Chapter 1: Introduction

1. History and background of contraception

When the modern family planning movement began in the United States and Europe in the early 20th century, its primary purpose was to liberate women from the social and health consequences of unwanted pregnancies. When organized family planning programs reached the Third World, beginning with India in the early 1950s, these programs were viewed as the means to alleviate the pressure of rapid population growth on economic development. In the last decades, the purpose of family planning has broadened to encompass both these objectives and the objective of improving women's health and welfare.

Family planning programs are hypothesized to affect women's lives in at least six areas:

- personal autonomy/self-esteem -- the right to make and stand by one's own decisions; value or regard an individual places on herself;
• health -- both physical and psychological well-being;

• educational attainment -- the ability to obtain an education and the level of educational attainment;

• employment and economic resources -- the nature of employment; acquisition and allocation of resources;

• family relationships -- degree of equality with spouse and role within kinship structure;

• public standing -- ability to participate in public activities and esteem accorded individual women by community.

1.1. History of contraception

From crocodile dung to lactic acid anhydride, contraception dates back as far as ancient Egypt and Greece. Many methods, inventions and substances were used in order to prevent unwanted pregnancies. Oddly enough, using substances such as crocodile dung was never questioned!

How it was used can be left to the imagination........

Dating back to 1850 BC, ancient Egyptians were responsible for using the infamous dung in addition to the female irrigating her vagina with a mixture of honey and sodium bicarbonate. The Ancient Egyptians also developed a tampon-like object that contained lactic acid anhydride, a chief ingredient in modern contraceptive jellies. We can safely conclude that our ancestors were on the right path! According to an ancient
manuscript called Ebers Papyrus, 1550 BC, women were advised to mix together dates, acacia bark and honey into a sugary paste and place it in the vulva. This method was often efficient because as the sugar ferments it is converted into lactic acid, as mentioned before, a well-known spermicide.

Commonly used and popular among young adults today is the condom. The condom has a rich history and the concept has been known for some time now. Long before condoms came in different sizes, shapes and colors, animal membranes and pieces of linen were sewn together to form a covering for the penis. The rubber condom was developed shortly after the creation of vulcanized rubber in the 1840’s, by Goodyear. Vulcanized means that the rubber is subjected to sulfur and extreme heat, which in turn processes the rubber into a strong elastic material. By 1930 liquid latex was used and is still what is used today to manufacture condoms. By the 1990’s new technology has improved the quality an effectiveness of the condom enabling manufacturers to make them in different sizes, colors and even flavors.

The origin of the condom is still unknown but it is said that a “Dr. Condom” supplied King Charles II of England with animal tissue sheathes to prevent him from fathering illegitimate children. Public Health concerns started to win over the moralistic attitudes of the time regarding promiscuous sex, when syphilis became rampant among American soldiers in World War 1. By the Second World War, military
leaders had a more realistic attitude about condoms and their use was strongly enforced. Today, condoms are widely used to protect against STD’s, (however recent finding tells that infection against HPV virus cannot be protected by condom use) HIV, and pregnancy. The condom’s effectiveness can range between 85-98%, depending on how it is used and the concurrent use of spermicide.

After World War II, the increasing rise in world population was alarming. The birth control pill was developed in order to curve this increase. In 1950 an American biologist Gregory Pincus developed the “ideal” oral contraception, which was tested on women from Haiti and Puerto Rico. In 1960 the first oral contraception, Enovid-10, was launched in the US market, known as the “pill”. Women were finally enthused about a form of contraception marketed as “safe and effective” and readily used the pill. Within two years oral contraception was used by over 1.2 million women and the numbers continued to rise.

