Intra uterine and Intra vaginal Drug Delivery systems: an Overview

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Abstract:

In the view of reducing the unintended pregnancies all over the globe there is a need in the development of the efficient delivery systems of drug to uterine and vagina. There are many women who rely on the intrauterine and intra-vaginal devices than in past. These devices are inserted into the uterine and vaginal cavity with the help of expertise medical practitioner. At present there are 3 hormonal devices and 1 copper-T uterine device is available. Around fifty percent women stop using intrauterine device within the five years and the occurrence of pregnancy is less than two per hundred insertions. The sterile inflammatory reaction that interferes with the sperm function in the endometrial cavity is responsible for the contraceptive effects of intrauterine devices. The pregnancy rate is same as that of tubal interruption even with the effective use of devices for ten years.

Keywords: Intrauterine, intravaginal, pregnancy, copper-T, sperm.

BACKGROUND:
Vagina and uterus are the routes of administration of contraceptives (for the prevention of pregnancy), antimicrobials, and anti fungal agents (for the treatment of vaginal and uterine infections) because of less activity of enzymes, permeation area, avoidance of first pass metabolism and high vascularity. The vaginal wall contains a vast blood vessel network, so it is suitable for drug absorption. Vagina and uterus are used for the local and systemic absorption. But in most cases these route is useful for the contraception (Manikanta Kumar et al, 2018).

Why to use contraceptives (New Zealand family planning):

1. Family planning
2. Decreasing of risks related to the pregnancy
3. Reducing the teenage pregnancies:
4. Giving birth to the children with less health issues.

According to the survey conducted in United States in 1975 around 27 million couples of child baring age 76.3% showed interest to prevent contraception either temporarily or permanently.
Table 1: Methods of contraception that served, Source: United States family planning survey, 1975.

<table>
<thead>
<tr>
<th>Method of contraception</th>
<th>% of those served</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptive pills</td>
<td>26.3</td>
</tr>
<tr>
<td>Condom or Diaphragm</td>
<td>10.0</td>
</tr>
<tr>
<td>Intrauterine devices</td>
<td>6.4</td>
</tr>
<tr>
<td>Foam</td>
<td>2.6</td>
</tr>
<tr>
<td>Rhythm</td>
<td>2.2</td>
</tr>
<tr>
<td>Other</td>
<td>28.8</td>
</tr>
</tbody>
</table>

Anatomical features of Female reproductive system:

The major parts of female genatalia includes:

- Fallopian tubes
- Uterus
- Ovary
- Vagina

Vagina:

Vaginal canal is a muscular canal about 3 inches long which receives the sperms and is the main organ during the birth process. In human beings, it is responsible for the excretion of the menstrual products.

The vaginal pH in premenopausal women is differs from 4.5 and may increase up to 7 in postmenopausal women.

Vaginal wall surface is covered with epithelium cells

Size:

<table>
<thead>
<tr>
<th>Vagina</th>
<th>Length</th>
<th>Width</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal women</td>
<td>7.8cm</td>
<td>2cm</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td>4.5 cm</td>
<td>1-1.5cm</td>
</tr>
</tbody>
</table>

Uterus:

The endometrial layer of the uterus is highly vascular and is made up of simple columnar epithelium and it is highly sensitive to hormonal secretions of ovary. During complete cycle endometrium goes on thickening with the hormonal impact.

Size: Uterus of the non pregnant lady is around 7.5 centimeter long, 5 centimeter wide and 2.5 centimeter thick.
Fallopian tubes or oviduct:

Fallopian tubes are also known as Oviducts or uterine tubes and are around 10cm long. The end portion is opened and funnel shaped containing finger like projection called Fimbriae. Internal surface is of ciliated columnar epithelium cells.

