coefficient reaches higher values. It is clearly observed from the graph that the difference in rise of temperature caused by overall convective heat transfer coefficients at 2000 $Wm^{-2}K^{-1}$ and 4000 $Wm^{-2}K^{-1}$ is very little when compared to the difference in rise of temperatures when the overall convective heat transfer coefficients varied from 125 $Wm^{-2}K^{-1}$ to 250 $Wm^{-2}K^{-1}$. This indicates that the difference in the rise of temperature decreases with increasing values of overall convective heat transfer coefficient. The above results are obtained when fluid temperature is 87°C

Table 5: Effect of various overall convective heat transfer coefficients on temperatures at endometrium surface

Overall convective heat transfer coefficient (h) inW $m^{-2}K^{-1}$	**Temperature at the surface of endometrium (T_s) in °C**
125	67.37
250	76.50
500	81.66
1000	84.31
2000	85.64
4000	86.31

From the Table 5, it is observed that as the overall convective heat transfer coefficient increases, the temperature at the surface of the endometrium also increases which is obvious. But the difference in rise of temperatures with varying overall convective heat transfer coefficient at endometrial surface is high for lower values and this difference in rise gradually decreases as the convective heat transfer coefficients reaches higher values.

3.5. EFFECT OF FLUID TEMPERATURE ON ENDOMETRIAL SURFACE TEMPERATURES:

When fluids at different temperatures are employed in the silicone balloon, the rise in temperature across the uterine cavity varies. This variation is studied by plotting a graph of temperature against the thickness of the tissue for various temperatures of the fluid. Three temperatures 87°C, 90°C , and 93°C which are generally used have been taken into consideration and the variation of temperatures at the endometrium surface and at various depths in the tissue are examined from the graph.

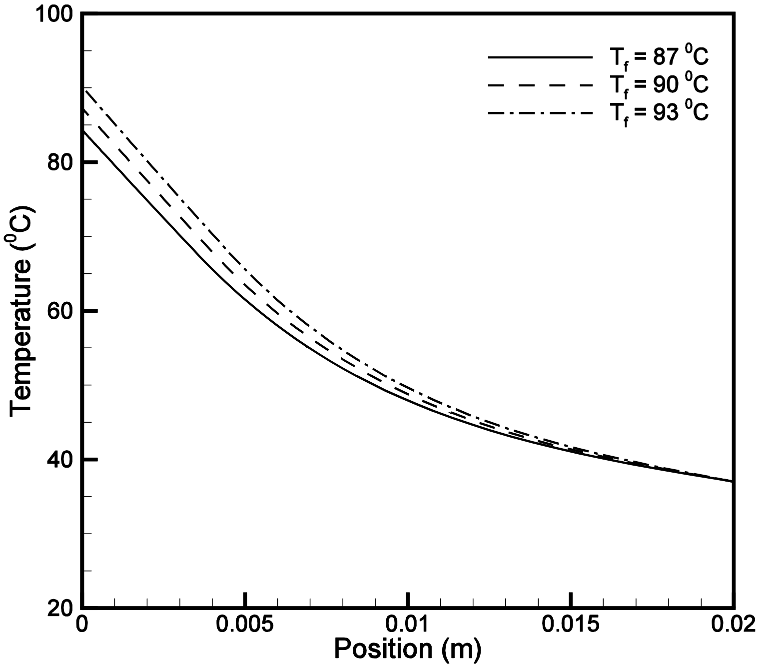

Figure 5: Variation of temperatures at endometrial surface for different fluid temperatures.

Figure 5 indicates the variation caused in temperature at the endometrial surface when different fluid temperatures are used. The temperature at the surface of the endometrium in contact with the balloon is not the same as the fluid temperature due to convective heat loss. In all the cases overall convective heat transfer coefficient is taken to be 1000Wm^{-2}K^{-1}. It can be seen that as the fluid temperature increases, the temperature of the tissue also increases.

Below is a table that represents temperatures at endometrial surface for different fluid temperatures used in the balloon.

Table 6: Effect of various fluid temperatures on temperatures at endometrium surface

Temperature of the fluid (T_f) in °C	Temperature at the surface of endometrium (T_s) in °C
87	84.31
90	87.23
93	90.15

From Table 6, it can be observed that the temperature at the surface of endometrium is less than the actual fluid temperature which could be accounted to convective heat loss. The values tabulated above are considered for a fluid with an overall convective heat transfer coefficient 1000 $Wm^{-2} K^{-1}$.

CONCLUSION:

A thermal balloon endometrial ablation model is presented. The mathematical findings lie within the range of experimental values which proves the validity of the presented model. The effect due to variation of overall convective heat transfer coefficient on ablation depth is studied. Along with it, the effect of different fluid temperatures and its influence on the ablation depth is discussed. Similar study has been performed for studying influence of varying convective heat transfer coefficients on the temperature across the uterine cavity. However, there might be some procedural risks and some adverse effects associated with thermal balloon ablation. Hence, a clear pathological history and good examination is required before performing thermal balloon ablation. There might be some pathological responses that may cause inaccuracy of the results from those studied in the current model. Therefore, proper care should be taken while implementing the current model.

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