Technology has allowed the contraception industry to flourish, coming up with many different types of contraception for females, with varying degrees of acceptance and success e.g. lower estrogen birth control pills; progestin-releasing intra-uterine device; new ways to deliver spermicides – Vaginal Contraceptive Film, Advantage 24 (bioadhesive gel), Leah’s Shield (a fusion of the diaphragm and cervical cap), spermicidal sponge; longer-acting hormonal contraceptives such as Depo-Provera; the female condom; the emergency contraceptive pill (ECP) (called as “morning after
pill); Recently launched and quite innovative is the Evra transdermal contraceptive patch, which is worn on the abdomen area or on the back, a similar idea to the nicotine patch for quitting smoking, it slowly releases estrogen and progestin into the body. Its effectiveness is similar to the oral contraceptive pill and is available from late 2003. Research continues to be done in the areas of contraceptive injections, pills, nasal sprays and implants for men. However there has been little interest in the drug companies developing them, perhaps due to the lack of enthusiasm from men.

There will continue to be research and development in methods of birth control. Though factors such as the high cost of developing drugs, less money for research from governments, and the concern of lawsuits for manufacturers will have a definite influence. The hope is always there for effective, safe and satisfying methods of contraception.

1.2. Contraceptive methods

There are many types of contraceptives in use today much more effective much less harmful to female body but none of which are totally ideal. However each method has been helpful in guiding us to the next step in development of contraceptive technology. Many contraceptives concentrate on keeping sperm out of the uterus, like diaphragms and condoms which provide a physical barrier; spermicides or sponges provide a chemical barrier; Natural Family Planning (NFP) or withdrawal
modifies the sexual act itself. Other methods, generally much more effective, concentrate on interfering with fertility (ovum). The oral contraceptive pill affects the ovum's development and release, an injectable such as Depo-Provera suppresses ovulation or an implant such as Norplant also suppresses ovulation. Intrauterine devices (IUD) help to prevent the fertilized egg from implanting in the uterus.

The major types of contraceptives available today are:

1) Barrier Methods

   a) Male Condoms: Male condoms are thin sheaths made of rubber, vinyl or natural products which are placed on the penis once it is erect. Male condoms may be treated with a spermicide for added protection. Male condoms prevent sperm from gaining access to the female reproductive tract and prevent microorganisms (STDs, except HPV virus including HBV and HIV/AIDS) from passing from one partner to another (latex and vinyl condoms only).

   b) Female Condoms: Female condoms are thin sheaths of polyurethane plastic with polyurethane rings at both ends. They are inserted into the vagina before intercourse. Like male condoms, they prevent sperm from gaining access to the female reproductive tract and prevent microorganisms (STDs, except HPV virus including HBV and HIV/AIDS) from passing from one partner to another through vaginal route.
c) Diaphragms: A diaphragm is a dome-shaped latex (rubber) cup which is inserted into the vagina before intercourse and covers the cervix. Diaphragms prevent sperm from gaining access to the upper reproductive tract (uterus and fallopian tubes) and serve as a holder of spermicide.

d) Spermicides: Spermicides are chemicals (usually nonoxynol-9) that inactivate or kill sperm. They are available as aerosols (foams), creams, vaginal tablets, suppositories, and dissolvable films. Spermicides cause the sperm cell membrane to break, which decreases sperm movement (motility and mobility) and their ability to fertilize the egg. The FDA, however, recently banned nonoxynol-9 for marketing.

2) Natural Methods

a) Lactational Amenorrhea Method: LAM is the use of breastfeeding as a contraceptive method. It is based on the physiologic effect of suckling to suppress ovulation. To use breastfeeding effectively as a contraceptive requires that the mother either feed the baby nothing but breast milk or, at the very least, breastfeed for almost all feedings. In addition the baby must be less than 6 months old and the mother's menses cannot have returned.

b) Natural Family Planning: To use NFP, a couple voluntarily avoids sexual intercourse during the fertile phase of the woman's cycle
(time when the woman can become pregnant) or has intercourse during the fertile phase to achieve pregnancy. There are four types of NFP: Calendar (Rhythm) Method, Basal Body Temperature, Cervical Mucus Method and Symptothermal Method.

c) Withdrawal (Coitus Interruptus): Withdrawal is a traditional family planning method in which the man completely removes his penis from the woman's vagina before he ejaculates. As a result, sperm do not enter the vagina and fertilization is prevented.