**INTRAVAGINAL DRUG DELIVERY SYSTEM (IVDDS)**

IVDDS is a system which is used for the treatment of various vaginal infections and also used as a contraceptive for the prevention of pregnancy. Because of vast blood vessel supply it is well suited for the drug absorption both systemically and locally. This delivery system mainly offers the advantages like avoiding the hepatic first pass metabolism and reducing the gastric and hepatic side effects. The drugs that are administered through vagina provide both activities like contraception and microbial protection. The vaginal controlled drug delivery systems are firstly developed and used in 1970, the vaginal ring that was first delivered is consisting of medroxyprogesterone acetate for contraception. Currently used long term drug delivery system is vaginal rings. The devices that deliver the therapeutic agent to the vagina for the treatment of vagina associated disorders are known as intravaginal drug delivery devices.

**Absorption through vagina:**

**Factors affecting vaginal drug absorption:**

Factors can be categorized as:

1) **Physiological factors:-**

The factors that are effecting the absorption through vagina are as follows:

a. pH of vagina is around (3.5 to 4.9)

b. Menstrual cycle effect on vaginal epithelium permeability.

c. Fluid volume of vagina

d. Viscosity of vaginal fluid

e. Pressures exerted by rectal wall on dosage form affect vaginal blood flow.

2) **Physicochemical factors:-**

Factors related to physico-chemical properties of drug that influences the drug absorption such as:

1) Viscosity (semisolids)

2) Administration volume and concentration of the drug.

3) Dosage form type

4) Drugs molecular size
5) Lipophilicity
6) Ionization
7) Chemical stability

The aliphatic alcohols of straight chain will increase the permeability of the agent with increase in chain length. The drugs with higher lipophilicity will absorb faster than the hydrophilic drugs. To easy release of drugs from the formulations the drug should have good solubility and dissolution profile even though the dissolution is the rate limiting step. The drugs which are in unionized form will be absorbed more than the drugs in ionized form (Justin-Temu et al. 2004).

Ideality of Intravaginal DDS:

1) The system should melt at vaginal temperature i.e. at 37°C.
2) Device should be nontoxic and nonirritating.
3) Formulation should be non sensitive on vaginal pH.
4) It should contain properties like wettability and emulsification property.
5) Upon storage it should be stable.
6) The viscosity of the formulation should be in such a way that will avoid leakage of the medicament from the vagina.
7) To improve the contact time in between membrane and formulation. It should have proper bio adhesive properties (Lohithasu Duppala et al., 2018).

Classification of Intravaginal DDS:

Localized:

1) Barrier contraception
Barrier contraception mainly contains the diaphragm, condom (for both genders), cervical cap, film, sponges, spermicidal foam. Barrier method mainly stops the entry of sperm to uterus. It was suggested that the use of spermicide with the barrier will give good results in the contraception. The entered sperms in to vagina are killed by spermicide. This method will also protect the individual from the sexually transmitted diseases (Abramowicz et al., 2010).

2) Prevention/Treatment of infection.
For the prevention of vaginal infections there are some available formulations such as Gels, Creams and Ointments for the delivery of therapeutic substances by the vagina. Among which gels are found to be more
effective and convenient for the application of the drugs via vagina. Gels mainly contain gelling agent and high ratio of solvent. The dispersion of this gelling agent in selected solvent will form a colloidal network in 3D dimension, this dimension stop the fluid flow by entrapment and immobilization.

B. Systemic:

A. Suppositories or pessaries

The vaginal suppositories and pessaries are the formulations that release the medicament in the vaginal cavity by melting at the body temperature for a prolonged period of time. To increase the residence time of the vaginal suppositories mucoadhesive polymers are used.

B. Bio (muco) adhesive semisolids.

These are the polymers are in contact with the mucous layer. Bio-adhesion of these formulations is because at normal body pH. These mucous layers carry negative charge because of acid residues.

- These are emulsion bases formulation to deliver antifungal agents such as imidazole. Give controlled delivery for 3 or more hrs.

