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Controlled-Release Hormone Delivery Systems for Long-term Fertility Control: The Missing Dimension

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Viewed in retrospect, the development of hormonal methods of fertility control could be broadly divided into three main phases: (i) development of the oral contraceptive 'Pill based on synthetic ovarian steroid hormones; (ii) the demonstration that continuous oral administration of progestins in microdoses could effectively prevent an undesired pregnancy[1]; and (iii) the development of sustained-release technology engendered by observations that steroid hormones diffuse at relatively constant rates throughbiocompatible polymeric rubber membrane, poly-dimethyl-siloxane (Silastic) [2]. The concept of controlled-release hormonal contraception is, due to the need to have a method of fertility control with minimal hormonal intervention. The development of controlled release contraceptive technology, though evolved out of serendipitous pursuit rather than approaches based on inductive physiological reasoning, has reached incredible levels of sophistication leading to the development of quite a good number of long-acting contraceptives such as silastic progestin implants, intravaginal rings releasing progestin, hormone-releasing biodegradable particulate delivery systems (microspheres and microcapsules), and so on. Many of these systems are either already in use or in advanced stages of clinical evaluation.

Controlled-Release Technology: State of the Art

The research and development efforts during all these years have resulted in the formulation of delivery systems in two basic forms: those using non-

biodegradable matrix for making the hormone reservoir, and the others that are based on matrices of biodegradable materials.

Non-biodegradable Systems

For non-biodegradable systems, silicone-rubber (silastic) has been found to be the most appropriate matrix for incorporating the contraceptive progestins, and delivery-systems based on this matrix have been found to be highly effective in providing protection against an undesired pregnancy over extended periods of time, from 1-5 years. Some of these systems are: subdermal silastic implants[4-6], silastic vaginal rings [7], medicated intrauterine devices[8-9]. Many more forms of silastic and other non-degradable material-based delivery systems are being evaluated. In so far as the drug component of these delivery systems is concerned, a very large number of synthetic progestins have been evaluated for their therapeutic (contraceptive) potential.

Features

Those belonging to the 19-nor-testosterone series have been found to be most effective and accompanied with much less menstrual and metabolic disturbances as compared to those belonging to the 17-alpha-acetoxyprogesterone series or others. The latest and the most promising among the silastic-based delivery systems for long-term female contraception is the Norplant. Comprising a set of two or six, 3.5cm long silastic capsules, releasing a total of approximately 65 ug of levonorgestrel per 24 hour, the Norplant system has been tested in more than 1,00,000 women all over the world so far. It has been found to give highly encouraging protection for upto five years against pregnancy (Pearl Index comparable to oral contraceptives, or IUDs) [5,10,11]. Based on the clinical experience, one might not be too misplaced in considering this system as the most promising for long-term hormonal contraception in women in the foreseeable future.

Biodegradable Delivery Systems

Biodegradable hormone-delivery systems, on the other hand, are yet to reach the level of advancement in technological sophistication so as to be compatible with effective long-term contraception. These systems involve the use of poly-(DL)-lactide and glycolide in an optimized ratio that would determine how long the system is going to last following its injection into the body.

Since biodegradable delivery systems provide greater maneuverability in terms of dosage formulation, besides the obvious advantage of obviating the necessity of surgical removal of the 'spent' drug module, these have been designed in a number of forms. However, in most of these systems, the matrix used always consisted of the lactide-glycolide copolymer. These delivery systems, which release levonorgestrel or norethisterone in sustained microquantities, have been found to be quite promising in providing effective contraceptive protection in women from 3-18 months, following single intramuscular/subcutaneous administration[12-14]. An implantable capsule called Capronor uses poly(caprolactone) and grain like pellets using fused cholesterol as the matrix.

Peptide Delivery Systems

The successful use of biodegradable matrices for controlled delivery of progestins led to the development of a radically new approach to long-term fertility control based on the principle of pituitary down-regulation (desensitization) by continuous 'discharge' of gonadotrophin-releasing hormone (GnRH) agonist analogues in the body. In fact, the hypothalamic peptide, polylactic acid and polyglycolic acid (PLGA) based delivery systems have been found to be highly promising in terms of effectiveness and acceptability because GnRH receptors being not so ubiquotous as the steroid receptors, the peptide contraception would hopefully be associated with much less metabolic side-effects than those accompanying the steroidal contraceptives. Furthermore, since hypothalamic regulatory mechanisms involved in the regulation of gonadal function in male and female are largely similar, primarily through modulation of gonadotrophic function of pituitary, it offers a potentially promising approach to the development of an 'Unisex' contraceptive method. As a matter of fact such an approach is already under evaluation and the initial experimental results appear quite encouraging[15,16].

Other Uses in Reproductive Endocrinology

GnRH based biodegradable microcapsules and microspheres also offer tremendous promise in the therapeutic management/treatment of various hormone-dependent pathological disorders and malignancies of the reproductive system, both in the male as well as in the female. For instance, microcapsules containing D-Trp-6- LH-RH, the most widely tested agonistic analogue of LH-RH, have been found to be extremely effective in the treatment of endometriosis, reproductive disorders: polycystic fibrosis, precocious puberty and various forms of cancers[17-20].

The Enigma

Not with standing the technological advances having been made in the area of contraceptive drug delivery systems, nearly all-available methods, including those with control release technology, fall short of the attributes of an 'ideal' hormonal contraceptive. What is the riddle? Why must the therapeutic efficacy be always accompanied by metabolic and menstrual disorders? Could this parallelism between the contraceptive efficacy and the method-related side effects be removed?

The Missing Dimension in Controlled-release Contraceptive

Most controlled-release contraceptive systems have two integral components viz. The contraceptive hormone and the appropriate, drug-carrying matrix. As part of the efforts to achieve better drug-delivery, a vehicle for uniform dispersion of the drug in the matrix is also being tested. This would constitute the third component of such a delivery system, if ever found successful. These components are so integrated that they ensure sustained delivery of the contraceptive agent at predetermined rates over extended periods of time, from few months to years few.

Despite the fact that the release rates of the incorporated progestins remain fairly controlled, drug-induced menstrual and metabolic side effects of sorts continue to cause concern and restrict their mass use. This is because of the indiscriminate 'flooding' of the whole body with the drug and/or its noxious metabolites, subjecting even those organs/ tissues which do not require the given contraceptive hormone to a kind of 'pharmacological assault which eventually leads to all kinds of overt and covert metabolic and menstrual disorders. Therefore, the shortcomings of the present generation contraceptive delivery systems could, perhaps, be attributed to the fact that the concept of hormonalcontraception has been pursued and developed to its present stage in isolation without taking into account the physiological 'nuances' of the organs making up the reproductive axis (hypothalamo-hypophyseal-ovarian-uterine axis). Thus, the very concept of continuous hormone-delivery for contraceptive purposes seems to be ill-conceived as it presupposes the body to be a biostatic entity in which the physiological requirements, including those of the hormones, of different organs/tissues are of a continuous nature, when we know that this is not the case.

Biorhythms and Hormonal Needs

Different organs of the reproductive system, and even different components of the same organ, exhibit characteristic differential, preferential and even spatial requirements with respect to different hormones. Besides, there are tenuous fluctuations in respect of these requirements through the follicular maturation, ovulation, implantation and gestation. For instance, pituitary gonadotrophs have an intrinsic requirement of pulsatile stimulation by GnRH for their own episodic secretion of gonadotrophins, Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). Likewise, fallopian tubes, uterus, cervix and vagina have in-built mechanisms by which they show characteristic preferential and differential responses to steroidal sex hormones, estradiol and progesterone, themselves being released in a pulsatile manner. Metabolic activity of reproductive organs is thus a function of the overall hormonal modulation, which in turn depends on the dynamic biorhythmicity of the neuroendocrine-gonadol axis.

Viewed in the aforesaid perspective, the concept of a critical 'time window' for hormonal intervention to achieve effective, fertility control, with minimal side effects, appears physiologically sound and, thus, quite tempting. Unlike the controlled continuous delivery approach, the concept of 'critical intervention' (or modulated controlled release) and 'targeted drug delivery' are based on inductive physiological reasoning. The need to device a method by which the drug release from the delivery systems could be 'shunt -off', when not required, thus appears to be a physiological imperative, if the present generation delivery systems were to be used on a mass-scale.

Visualization

The ultimate drug-delivery system should, therefore be one from which drug release could be regulated either from outside (for instance, through the application of a magnetic field), or by a biological sensing mechanism incorporated into the drug-delivery 'compact' itself, that would permit the drug release only when needed i.e. during the critical period while keeping it off at other times of the in-situ placement. During the last few years, increasing attention has been focussed on the development of regulated controlled release. Application of an oscillating magnetic field from outside has been found to be quite encouraging in achieving a regulated release of insulin, from a delivery system composed of ethylene-vinyl acetate copolymer; with specified magnetic

field application, nearly 30-fold increased release of insulin could be obtained[21].

In so far as the concept of auto- regulation through incorporation of a biosensing mechanism in the drug delivery system is concerned, initial efforts in identifying potential agents that could be employed as a biological sensor do point to the feasibility of the approach. Certain enzymes appear to offer good opportunities for exploitation as a biological-sensing mechanism for incorporation into the delivery systems. For instance, subtle pH changes in body/ tissue fluid are quickly perceived by the enzyme, Urease, and the susceptibility of this enzyme to pH changes has been successfully exploited for achieving modulation of hydrocortisone from a delivery system[22]. From an extrapolation of these observations, the possibility of achieving modulated controlled-release of contraceptive hormones from biodegradable as well as non-degradable delivery systems does not sound utterly 'a wild imagination'. In fact, one could think of a potential antigen from the sperm, which upon incorporation into a steroid-releasing IUD on intravaginal ring could trigger the release only when sperms were present around it. Similarly, incorporation of a specific antibody to hCG into a specifically- designed sensing device(s) on a medicated IUD could, perhaps, be another good approach to achieving a release of the drug from the IUD when needed, while 'switching the system off' when not required. The presence of such anti-hCG antibodies in an intrauterine drug delivery system would permit the release of the drug only after ovum has been fertilized and not before. Since blastocyst secretes hCG, sperm metabolites could also be exploited as possible biochemical sensing entities for incorporation into intrauterine and intravaginal drug-delivery systems as auto-regulatory mechanisms.

Thus, with the current pace of technological advances being made in the field of biopolymers and the concept of biosensing methodologies, the prospects of the development of an efficacious, trouble-free, long-acting auto-regulated and/or externally-regulated hormone-delivery system for long-term fertility control seem to be quite a possibility today than one could have imagined, perhaps, a decade ago.

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