3) Combined (Estrogen/Progestin) Contraceptives

a) Combined Injectable Contraceptives: The two combined injectable contraceptives (CICs), Cyclofem® and Mesigyna®, are injections of the hormones estrogen and progestin which are administered once a month. CICs suppress ovulation, thicken the cervical mucus (preventing sperm penetration) change the endometrium (making implantation less likely), and reduce sperm transport in the upper genital tract (fallopian tubes).

b) Combined Oral Contraceptives: Combined Oral Contraceptives (COCs) are pills, which contain the hormones estrogen and progestin. They are taken daily. COCs suppress ovulation, thicken the cervical mucus (preventing sperm penetration) change the endometrium (making implantation less likely), and reduce sperm transport in the upper genital tract (fallopian tubes). Women above
the age of 35 who smokes cigarettes are not advised to use oral pill. Use of oral pill in smokers increases the risk of Miocardial infarction. (WHO Lancet 1995; 346:1575)

c) Vaginal Ring: NuvaRing is a flexible plastic non biodegradable intravaginal ring about 2.1 inches in diameter it releases a continuous low dose of estrogen and progesterone hormone similar to those available in some oral pill NuvaRing shares similar risks with other hormonal contraceptives, including blood clots, heart attack and stroke. It may also create vaginal discharge and vaginal irritation. NuvaRing, if used correctly, has the same failure rate as the oral pill, however, since it is not a barrier method of contraception or a vehicle for the delivery of microbicite, this ring does not protect against sexually transmitted diseases.

4) Progestin-Only Contraceptives

a) Norplant Implants: The Norplant system consists of six small flexible capsules made of Silastic® tubing which are filled with a synthetic progestin (levonorgestrel). The capsules are inserted just under the skin on the inner side of a woman’s upper arm using a minor surgical procedure. Norplant implants work by thickening cervical mucus, changing the endometrium and reducing sperm transport. They provide highly effective contraception for up to 5 years.
b) Implanon: Single Rod Effective for two year duration. One of the shortcomings of these implants, IUDs and injectables is their invasiveness to the human body and need for trained medical professional to deliver them which increases the cost.

c) Progestin-Only Injectable Contraceptives: Depo-Provera® and Noristerat® are the two progestin-only injectables contraceptives (PICs). Both are injections of the hormone progestin. They are administered every 3 or 2 months, respectively. PICs work by thickening cervical mucus, changing the endometrium, reducing sperm transport in the upper genital tract and suppressing ovulation.

d) Progestin-Only Pills: Progestin-Only Pills (POPs) contain the hormone progestin. They are taken orally daily by the woman. POPs suppress ovulation, thicken the cervical mucus, change the endometrium, and reduce sperm transport in the upper genital tract.

4) Intrauterine Devices: The intrauterine device (IUD) is a small T-shaped flexible device inserted into the uterine cavity. IUDs can be inert, copper-releasing or progestin-releasing. Copper-releasing IUDs interfere with the ability of sperm to pass through the uterine cavity and with the reproductive process before ova reach the uterine cavity.
Progestin-releasing IUDs also thicken the cervical mucus and change the endometrial lining.

5) Voluntary Sterilization

a) Tubal Ligation (Female): Tubal ligation is a voluntary surgical procedure for permanently terminating a woman's fertility. Tubal ligation can be done by mini-laparatomy or laparoscopy. Tubal ligation blocks the fallopian tubes (tying and cutting, rings, clips or electrocautery) and sperm are prevented from reaching the ova and causing fertilization.

b) Male: Vasectomy (Male): Vasectomy is a voluntary surgical procedure for permanently terminating a man's fertility. Vasectomy can be done by the standard method or the no-scalpel technique, which is the preferred method. Vasectomy blocks the vas deferens (ejaculatory duct) so that sperm are not present in the ejaculate.

The table listed below provides a breakdown of contraceptive use, by category, among US women.

Table 1: Contraceptive use among US women

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of users (in 000s)</th>
<th>% of users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal ligation</td>
<td>10,727</td>
<td>27.7</td>
</tr>
<tr>
<td>Pill</td>
<td>10,410</td>
<td>26.9</td>
</tr>
<tr>
<td>Male Condom</td>
<td>7,889</td>
<td>20.4</td>
</tr>
<tr>
<td>Method</td>
<td>No. of users (in 000s)</td>
<td>% of users</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>4,215</td>
<td>10.9</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>1,178</td>
<td>3.0</td>
</tr>
<tr>
<td>Injectable</td>
<td>1,146</td>
<td>3.0</td>
</tr>
<tr>
<td>Periodic Abstinence</td>
<td>883</td>
<td>2.3</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>720</td>
<td>1.9</td>
</tr>
<tr>
<td>Other</td>
<td>670</td>
<td>1.8</td>
</tr>
<tr>
<td>Implant</td>
<td>515</td>
<td>1.3</td>
</tr>
<tr>
<td>IUD</td>
<td>310</td>
<td>0.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>38,663</td>
<td>100.0</td>
</tr>
</tbody>
</table>

2. **Rationale**

Contraceptive technology development has had a great impact on women’s reproductive health, however, there are two broad areas still requiring significant continued research and development.

These are:

1) Contraception failure

2) Contraception related adverse events
2.1. Contraception failure

Table 2: Contraceptive failure rates

<table>
<thead>
<tr>
<th>Contraceptive method</th>
<th>% Failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male condom:</td>
<td>14%</td>
</tr>
<tr>
<td>Withdrawal method:</td>
<td>19%</td>
</tr>
<tr>
<td>Diaphragm:</td>
<td>20%</td>
</tr>
<tr>
<td>Female condom:</td>
<td>21%</td>
</tr>
<tr>
<td>Rhythm method:</td>
<td>25%</td>
</tr>
<tr>
<td>Spermicide:</td>
<td>26%</td>
</tr>
<tr>
<td>Sponge:</td>
<td>40%</td>
</tr>
<tr>
<td>Cervical cap:</td>
<td>40%</td>
</tr>
<tr>
<td>No birth control:</td>
<td>85%</td>
</tr>
<tr>
<td>Male condom:</td>
<td>14%</td>
</tr>
<tr>
<td>Withdrawal method:</td>
<td>19%</td>
</tr>
<tr>
<td>Diaphragm:</td>
<td>20%</td>
</tr>
<tr>
<td>Female condom:</td>
<td>21%</td>
</tr>
<tr>
<td>Rhythm method:</td>
<td>25%</td>
</tr>
<tr>
<td>Spermicide:</td>
<td>26%</td>
</tr>
<tr>
<td>Sponge:</td>
<td>40%</td>
</tr>
<tr>
<td>Cervical cap:</td>
<td>40%</td>
</tr>
<tr>
<td>No birth control:</td>
<td>85%</td>
</tr>
</tbody>
</table>
As is evident from the Table 2 above, the most effective form of birth control is sterilization, with a failure rate of less than 1%, but hormone implants and injections also enjoy a failure rate of less than 1%. Male and female sterilization must be considered irreversible and permanent; therefore appropriate only for people certain they will never desire children. Hormone implants and injections have one advantage over sterilization: they are completely reversible, and therefore most appropriate for young sexually active people. While IUD intrauterine devices have a low failure rate, they may not be appropriate in some cases due to health risks. The progestin birth control pill, once suspected to suffer health risks, has now been proven safe and even beneficial to health, therefore it is appropriate for young sexually active people, because it has a low failure rate and is completely reversible. However, the pill is effective only if women remember to take it every day—hormone implants and injections have an advantage of requiring no daily maintenance. Each method has been helpful in guiding to the next step in contraceptive technology.

Table 3: First year contraceptive failure rate in perfect use vs. typical use for various methods.

<table>
<thead>
<tr>
<th>Method</th>
<th>Perfect Use</th>
<th>Typical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Method</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Implant</td>
<td>0.05</td>
<td>1</td>
</tr>
</tbody>
</table>

14
<table>
<thead>
<tr>
<th>Method</th>
<th>Perfect Use</th>
<th>Typical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable</td>
<td>0.3</td>
<td>3</td>
</tr>
<tr>
<td>Pill (combined)</td>
<td>0.1</td>
<td>8</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Cervical Cap</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Sponge</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Male Condom</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Spermicides</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Periodic Abstinence (calendar method)</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>IUD (Copper-T 380A)</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>Tubal Sterilization</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

2.2. Contraception related adverse events

By providing daily hormones to the woman’s body, hormonal methods interfere with normal endocrine and metabolic processes and thus come with a variety of potential serious health risks such as heart disease, stroke, various thromboembolisms, genital cancers, and other physical side effects like weight gain, acne, mood changes, nausea, amenorrhea, and delayed reversal of fertility.
Furthermore, in a discussion of the risks of intercourse due to an exchange in bodily fluids, the topic of sexually transmitted diseases is very relevant. Sexual relations can result in conception as well as infection, in the form of STDs and HIV. New technology is needed that will protect women against both. However, to avoid STDs a woman currently would need to use a barrier method in addition to the most highly effective birth control method available, i.e. hormones. As a result, a woman, who is not in a monogamous relationship with an STD-free partner, would need to end up using two forms of birth control.

2.3. Future contraceptives

Contraceptives prevent unwanted pregnancies and provide better family planning and health care. Convenience, safety, efficacy, and cost as well as the quality of life are usually the concerns in choosing a contraceptive, and these very factors motivate the development of newer and better contraceptives. There is a pressing need to develop a non-hormonal, biocompatible, non-invasive, cost-effective, biodegradable, and convenient barrier device to prevent pregnancy and infection without interfering with sexual relations. The success rate of a contraceptive depends not only upon the efficacy of the contraceptive method, but also upon the users' preference, reversibility, convenience, and compliance. Besides pregnancy, sexual relations can also result in infection. It is thus beneficial that the design of newer contraceptive devices should also
consider the option of protecting women not only against pregnancy but also against transmission of sexually transmitted diseases (STDs). In the future, effective and emerging new antimicrobial (STDs) and antiviral (HIV) agents, which are benign to the vaginal mucosa yet effective as virucides, could possibly be incorporated in this delivery system. The public health significance of developing dual protection for women with a single and reliable device can hardly be exaggerated. Women are the fastest-growing AIDS group, in part because increasingly the primary transmission of HIV is through heterosexual sex, making women particularly vulnerable.

A novel approach for the delivery of birth control through vaginal route arose from the observations of Elsimar Coutinho, MD, who studied the effects of inserting a birth control pill into a woman’s vagina. He found that it was absorbed just as efficiently vaginally as orally. Additionally, to cause a contraceptive effect, the hormones avoided the hepatic and gastric pathways and were directly absorbed into the blood circulation, thus reducing some of the systemic side effects.

Further research indicated that vaginal application would require lower levels of hormones rather than oral administration. Thus, in order to avoid the need for daily upkeep, as in oral pill, the need for the development of a long-term vaginal delivery system was identified. Except for barrier methods, surgical procedures, and some IUDs, all birth control methods rely on using hormones to systemically affect the
reproductive function The hormonal class of non-barrier contraceptives are taken orally (e.g., the Pill), implanted (e.g., Norplant, Implanon), or injected (e.g., Depo-Provera) and are based on the understanding that by supplying extra hormones to a woman's body, the uterus is tricked into not developing a thick, nurturing endometrial lining to which a fertilized egg can attach. Although, these contraceptive devices do not depend on the lack of proper usage since they are directly inserted, injected, or implanted by health care professionals, they are not without drawbacks. Long-term hormonal contraception use and associated problems such as heart disease, stroke, various cancers, and other physical side effects like weight gain, acne, mood changes, and nausea are well documented.