Solid polymeric carriers.

a. Solid hydrogels:

Having swelling property which enables the drug to diffuse out of the macromolecular network.

eg. Nu-gel (Johnson & Johnson)

Elastomeric intravaginal rings (IVR):

IVR are the circular shaped rings that are developed to deliver the agent in controlled manner after insertion into the vaginal cavity.

Advantages:

✓ The use of these formulations can be controlled by the user themselves.
✓ There is no interference with the coitus.
✓ These formulations allow the delivery of the drugs continuously.

1) Matrix (homogeneous dispersion)

2) Reservoir (core)
3) Sandwich (shell)

Elastomer exert slight tension on vaginal wall,

More suitable for hydrophobic drugs. Normally designed to contain steroidal hormones.

1) Matrix type:-

- Drug is homogeneously dispersed throughout the polymer matrix.
- Drug release from this type follows First order.

2) Reservoir type:-

- Drug is located within the centralized core that is surrounded by drug free silicon sheath acts as rate controlling membrane for drug diffusion.
- It follows Zero order fashion.
- Commonly used elastomeric polymers are dimethylsiloxane and ethylvinyl acetate

3) Sandwich type:-

It consists of narrow drug containing layer situated between non-medicated impervious central core and non-medicated outer rate controlled band.

It is small and there is a constant release of drug.

Novel approaches:

**Vaginal Tampons- Medicated** –

These tampons are approved by the FDA as medical devices.

- These tampons are amphipatic in nature which has polymer system which absorbs the fluid released during mensuration that also releases the acids like citric and lactic acids.

**Vaginal Films**-

- These are thin shaped sheets having the frequency of 200 to 240 micro meters and also contain the polymeric system for the delivery of the medicaments.
- These are homogenous systems with square shape, and are colorless soft surface.
- The polymers such as PA, PE, PEG and ethyl cellulose are used for the development of vaginal films, like VCF (vaginal contraceptive films)
Intrauterine drug delivery systems (IUDDS):

Introduction:

Uterus is mainly involved in the development of embryo and fetus by harboring of the reproductive organ. It is also considered as one of the potential organ for the systemic administration as it has rich blood supply. Intrauterine devices are suggestible vehicle for inserting into the uterus for longer time because of its minimal complications.

The anatomical features of uterine cavity include, it is a pear shaped hollow fibro muscular organ the shape, dimensions and mass varies noticeably depends on the stimulation of estrogen. The main purpose of the uterine cavity is to residence, promote the embryo, fetous and labor by applying the dominant contraction of its thick muscular walls. The weight of the uterus is 30 to 40 grams and it measures width of five centimeters, length of eight centimeters, thickness of two half centimeters. It comes down gradually from lower abdomen to pelvis between birth and puberty. It locates in the middle line in the pelvic region at back symphysis pubic region and urinary bladder and in frontage of rectus after puberty. Muscular corpus at upper and fibrous cervix at lower are the two portions of the uterus. The cervix is smaller than corpus in reproductive women, while their sizes are similar after menopause and before menarche. It is triangular in coronal section the base is formed with internal funds surface in between the opening of the tubes of the uterus, the internal orifice is apex, most important to the cervical canal.

The device which is used in the intrauterine drug delivery system is known as Intrauterine device (IUD). IUD is made up of plastic which is inserted in to the uterine cavity to prevent the pregnancy. The length of the IUD is about 3cm. The IUD are developed in various shapes out of which the well known is the T-shaped device and copper-T that is coated with copper metal. Copper has the spermicidal activity this inserted IUDs has the effect for five years. Some IUDs are also prepared by using hormones like progesterone instead of copper but they have to replace once in every year. IUD is the better option in the contraception for the women’s who want reversible, long term, and effective contraception. These formulations will not protect from the sexually transmitted diseases so it no preferable in the individuals who are suffering from the high risk of sexually transmitted diseases. These IUDs are inserted in to the upper tract of the vagina with the help of the attached strings. IUDs mainly prevent the fertilization by affecting the mobility of the sperm and egg. Before the insertion of the IUDs the expert should examine the pelvic region to measure the shape, shape and position of the uterus, and then an antiseptic solution should be applied to the cervix and inserted in to the uterus. There is chance of cramping sensation but it not so high. The size of the strings may be cutted after the insertion so that it will not produce any disturbance to the participating individuals. The lining of the uterus will be changed with the IUDs to prevent the fertilization of the egg in the lining. The IUD can be removed from the uterus when there is a need of pregnancy.

