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OVERVIEW OF INTRAUTERINE DRUG DELIVERY SYSTEM

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ABSTRACT:

Writing this overview of intrauterine drug delivery systems was done with the intention of gathering the most recent research, paying particular attention to the many intrauterine techniques that have emerged as the most effective methods for site-specific oral controlled release drug delivery. To end the pregnancy, the medication releases in the uterus. Details about the benefits and drawbacks of IUDDS are provided. IUDs, or intrauterine devices, are used in intrauterine medication delivery systems. They come in a variety of forms and, depending on the type, can be effective for three to 10 years. An effective, reversible form of long-term contraception is the IUD. A unique device that fits into the uterus is called an intra-uterine device. A tiny device called an intrauterine device (IUD) is put within the uterus through the cervix in order to prevent conception. From the IUD, a tiny string extends into the vagina's upper region. During sexual activity, the IUD is undetectable. IUDs may endure one to ten years. In order to stop fertilization, they interfere with the motions of sperm and eggs. They also hinder implantation and alter the uterine lining. The effectiveness of IUDs as birth control is 99.2-99.9%. They offer no defense against HIV/AIDS or other sexually transmitted illnesses. An IUD can be inserted in as little as five to ten minutes. IUD insertion requires a clinician. Usually, you do it during your menstrual cycle. The medical professional will examine your pelvis and determine the exact location of your uterus. After seeing your cervix with a speculum inserted into your vagina, they will clean it with an antiseptic solution. By preventing sperm from accessing an egg that your ovaries have released, an IUD prevents conception.

Keyword: IUD, Non-Hormonal IUD Copper-T, Hormonal (Progestogen) IUD.

I. INTRODUCTION

An intrauterine device, commonly known as an IUD, is a small contraceptive device inserted into the uterus through the cervix to prevent pregnancy. A thin string attached to the IUD extends into the upper vaginal region, facilitating easy removal using forceps. The contraceptive effectiveness of IUDs is estimated to be between 99.2% and 99.9%. However, it is important to note that IUDs do not provide protection against sexually transmitted diseases, including HIV/AIDS. While the precise mechanism of action of IUDs remains uncertain, it is believed to induce general biochemical and histological changes in the endometrium. Ionized copper in IUDs is thought to contribute to spermolytic and gametotoxic effects, reducing the viability of gametes and thus lowering the chances of fertilization (not implantation). Copper ions impede sperm motility,

capacitation, and survival. Additionally, hormone-releasing IUDs increase the viscosity of cervical mucus, preventing sperm entry into the cervix. The combination of elevated progesterone and reduced estrogen levels created by hormone-releasing IUDs establishes an environment unfavorable for implantation. It is advisable to replace the IUD every three years for optimal contraceptive efficacy.

A) Advantages IUD system has the following advantages:

1) It provides long lasting and reversible contraception.

2) It is a private and discreet method.

3) It is highly effective and safe in use.

4) Its initial cost is high but has no later expenses after its insertion, thus is considered as a cost-effective contraceptive.

5) It is convenient.

6) It is rapidly reversible, hence is preferred for females who opt for long-term birth control and want to retain fertility.

7) It does not cause any effect in breast milk or breast feeding.

8) It does not interfere with sexual life.

9) It does not undergo any drug interaction.

10) Upon its insertion, the user has no botherance to remember about it.

11) The user has nothing to do with it, therefore user related errors are reduced.

12) It does not disturb the hormonal cycle.

13) It is a better option for women avoiding pill.

14) It safety and effectiveness is equivalent to sterilisation, injectable contraception, and sub-dermal implant.

15) Its failure rate is only 1-2%.

16) A hormone-releasing IUD (Mirena) is suitable for heavy menstrual bleeding.

17) Copper IUD may reduce the risk of endometrial cancer as does the levonorgestrel IUD.

18) Hormonal IUD is preferred over surgical or oral hormonal treatments for heavy menstrual bleeding and for menopausal women ingesting estrogen who can tolerate other progestogen forms.

B) Disadvantages IUD system has the following disadvantages:

1) A trained medical professional should only insert and remove it.

2) In the first 3-6 months, the user undergoes longer, heavier and sometimes painful menstrual bleeding. Sometimes, spotting and light bleeding occurs in between periods. This condition is, however, normal and reduces over time.

3) Use of levonorgestrel may result in unpredictable bleeding lasting for about 4 months of use. The menstrual flow reduces with increase in duration. In the initial first year, around 20% of women experience amenorrhea (absence of menstrual bleeding).

4) Side effects of levonorgesterel IUD are lower abdominal pain, complexion alteration, back pain, breast tenderness, headache, mood swings, and nausea. These adverse symptoms decline with time and are observed in less than 3% of patients. On using progestin-only methods, benign follicular cysts are reported in 8-12% of users. Most cysts resolve suddenly without medical supervision.

5) Some users undergo hormonal side effects, like mood swings or breast tenderness.

6) Occasionally IUDs can be excluded.

7) IUDs may develop Pelvic Inflammatory Disease (PID), which may cause infertility, in the users within the first three weeks of insertion.

8) In some cases, IUD may perforate the uterus wall due to improper insertion.

II. TYPES OF INTRAUTERINE DEVICES

Intrauterine Devices (IUDs) for controlled drug delivery are classified into the following two categories:

A) Non-Hormonal IUDs/Copper-Medicated IUDs:

The intrauterine devices (IUDs) are constructed with a support made of either polypropylene or polyethylene plastic, designated as number 7 or letter T. This design incorporates a fixed quantity of copper wire wound around the device. The T-shaped IUD is widely utilized due to its resemblance to the uterine cavity, preventing displacement, rotation, and expulsion from the cavity [refer to figure 11.1 (a)]. The device features two pliable arms that facilitate insertion by folding during the process and subsequently expanding into a T-shape within the uterus. When fully open, the device measures 36mm in height and 32mm in width. Additionally, the device includes a vertical stem encased with fine copper wire and two horizontal arms covered with copper.

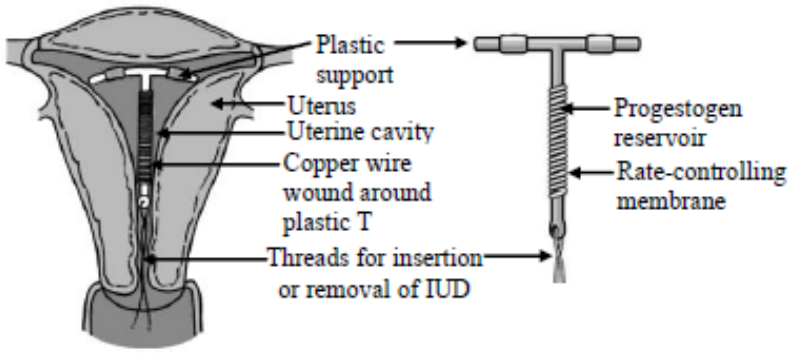

Figure 1.1: Contraceptive IUDs – (a) Non-Hormonal IUD – Copper-T, and (b) Hormonal (Progestogen) IUD

The exposed copper surface area measures 380mm. A 3mm bulb is located at the base of the vertical stem, housing a monofilament polyethylene string for convenient device removal. The device remains effective for a duration of up to 12 years. By releasing copper ions, enzymes, prostaglandins, and macrophages into uterine fluids, the copper-T IUD establishes an inhospitable environment for sperm, preventing ovum fertilization. Additionally, this device disrupts the normal division of oocytes and the formation of ova.

Copper-T has the following advantages:

i) It is safe being a non-hormonal device.

ii) It works immediately and is highly effective.

iii) It produces a long-term effect (for up to 10 years), thus the user does not have to use a contraceptive regularly or at the time of intercourse.

iv) It is a cost-effective device.

v) It is a reversible device, i.e., fertility returns on its removal.

Copper-T has the following disadvantages:

i) It should be inserted and removed only by trained clinicians.

ii) It may get expelled in the first year.

iii) Increased menstrual bleeding and cramping occurs in some users.

iv) It does not provide protection against STDs, including HIV.

B) Hormonal IUDs/Progestogen-Containing IUDs:

The T-shaped contraceptive device is constructed with a polyethylene frame, measuring 32mm both vertically and horizontally. Incorporated within the device is a silicon reservoir containing either levonorgestrel or progesterone, dispersed along the vertical stem. Encasing this stem is a membrane made of ethylene-vinyl acetate copolymer, as depicted in Figure 11.1 (b). This contraceptive mechanism functions by continuously releasing progestogen directly into the uterus, providing effective prevention of pregnancy for a duration of up to 5 years.

The IUD that releases progestogen, prevents pregnancy by:

i) Thickening the mucus of cervical mucosa, thus preventing the entry of sperm in uterus.

ii) Alternating the uterus lining, thus making it unsuitable for pregnancy.

Specific advantages of this IUD are:

i) After 5 months of using the device, the users will have light periods.

ii) After 12 months of using the device, 20% of women will get no periods. Plastic support Uterus Uterine cavity Copper wire wound around plastic T Threads for insertion or removal of IUD Progestogen reservoir Rate-controlling membrane Figure 1.1:

Contraceptive IUDs:

(a) Non-Hormonal IUD – Copper-T, and

(b) Hormonal (Progestogen) IUD

iii) It can be used for treating heavy menstrual bleeding.

iv) The pain associated with period is reduced with the use of this device.

v) It is suitable for women approaching menopause as it provides effective contraception and can be used as the progestogen component for hormone replacement therapy.

Apart from the disadvantages of copper-T, some other drawbacks of this IUD are:

i) It causes disturbed bleeding pattern in the initial stages.

ii) The users may experience weight gain.

III. MECHANISM OF ACTION IUDS BLOCK FERTILISATION:

Hormonal intrauterine devices (IUDs) release progestogen to prevent ovulation effectively. Additionally, progestogen thickens the cervical mucus, creating a barrier that hinders sperm from reaching the fallopian tubes. On the other hand, copper IUDs, devoid of hormones, release copper ions into the cervical mucus. These ions exhibit spermicidal properties, affecting the sperm, uterus, and fallopian tubes. Consequently, these devices generate a fluid containing copper ions, white blood cells (WBCs), prostaglandins, and enzymes. Copper-releasing IUDs are notably effective as emergency contraceptives by preventing the implantation of the blastocyst in the uterus. In non-emergency applications, the inhibition of implantation lacks a specific mechanism of action.

IV. DEVELOPMENT OF INTRAUTERINE DEVICES (IUDS):

The history of IUDs is uncertain, with no clear evidence supporting the insertion of foreign objects into the human uterus for contraception prior to the 20th century. Nonetheless, historical reports suggest that centuries ago, Middle East traders employed a method to prevent pregnancy in camels by inserting pebbles into their uteri before embarking on long treks across the desert.

In 1909, Dr. Richard Richter proposed the idea of inserting a ring made of silkworm gut into the uterus. The ring had two ends outside of the cervix for easy checking and removal. In the mid-1920s, Karl Prust and Ernest Graefenberg presented similar theories. Prust advocated for silkworm insertion with a stiff cervical extension

of a tightly wound thread and a glass button covering the cervix. Graefenberg proposed a similar model but removed the extensions of the silkworm ring to prevent infections. Detection of the ring's position in the uterus involved the use of X-rays, with a silver wire attached to the ring. This particular device demonstrated a pregnancy rate of approximately 3%.

Dr. Graefenberg later modified the ring by wrapping pure silver around it, resulting in gingival argyrosis, where the user's gums turned bluish-black due to silver absorption. Subsequently, he switched to a wire made of German silver, an alloy composed of various metals like copper, which reduced the pregnancy rate to around 1.6%. While this ring gained widespread acceptance in England and other British Empire countries, its sales did not fare well in continental Europe or the United States.

During World War II, research and development in the field of contraception were limited. Both Germany and Japan ceased the use of contraception during this period. A significant breakthrough occurred in 1949 when a method involving silkworm gut was demonstrated. The innovator wrapped the material around her finger, placed it inside a gelatin capsule, and then inserted the capsule into the uterus. As the gelatin liquefied, the thread spread out, resulting in a remarkable drop in the pregnancy rate to a mere 1.1%.

Doctors globally celebrated success with various versions of intrauterine devices (IUDs) for several years. Initially, concerns arose regarding the "tails" on IUDs causing pelvic infections, leading to modifications in device designs. In 1960, Dr. Lazar Margulies introduced a breakthrough device made of polyethylene, addressing concerns by allowing the device's end to protrude through the cervix. The first patient to receive this new device was Dr. Margulies' wife. Dr. Alan Guttmacher, Dr. Aqviles Sobrero, and Dr. Christopher Tietze reviewed the inserter tube, coil, and a copy of the hysterogram.

Dr. Jack Lippes played a pivotal role in 1962 by developing and inserting the first plastic IUD, known as the Lippes Loop. Available in various sizes based on a woman's pregnancy history, this inexpensive device featured a string for easy detection and removal. Its simplicity and cost-effectiveness led to widespread adoption worldwide. Subsequently, various IUDs were introduced, with differing levels of success and complications.

A significant development occurred in 1969 when some women reported increased cramps and bleeding associated with IUD usage. In response, Dr. Howard Tatum attempted to address these issues by reducing the size of the IUD, resulting in the creation of the plastic T. Although tolerable, this version had a higher pregnancy rate of 18%. Concurrently, Dr. Jaime Zipper made a groundbreaking discovery involving a copper wire in one horn of a rabbit's uterus, establishing the contraceptive effect of intrauterine copper and broadening the effectiveness of IUDs.