The new contraceptive devices could be free of hormones and should allow women the freedom to use it by themselves, in the privacy of their own home thus enhancing the quality of life.

One of the recommendations made by the Committee on Contraceptive Research and Development in 1996 was to identify agents that are spermiostatic rather than spermicidal, modify mucus secretions from cervical epithelial cells to prevent sperm penetration and are antimicrobial and anti-viral. With current interest in the delivery of steroids, as a contraception method and hormone replacement therapy (HRT) for post-menopause, via non-biodegradable, hormonal intravaginal rings it is innovative to create a biodegradable, non-hormonal and biocompatible intravaginal ring that acts locally and avoids a systemic route to deliver
contraceptive agents. The new device could also carry anti-STD agents (Although the N9 spermicide is banned by FDA for human use, many women depend on them). Thus the development of BioRing is timely and has innovation and significance for women's health care.

Future development of novel contraceptive methods, which in addition to providing contraception could also incorporate drugs against diseases, would provide a major breakthrough in contraceptive development. Along the lines of this development we propose the following:

1) BioRing: As a response to the growing need for a non-hormonal yet equally effective contraceptive system, we have developed a delivery system, namely BioRing, which truly is the birth control for the new millennium. The BioRing can deliver effective contraception as well as anti STD/HIV medication.

A Non-hormonal, biodegradable, biocompatible hydrogel based intravaginal delivery system acts locally to minimize adverse metabolic effect. For contraception Iron II, Ascorbic acid, and Ampholines are delivered through the device.

- Barrier
- Local (intravaginal, discrete)
- Biodegradable
- Biocompatible
• Non-hormonal

Delivery of anti-STD and anti-viral (HIV) agents

• Delivery of drugs for pelvic infection/ diseases

• Duration: 1 to 28 days

2) Contraceptive Vaccine: made up of Lutropin Receptor and hCG-beta based antigen

• Immunocontraceptive

• Systemic

• Duration one year

2.3.1. The BioRing

The development of a novel protection mechanism, which incorporates a chemical barrier, against STD and HIV, in addition to providing contraception, is a major leap in contraceptive technology development.

The intravaginal, non-hormonal, contraceptive ring, BioRing, provides such a solution. BioRing upon insertion will begin to release a steady and safe flow of contraceptive agents to prevent pregnancy on a monthly basis, month after month. BioRing will allow women the freedom to be spontaneous because they no longer have to worry about their birth control on a daily basis and yet they can count on effective month long
protection. In addition, BioRing can provide a safe non-hormonal effective form of birth control, and protection against STDs.

Some other advantages of the BioRing are:

1) Non-systemic: By acting locally, the intravaginal device avoids the systemic route and thus eliminates undesirable systemic effects.

2) Non-hormonal: Instead of being invasive, for example by overpowering the woman’s cycle with hormones, the intravaginal device moves in the direction of a natural and gentle form of contraception.

3) Biocompatible: The proposed ring is currently made of hydrogel, which has high water content similar to body tissues, adjustable to the contours of the inner vagina, causes no discomfort, and would not interfere with sexual relations. This hydrogel vastly used to make medical implants and wound closure but never previously used as drug delivery system. All the ingredients used in this device are FDA approved for human use, are inexpensive and since women can use it themselves in the privacy of their own home without going to the physicians office brings the cost further down.

4) Biodegradable: The hydrogel, made of natural polysaccharide and synthetic biodegradable polymer, is hydrolytic, i.e. bioerodes slowly when in contact with water. The body easily absorbs the other ingredients.
3. Literature review


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