

## UPDATES ON CONTRACEPTION

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### Introduction

Contraception, which is the prevention of conception or impregnation by methods other than abstinence from coitus<sup>1</sup>, has become an important subject the world over and in particular the Sub-Saharan African which has one of the highest fertility rates in the world.<sup>2</sup>

In the past, a high conception rate was counteracted by high fetal and maternal death rates as well as reduced life expectancy occasioned by disease, violence and war hence stabilizing the size of the family and community<sup>3,4</sup>. However with the advancements made in medicine and relatively improved socio-political environment, there has been increased survival rates and increased life expectancy with consequent increase in population. Hence contraception which until recently was, a very sensitive subject among Africans given our moral, religious and cultural beliefs, is now being increasingly accepted as a necessary ingredient of socio-economic development.

This contraceptive evolution was heralded by the introduction of 'the pill' in the 1960s<sup>4</sup>. Despite this, the fertility rate and population have continued to increase, as shown by a fertility rate of 6.1 in Nigeria<sup>3,4</sup>. In the light of the above, a discussion of the updates on contraception is therefore imperative in order to add to information already available on the provision of safe, acceptable, affordable and effective methods of contraception.

### Rationale for advances in contraception

The world population is expected to increase by 2.6 billion to 9.1 billion in 2050<sup>2,3</sup>. This will occur, if

fertility decreases from today's 2.6 children to about 2 children per woman. If fertility were to remain at the present level, 34 million persons would be added annually by mid-century and thus the world population would reach 10.6 billion by 2050<sup>2,3</sup>. The most notable increase in the world population will occur in third world countries. Therefore immense investments are being made to develop safe, reliable and easy to use contraceptive methods.

On the local scene, the population of Nigeria was put at 140 million as at March 2006 by the National Population Commission giving a 63% increase over the 1991 figure and an annual population growth rate of 3.2%. If unchecked a figure of 281 million has been projected by 2015 by expects giving a doubling time of less than 10 years compared to a doubling time of 42 years for the entire world population<sup>2,3</sup>. The implications of the above trend are enormous increasing poverty, unemployment and a high dependency ratio among others.

Apart from the rapidly increasing population, there is a global need for new contraceptive methods because the currently available methods are not adequate to meet the diverse interest of millions of users. Several concerns have made the current array of contraceptives grossly inadequate to meet the growing worldwide needs.

The concerns that have been raised include safety particularly the risk of long-term use such as malignancy and thromboembolism. There are also concerns about side effects such as headache, nausea, weight gain, menstrual disorders such as menorrhagia, irregular menstruation and

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amenorrhoea. The fear of conditions associated with changing lifestyles such as HIV/AIDS and infertility as well as the problem of litigation further strengthens the need for development of new methods.

Hence research must continue so that women can have a variety of 'ideal methods' to meet their ever growing needs. The methods should be very effective, safe, free of side effects, convenient to use and not provider dependent. They should also be long acting, independent of coitus, easily available and affordable. The contraceptive methods newly developed cut across the various categories of contraceptives.

### **The new methods**

#### **The combine oral contraceptive pills**

The combine oral contraceptive pills which has become the most used pharmacological agent since it was first marketed in 1960<sup>4</sup> has undergone several modifications in order to reduce the side effects associated with its use. Both the oestrogen and progestin components have been modified without compromising its effectiveness. Aside from the second generation progestogens like the norethisterone and levonogestrel, new compounds are now widely used namely norgestimate, gestodene and desogestrel. These are the third generation progestogens. The combined oral contraceptives containing these progestins have shown almost no adverse changes in carbohydrate and lipid metabolism and on the haemostatic system<sup>4,9</sup>.

#### **Yasmin<sup>®</sup>**

This is a combined pill containing 30mcg ethinyloestradiol and 3mg of a new progestogen, drospirenone. Drospirenone appears to have an

inyloestradiol which tends to cause water retention, and some women do complain of bloating when they take the pill. Drospirenone, which is related to spironolactone, counteracts this by having a natriuretic effect. Trials suggest Yasmin may be as effective as Dianette for mild to moderate acne, and it may be particularly suitable for those who suffer bloating, weight gain and breast tenderness on other pills.