HISTORY:

In the olden days the arabs used to insert the small stones in to uterus of the camel for the prevention of the pregnancy during the long desert tripping. By taking this as the base after the acceptance of the experts starting
materials for the manufacturing of the IUD were done and marketed in the year 1902. These IUDs are mainly
developed from the stem pessaries, the stem of the pessary mainly extends in to the uterus and so called as the
intrauterine devices. The initial intrauterine device is published in the Germany in 1909. In 1929 the first IUD was
reported by Dr. Ernst Graifenberg which was made from the silk worm gut. The large scale adaption of the initial
IUD was prevented because of their local action by the general physicians. The Margulies spiral introduced the next
generation IUD in 1960. The devices made from plastic are known as second generation devices which render their
radio sensitivity. Lippes loop were discovered in 1962, most widely used IUD till now which was tied with a thread
made from nylon that is attached to the lowest part of the device that facilitate easily removal form uterine cavity.
Some of the reported works shown that by the use of carrierT by the addition of wire of copper decreased the
fertility rate at 18% in ladies per year by plain T carrier to 1% women year. The devices that contain huge amount
of progesterone which is released at a subordinate rate and effective for two years.

Mechanism of action of IUDs:

IUDs mainly interfere with the capacity of the sperm to stay alive and to climb the fallopian tubes where the
fertilization occurs to prevent the fertilization. The presence of the IUD as a foreign body in the uterus make
anatomical and biochemical changes which produce toxicity to the sperm. Reactions of the endometrium with the
white blood cells, enzymes and prostaglandins will prevent the sperm from reaching the fallopian tubes (Bonnie et
al., 2010).

Complications:

✓ There is a chance of introducing the bacteria in to the uterus by the insertion of the IUDs and it also carry an
enlarged danger of pelvic seditious disease in the initial 20 days.
✓ The provider should use appropriate infection hindrance technique during placing.
✓ The cervix be supposed to be dilated previous to the insertion in order to compute the uterus and place in the
IUD. The dilation of the cervix mainly causes the discomfort and it is painful. To reduce the discomfort
NSAIDS are recommended before insertion.
✓ There are heavier menstrual periods and painful or both after insertion of the IUD for the first few months.
✓ After insertion of the copper-T IUD on an average of 20 to 50% of blood is lossed and also increase the
menstrual discomfort.
✓ Non hormonal IUDs are considered safe during the breast feeding (Maria et al., 2014)

Different types of IUDs:

1. Non medicated IUDs Ex: Lippes loop
2. Medicated copper containing IUDs Ex: Cu T200, Cu T 380A, Multiload-250, Multiload-375, Nova T.
3. Hormone containing IUDs Ex: LNG-20 (Saltzman et al., 2009).
Copper containing IUDs:

Cu T200:

In this copper wire is wound around the vertical stem, T shaped frame made of polyethylene, with polyethylene threads. There life span is about three years and rate of failure is 3%. They are replaced with the more copper with increased efficacy and life span (Magoon et al., 1982).

Steps of insertion:

1. Before insertion inspect the cervix and vagina carefully
2. Bimanual examination should be performed.
3. Vagina and opening of the cervix should be disinfected.
4. Measure the uterus
5. Insert the IUD carefully (Meyer et al., 2008).

Conclusion:

Intrauterine and intravaginal drug delivery systems are very effective drug delivery system for the prevention of the unintended pregnancies. Even though there are some disadvantages the usage of such devices are more. Further there is a need in developing the devices with less side effects and more responsive.

References:


