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VALUES OF STEROIDAL INTRAUTERINE CONTRACEPTION FOR DEVELOPING COUNTRIES

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SUMMARY

Clinical experience with the intrauterine progesterone contraceptive system (IPCS) indicates that steroidal intrauterine contraception offers medical advantages of potential value in nonindustrialized countries. These values include: high efficacy; postinsertion decreases in menstrual blood loss of about 40%; decreases in menstrual pain; low expulsion and perforation rates; and, in cases of accidental pregnancy, low spontaneous abortion rates. Histologic regression of the endometrium has also been observed during IPCS use in women with adenomatous hyperplasia. Lengthening the duration of efficacy to 5 years or more appears feasible using progesterone, but achieving markedly longer duration might require more potent synthetic progestogens.

INTRODUCTION

It has been a long time since anyone has suggested that IUDs are the ultimate solution to the population problems of nonindustrialized nations. The weakening of that once-robust conviction represents a blend of realism and pessimism. The pessimism, however, now seems excessive, though early hopes were undoubtedly too high. The potential benefits of intrauterine contraception remain so attractive for developing nations that ignoring possibilities for improving its acceptability there would be a medical and human tragedy of sorts. In these pages, I shall address some of those possibilities, particularly as they relate to the steroidal IUD.

THE SHORTFALL IN IUD USE IN NONINDUSTRIALIZED COUNTRIES

Rational improvement of intrauterine contraception requires some understanding of why it did not fulfill its original promise in developing countries. Certainly it lived up to expectations that it could provide efficacious long-term contraception unrelated to coitus and free of systemic side effects. Its shortfall in use-effectiveness arose from a paradox: just as its advantages were particularly valuable in developing countries, its flaws were in equal measure more serious in those countries. These flaws were medical problems —irregular bleeding or excessive menstrual blood loss, perforations, expulsions, painful or difficult insertions/removals, infections (especially septic abortions), and extrauterine pregnancy. Clearly, the health hazard of such risks increases where populations are poorly nourished or lack ready access to medical care.

Medically, the issue of bleeding is paramount in nonindustrialized areas, where anemia may affect 50% of women. One IUD study done under the auspices of the World Health Organization (WHO) has shown that, 12 months postinsertion, a significant proportion of women had iron deficiency [1]. The well-known tendency of IUDs to increase menstrual blood loss (MBL)—doubling or tripling it in many women—may well be associated with such deficiency.

The most severe instances of increased MBL have, of course, involved the larger nonmedicated units. Since those devices first brought intrauterine contraception to developing nations, they figured heavily in forming opinions about its acceptability. Those opinions may still prevail, even in the face of recent improvements in the bleeding picture.

High expulsion and perforation rates for many IUDs have also been of particular concern where midwives or other paramedical personnel must perform insertions, because proper fitting looms large in retention and safety. In addition to these problems, the spontaneous abortion rate for accidental pregnancy during IUD use historically has ranged up to 50% and raises the life-threatening hazards of hemorrhage and sepsis.

Lack of medical facilities also intensifies concern about pelvic infection, particularly following insertion, and about ectopic pregnancy. The latter complication appears to be a serious factor mainly among populations with high rates of pre-disposing factors, which may be much more prevalent in industrialized countries than in developing nations.

Early approaches to reducing expulsion and bleeding involved altering device sizes and shapes. One outstanding contribution—the T configuration developed by Tatum under Population Council auspices—decreased both problems but also diminished efficacy. Eventually, the advent of medicated IUDs was to make this advance productive.

In 1971, the Human Reproductive Program of the WHO began systematically to address shortcomings of the IUD in order to find an optimum approach to this mode of contraception [2]. One of its early

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interests lay in the delivery of steroidal substances topically to the uterus to improve both efficacy and acceptability.

Various other medical approaches to the bleeding problem, developed under WHO auspices, included administering such substances as vitamin K, oral steroids and antifibrinolytic substances, but success was either temporary or elusive in actual use. One observation, however—that prostaglandin synthetase inhibitors, taken orally, stopped normal menses—proved later to have significance in dealing with one problem of IUD use, though in a somewhat unexpected way.

WHO-supported studies also focused on possibilities of inserting IUDs postabortally or during the puerperium [3]. The practicality in developing countries of dealing with delivery (or pregnancy termination) and contraception in one visit to a remote Health Center is obvious. This line of investigation, as we shall describe, has proven encouraging.

Despite the many valuable WHO programs, growth in IUD use has been slow in the nonindustrialized nations, reflecting in part the pace of technological progress. The advent of the medicated IUD was a breakthrough permitting efficacious contraception with smaller and more tolerable devices. Such units, however, initially had short functional lifetimes, a serious drawback in areas with few medical facilities or personnel. Moreover, though the small size of the metal-releasing units lessened MBL compared with nonmedicated IUDs, bleeding remained at levels that were unsatisfactory for many women, particularly in developing nations. This problem has yielded to the next stage of development of the medicated IUD—its use to deliver progestational hormones.