### **The progestogen-only pills**

#### **Cerazette<sup>R</sup>**

This is new Progesterone-only pills (POP) (75mcg of desogestrel daily) is designed to inhibit ovulation. A study comparing Cerazette with Microval (Levonogestrel 30mcg/day) showed that only 1.7% of cycles were ovulatory in Cerazette users, compared to 40% in Microval users<sup>15</sup>. In a randomized trial of Cerazette vs Microval, the Pearl Index was 0.17 (method failure) and 0.5 (user failure) for Cerazette compared with 1.4 (method failure) and 1.9 (user failure) for Microval in non-breast-feeding women<sup>15</sup>. Although the bleeding pattern in Cerazette users is more variable than with Microval, there is a greater tendency towards infrequent bleeding and amenorrhea by the end of the first year. It would also appear reasonable, in view of the ovulation inhibition, that there could be 12 hour pill taking safety margin rather than the three hours normally advised for conventional POPs and Cerazette now officially has a 12 hour missed pill rule<sup>15</sup>. This, combined with its higher efficacy, should make it a much more attractive proposition for many women.

### **The Injectable hormonal contraceptives**

The injectable hormonal contraceptives depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate are highly effective, long acting, safe and reversible agents. However,

continuation rates with these agents are unsatisfactory menstrual irregularities being the most frequent reason for discontinuation.

Recent developments have shown that the addition of a short or medium-acting oestrogens improves the endometrial bleeding pattern<sup>8,12,15</sup>. Two of such combined injectable contraceptives are **cyclofem** which contains low doses of medroxyprogesterone acetate (25mg) combined with 5mg oestradiol cypionate and **mesygina** which contains low doses (50mg) of norethisterone enanthate combined with 5mg oestradiol valerate. Other progestogen derivatives under trial include cyclobutyl carboxylate (HPP-001), butanoate (HRP-002) and cyclopentylcarboxylate (HPP-003) of levonogestrel. Their main advantage is that they allow a single and predictable bleeding episode every month with an extremely high efficacy<sup>1,6,8,15</sup>. However they are given monthly as against the conventional two or three-monthly injectables. The option of self injection is being explored.

### The subdermal implants

The observation that steroid hormones can be released at a constant rate from silicone rubber for long periods of time led to the development of the subdermal implants. The Norplant which has been available since 1993 with six silastic capsules each containing 36mg levonogestrel and which lasts for five years was very effective but relatively expensive<sup>6,7,11</sup>. Also many women complained about the menstrual pattern among other side effects and it has now been withdrawn<sup>6,11</sup>.

### Jadelle

The Jadelle is an improved version of the norplant, comprising two silicone rods each containing 75mg levonogestrel.

### Implanon

Many of the problems associated with Norplant were related to the insertion and removal of the six implants. Implanon has an advantage in that it consists of a single, semi-rigid rod, measuring 40mm by 2mm. It releases 30-40 mcg of etonogestrel (3 keto-desogestrel) per day and lasts for three years. This hormone level is designed to achieve complete inhibition of ovulation and so far, in the worldwide phase III clinical trials, there has not been a single pregnancy<sup>10,11</sup>. The implant comes preloaded in a disposable inserter which is about the same size as a blood transfusion needle, and the insertion procedure is very simple, not requiring a skin incision. Insertion takes, on average, two minutes. Removal, using a 'pop-out' technique, is facilitated by the rigidity of the capsule and takes three minutes. Amenorrhoea is more common in implanon users than with Norplant (21% vs 10% respectively). However, there is no evidence that hypo-oestrogenicity is a problem in implanon users. Etonogestrel appears to inhibit LH, but not FSH, so follicles, and therefore oestradiol, are still produced. The incidence of acne appears to be slightly lower than with the levonogestrel implants. However, irregular bleeding can be a problem, as with all progestogen-only methods.

### The biodegradable implants

These are a new generation of implants designed to eliminate the need for removal of the capsules. An example is the **capronor II** which consists of two implants, each is a 4cm capsule of polymer caprolactone filled with 19mg levonogestrel. It is effective for one year. Another example is the **capronor III** which is a single implant consisting of 4cm capsule containing 32mg levonogestrel. It is effective for one year. The capsule is a copolymer which releases the drug more readily and also

biodegrades more quickly than the simple polymer used in capronor II. There is also the **annuelle** which comprises 4-5 pellets each about 8mm, made of norethidrone (90%) and cholesterol (10%). Each pellet contains 35mg norethidrone. It is effective for one year.