In 1970, Dr. Antonio Scommegna introduced a novel T-shaped contraceptive device containing progesterone encased in a semi-permeable capsule in the lower section. The FDA granted approval for its safe usage for a year, and it remained on the market until the early 2000s.

The A.H. Robins Company launched the Dalkon Shield IUD in 1971, aggressively marketing it as a highly effective and affordable pregnancy prevention device. Unfortunately, after just three years, it was recalled due to a poorly designed removal string. The unsealed string permitted the entry of bacteria into the uterus, leading to pelvic inflammatory disease, sepsis, and ultimately infertility. A.H. Robins faced around 300,000 lawsuits, resulting in demands for the company's bankruptcy. Subsequently, during the late 1970s and early 1980s, the use of IUDs declined, with several being withdrawn from the market. Only the progesterone-T variant remained available in the U.S. market.

In 1988, the Copper-T 380A (Para Gard) was introduced, initially approved for four years and later extended to 10 years based on supporting effectiveness data. In 2001, the levonorgestrel-releasing IUD (Mirena) was introduced in the U.S. On January 9, 2013, the FDA approved a low-dose hormone IUD known as Skyla by Bayer – the first new IUD in 12 years. This device provides protection against pregnancy for three years and is suitable for women without children. It was launched in February 2013.

At present, IUDs are considered safe, effective, and a low-risk form of contraception. According to a 2012 study by the Guttmacher Institute, the percentage of women using long-acting, reversible contraceptive

methods, such as IUDs, increased from 2.0% in 2002 to 7.7% in 2009. This upward trend continues as more women become aware of contraceptive options and have increased access to the best birth control methods for their needs.

V. APPLICATIONS

Intrauterine drug delivery system has the following applications:

1) Emergency Contraception:

The copper IUD (marketed as Paraguard) can be inserted within 5 days after unprotected intercourse.

2) Treatment for Heavy Menstrual Bleeding:

The progesterone intrauterine device (IUD), commonly known as Mirena, is employed to alleviate excessive menstrual bleeding. Comparative studies indicate its superior efficacy when compared to oral progesterone medications. The clinician should recommend the insertion of the IUD only after addressing and resolving other underlying causes of significant bleeding. This method stands as a viable alternative to hysterectomy in the management of such conditions.

3) Menopausal Hormone Therapy:

Mirena offers an alternative approach to administering progesterone as part of combined menopausal hormone replacement therapy. It is particularly beneficial for women who may face challenges with oral progesterone pills. Similar reductions in hot flashes and night sweats are observed in women using Mirena, akin to those utilizing conventional hormone replacement methods involving estrogen and progesterone in pill and patch forms.

4) Treatment for Pelvic Pain:

Some studies reveal that Mirena IUD reduces pelvic pain associated to endometriosis.

VI. CONCLUSION OF IUD:

The intrauterine device (IUD) stands out as a highly effective contraceptive option, especially for individuals not at risk of contracting sexually transmitted diseases. It is particularly suitable for women who have previously given birth and are in stable, monogamous relationships. Health care providers often recommend the progestin IUD for women experiencing extremely heavy, prolonged, or painful menstruation, as it tends to alleviate or even suppress such conditions. By reducing menstrual blood loss, women using this IUD are less prone to developing iron-deficiency anemia, a condition associated with fatigue and other symptoms. Studies have suggested that women with copper IUDs may have a lower risk of endometrial cancer, and some experts speculate a similar effect for the progestin IUD, akin to progestin-only contraceptives like the minipill and the shot. An IUD functions by preventing the meeting of egg and sperm, thereby preventing pregnancy. It may also inhibit the development of a fertilized egg in the uterus. The Nova T or Flexi T 300 IUD boasts about 98.7% efficacy in preventing pregnancy, while the Irena IUD is approximately 99% effective. Although the risk of pregnancy after IUD insertion is minimal, there is always a slight chance. In the event of pregnancy, the IUD should be promptly removed, and a healthcare provider consulted to rule out an ectopic pregnancy. If the pregnancy is not ectopic and the decision is made to continue it, the caregiver can easily remove the IUD if the strings are visible. While there is a slight risk that removing the IUD might lead to pregnancy loss, retaining it poses a greater risk of infection and jeopardizes the woman's health. In rare cases where the IUD cannot be easily removed, the woman may need to decide on the appropriate course of action.

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