### The vaginal rings

This is a long-acting method of contraception that does not require daily intervention and is entirely under the user's control. Most steroid hormones are absorbed effectively through the vaginal wall and can be released from a silastic ring. The ring can be easily inserted into the vagina, checked, removed and replaced by the woman herself. It offers several advantages. It can be worn continuously for a number of weeks, its use is unrelated to coitus, it causes fewer side effects, and daily intake of hormones and the hepatic first pass phenomenon seen with the oral contraceptive pills are avoided. Also, there is a rapid return to fertility on removal.

There are two types of formulations of the vaginal ring. There are vaginal rings that contain only progestogen (progestogen only rings). Examples are the levonogestrel ring which delivers 70mcg per day and the nestorone ring which delivers an average of 100mcg nestorone<sup>10,11,20</sup>. There is also the progesterone ring which delivers progesterone and can be used for up to 90 days. It is suitable for lactating women because it prolongs lactational amenorrhoea and it uses a natural progestogen progesterone to which the fetus is exposed to in-utero. The new type of formulation is the combined ring which contains both oestrogen and progestin. An example is the Nuvaring.

### The Nuvaring

This is a vaginal ring containing 15 micrograms of ethinyloestradiol and 120 micrograms of etonogestrel (3-ketodesogestrel). The ring is flexible and transparent; it is made of ethylene

vinylacetate (EVA) copolymers, with an outer diameter of 54mm and a cross-sectional diameter of 4mm. Each ring is to be used for three weeks, followed by a one-week ring-free interval. Like the EVRA patch, Nuvaring can be inserted and removed by the woman herself. In a large multicentre trial the method failure was 0.77 per hundred women years, and the user failure rate was 1.18 per hundred women years<sup>10,11</sup>. Nuvaring has good cycle control and is well tolerated.

### The transdermal patches

These are another group of recently introduced contraceptives. They contain both oestrogens and progestogens that are easily absorbed through the skin. An example is the EVRA.

### The EVRA<sup>R</sup>

The EVRA is a contraceptive patch containing 20 micrograms of ethinyloestradiol and 150 micrograms of norgestimate, was launched in the UK in 2003<sup>5,6</sup>. Each patch is worn for a week, and can be placed on the buttocks, abdomen, the back or the upper arm. Showering, bathing and swimming do not appear to affect adherence. In the clinical trials, approximately 20% of women experienced mild to moderate application site reactions, although only 2% discontinued the method for this reason. Efficacy was high, with a failure rate of only 0.7-1.2 per hundred women years overall. Cycle control was good and comparable to that of Mercilon (approximately 10-15% having spotting or bleeding in the third cycle). The main side effect was transient breast tenderness in the first couple of months, experienced by 18% of users<sup>6,12</sup>.

### The intrauterine contraceptive device (IUCD).

The IUCD has undergone a lot of development from the first generation or non-medicated devices of the 1960's such as the Lippe's loop and Saf-T-coil which

were large plastic inert devices and the Dalkon shield made of polyvinyl acetate. These were large inert devices which often caused heavy and painful menstrual periods. They are not common anymore although some women may still have them in-situ because once fitted, they could be left in place until the menopause. From these we have the second generation devices of the 1970s and 1980s that had copper added to them such as the Nova-T (Noncord) and multiload 250. The third generation intrauterine contraceptive devices are copper-containing devices such as the copper T-380A which caused less menstrual disruption. They are effective with failure rate of 1 per 100 or less. They however still cause the problems of bleeding and pain<sup>2,3,11</sup>.

Researchers have been working to design copper intrauterine contraceptive devices that are highly effective, have minimal pain and bleeding associated with their use, can be provided to nulliparous women, are easy to insert and remove, have lower accidental expulsion rates and have higher continuation rates. The new intrauterine devices are discussed below.

### **The Progestasert**

Progestasert is a device made of a semi-permeable membrane of ethylene vinyl acetate which releases progesterone at a rate of 65mcg per 24 hours for one year. It causes a dramatic reduction in menstrual blood loss.

**The Mirena** (Levonorgestrel-releasing intrauterine system)

This is based on the the well-established Nova T, on the vertical limb of which has been added a silastic capsule containing levonorgestrel. The device releases 20 micrograms of levonorgestrel per day and is now licensed for five years. This mechanism of action has been associated mainly with atrophy of the endometrium, and the majority of women will

ovulate only occasionally after the first year of use<sup>1,12,15</sup>.

In contrast to other IUDs, it has a failure rate of around 0.2 per hundred women years, and, unlike its progesterone-releasing predecessor, is therefore associated with a reduced risk of ectopic pregnancy. In addition, its use results in a major reduction in menstrual flow and dysmenorrhoea, prompting suggestions that it is a viable alternative to hysterectomy and endometrial ablation in women with menorrhagia (for which it now has a license). It does not appear to increase the risk of PID. Its major disadvantage is the width of the stem, making fitting more difficult in nulliparous women. The use of local anaesthetic in such women may be desirable. Irregular, though light, bleeding also occurs, particularly in the first few months of use. Only about 10 of women become amenorrhoeic. It should be noted that the Mirena is not licensed for post-coital use and there is evidence that it is not suitable for such cases.

The Mirena is already proving invaluable for perimenopausal women who still need contraception, as it also provides the progestogen part of Hormone Replacement Therapy (HRT). It is hoped that a licence for use solely in HRT will be obtained in the near future. A smaller device, especially for use in post-menopausal women, is also being developed. A new inserter, which facilitates single-handed fitting, was introduced in 2000.

### **The Gyne-Fix**

This is a frameless IUD. Six copper tubes are threaded onto a nylon thread, which is knotted at one end and anchored in the muscle of the uterine fundus. Studies show that the Gyne-Fix has a failure rate of less than 1% up to five years of use. Gyne-Fix does not appear to increase the incidence of

dysmenorrhoea in multiparous women and it is hoped that it will therefore be suitable for nulliparous women. The fitting technique is very different to other IUDs and training is strongly recommended.

### **Nova T 380**

The Ortho Gynae T 380 has been withdrawn for commercial reasons<sup>10</sup>. The Nova T 380 contains the same amount of copper. Early studies show the efficacy to be comparable, though slightly lower (1.6 vs 0.4 at two years and 2.0 vs 1.6 at 5 years)<sup>11</sup>. Currently the Nova T 380 has a five year license, but it is hoped this will be extended<sup>10</sup>.

### **Natural family planning**

New developments in this area include the use of the standard day method and the persona.

#### **The Standard day method(Cycle beads)**

This is a new system assisting women to understand their menstrual cycles thereby helping a couple to avoid unplanned pregnancy by knowing which days they should not have unprotected intercourse. It identifies days 8-19 of the cycle as fertile and it is for women with menstrual cycle between 26 and 32 days long. A client can use a colour-coded string of beads to help her keep track of where she is in her cycle and know when she is fertile. Women are provided with Cycle beads as a visual aid to help them identify their cycle length, the first day of the cycle and the fertile days. There are three different colour beads. Red beads represent the first day of the cycle, brown beads represent the days when pregnancy is unlikely and white beads represent the fertile days. The Cycle beads have a moveable rubber ring to mark the days of the cycle<sup>1,11,17</sup>.

### **The persona**

Natural family planning has entered the age of technology. This is basically a micro-computer attached to a microlaboratory. The woman is required to insert test sticks dipped in her early morning urine: the device measures the levels of Luteinising hormone and oestrogen breakdown products, calculating the likely date of ovulation well in advance and allowing for sperm survival. She is thus shown 'green' days, when conception is unlikely and 'red' days when conception may well occur. With perfect use, failure rates are in the region of 6 per hundred women years. However, more typical user failure rates are much higher<sup>11,13</sup>.

### **The barrier methods**

Newly introduced barrier methods include the non-latex male condoms, the leas shield and the panty condom.

#### **Non-latex male condoms**

The non-latex male condoms are male condoms made from materials other than the natural latex. These include condoms made of polyurethane, plastic and other synthetics. They are stronger and better able to withstand storage conditions in developing countries.

#### **The Leas shield**

The Leas shield is a reusable cervical barrier made up of the same shape as the cervical cap. It contains a valve in the centre and a loop at the anterior end to facilitate removal. It acts by preventing spermatozoa from entering the cervix. For maximum effectiveness it should be inserted into the vagina anytime before intercourse and should be left in-situ for 8 hours after intercourse<sup>13</sup>.

#### **The panty condom**

The panty condom consists of a sensual, sexy cotton or nylon panty with an aperture in the front lower

section where an interior membrane (much like a feminine day pad) contains a self adhesive condom that develops during coitus. It is manufactured from a polyethylene resin, a material that is thinner and stronger than latex. Unlike latex, it is anti-allergic. It is lubricated, discreet, safe, easy to use and can be worn all day. It is protected inside a membrane until used. The panty is reusable and the condom is replaceable<sup>13,15</sup>.

### Emergency contraceptives

Recent improvements in emergency contraceptives include the development of a single dose regimen of levonogestrel 1.5mg instead of two doses of 750mcg 12 hours apart. It is easy and it has safety and efficacy comparable to the two-dose regimen<sup>12,13,14</sup>. The possibility of increasing the 12 hours interval to 24 hours is also being considered. The use of mifepristone, an antiprogesterone, both at 10mg and 25mg doses has been shown to be safe and effective. The use of gestrinone, a 19-nortestosterone derivative is also being considered as a method of emergency contraceptive.

### Female sterilization The Essure

A new method of female sterilization is the Essure that use the transcervical approach for sterilization. The Essure microinsert consists of a stainless steel inner coil, a nitinol superelastic outer coil, and polyethylene fibres. The coil is placed into the uterine end of the fallopian tubes using a hysteroscope. In clinical trials, Essure was 99.8% effective after two years of follow-up. Essure comes with a disposable delivery system. When released, the outer coil expands to 1.5 to 2.0mm in diameter to anchor the microinsert in the varied diameters and shapes of the fallopian tube. This results in tubal occlusion by the polyethylene fibres, eliciting a tissue in growth. The rest of the tubes remain normal.

The advantages of the Essure includes the fact that it does not require any incision on the skin and there is no scar, no general anaesthesia is required for the procedure which can be carried out in the outpatient setting. The procedure can be completed in 30 minutes and the client can go home 4-5minutes after the procedure. About 99% of the women experienced satisfaction up to 2 years after insertion<sup>5,16,17</sup>.

### Contraceptive vaccines

Contraceptive vaccines (CV) may provide viable and valuable alternatives to the presently available methods of contraception. The molecules that are being explored for CV development either target gamete production (luteinizing hormone-releasing hormone (LHRH)/GnRH, FSH), gamete function (sperm antigens and oocyte zona pellucida (ZP)), and gamete outcome (HCG)<sup>16,19,20</sup>. CV targeting gamete production have shown varied degrees of efficacy; however, they either affect sex steroids causing impotency and/or show only a partial rather than a complete effect in inhibiting gametogenesis. However, vaccines based on LHRH/GnRH are being developed by several pharmaceutical companies as substitutes for castration of domestic pets, farm and wild animals, and for therapeutic anticancer purposes such as in prostatic hypertrophy and carcinoma. These vaccines may also find applications in clinical situations that require the inhibition of increased secretions of sex steroids, such as in uterine fibroids, polycystic ovary syndrome, endometriosis and precocious puberty. CV targeting molecules involved in gamete function such as sperm antigens and ZP proteins are exciting choices. Sperm constitute the most promising and exciting target for CV. Several sperm-specific antigens have been delineated in several laboratories and are being actively explored for CV development. Studies are

focused on delineating appropriate sperm-specific epitopes, and increasing the immunogenicity (specifically in the local genital tract) and efficacy on the vaccines. Anti-sperm antibody (ASA)-mediated immunofertility provides a naturally occurring model to indicate how a vaccine might work in humans.

### Male contraceptives

The provision of safe, effective and reversible methods of contraception for men remains a challenge to scientists and clinicians alike. Researches are still ongoing on many aspects of male contraception.

### Vas occlusion

Vas occlusion using the no-scrapel vasectomy was developed in China many years ago and is rapidly gaining acceptance. Also, vas occlusion by percutaneous intravasal injection of sclerosants such as carbolic acid and n-butyl-cyanoacrylate is very effective but like surgical contraception, it does not offer increased chances of reversibility<sup>5,17,18,20</sup>.

### Hormonal male contraception

Hormones inhibit fertility in men by suppressing sperm production. Testosterone-enanthate induced azoospermia has proven to provide optimal contraceptive protection. Preliminary studies have shown that testosterone alone or androgen-progestin combinations induce profound sperm suppression in the Eastern and white populations, respectively<sup>17,20</sup>. Thus, these regimens may represent viable options for male contraception. New long-acting androgen formulations represent a major advancement in this field, allowing for the development of more acceptable and effective regimens.

### Conclusion

The provision of effective contraception has undergone enormous developments. Family planning clients however are still limited as to their choice of contraceptive methods because of myriads of side effects. Hence a continuous research is needed in this area to provide clients with an array of contraceptive options with minimal or no side effects without compromising efficacy.

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