POTENTIAL VALUES OF STEROIDAL CONTRACEPTION

At the inception of research on the steroidal IUD, its possible advantages were seen to number five: enhancing efficacy, decreasing menstrual blood loss, decreasing menstrual pain, lowering expulsion rates, and providing long-term protection of the endometrium against dysplasia. In point of fact, intrauterine hormonal contraception appears to be living up to all these expectations, to varying degrees, except the fourth, which mechanical design changes have now largely taken care of.

The pregnancy rate of the first steroidal intrauterine contraceptive—the intrauterine progesterone contraceptive system (IPCS)—is about 2 overall [4], and for parous women is about 1.5. Thus, its efficacy approaches that of the pill and surpasses that of nonmedicated IUDs.

Many studies have shown reduced menstrual blood loss during IPCS use [5–9]. This unit is the first intrauterine contraceptive actually to diminish MBL from pre-existing levels and to do so pharmacologically. Quantitative data indicate that the MBL reduction averages about 40% from pre-insertion volume [5, 6]. In contrast, copper units and placebo IPCS units—*i.e.* those lacking progesterone—cause substantial increases in MBL [5, 6].

Reduced MBL during use of the IPCS appears to be associated with its hormonal suppression of the endometrium, demonstrated in a number of studies [10, 11]. It is also of interest that the IPCS, unlike inert and copper-bearing IUDs, fails to increase fibrinolytic activity in the endometrium [12].

A second therapeutic effect of the IPCS, possibly related to reduced biosynthesis of $PGE_{2\alpha}$ during its use, has been an alleviation of dysmenorrhea [6]. While this benefit is not comparable medically to the reduction of blood loss, it does enhance acceptability.

The low expulsion and perforation rates attending use of this steroidal contraceptive are attributable not to its hormonal component but rather to design features introduced during its development: rounding of the vertical stem of the T; placement of a hemispherical, cervix-seeking protrusion at the center of its cross-arm; and use of a pre-curved, malleable, plunger-free inserter to facilitate safe system placement at the fundus. Cervical and uterine perforation rates with the final system/inserter design approached zero during the clinical trials, and have remained rare during general use of the contraceptive. Retention rates have been similar whether paramedical personnel or gynaecologists have fitted the unit; life table expulsion rates have been about four for parous and nulliparous populations combined.

Two types of observations suggested that the intrauterine delivery of progesterone might have a protective effect on the endometrium. One is the well-documented action of progestagens (given orally or parenterally) on endometrial adenomatous hyperplasia and endometrial carcinoma. The second is the observation that progestational suppression of the endometrium occurs routinely during use of the IPCS [13–15]. Recently, a study of use of this contraceptive in women with endometrial adenomatous hyperplasia, for whom surgery was contraindicated, showed histologic regression of the endometrium, decreases in mitosis, and glandular atrophy [16]. Expansion of such studies is indicated to confirm the therapeutic efficacy of exogenous intrauterine progesterone for this and other indications, and also to explore the protective potential of higher rates of delivery of the hormone, or of its more prolonged use.

One unexpected result of the clinical trials was the low spontaneous abortion rate (about 10%) associated with accidental pregnancies during IPCS use [4]. This 10% figure approaches that reported for non-IUD users. The reason for the low rate is unknown (though progesterone may play a part), but it has two advantages. First, it gives a woman a choice with respect to continuance of the pregnancy. Second—and probably more important in medically indigent areas—it gives her time to reach a Health Center, where the IUD may be removed or her pregnancy may be

terminated under conditions unlikely to result in infection or hemorrhage.

In the developing countries, pharmacologic IUDs have the disadvantage that depletion of the active substance limits their duration of effect. Now, however, copper IUDs are usable for three years and the IPCS-52 (loaded with 52 mg progesterone rather than 38 mg) has been approved for 3-year use in Mexico, and is undergoing clinical trials in the U.S., Europe, and elsewhere.

A subject that has generated a great deal of uncertainty is the incidence of ectopic pregnancies in women using the progesterone IUD. Clinical studies performed in the following regions—the Far East and Latin America, Continental Europe, North America, and Scandinavia—showed ectopic pregnancy rates varying by region over a 17-fold range. Concomitantly, other parameters of the progesterone IUD's performance—uterine pregnancy rate, expulsion, medical removal—as well as loss to follow-up, differed relatively little by region. This wide geographic variability of the incidence of ectopic pregnancy strongly suggests that its occurrence was linked to a factor other than the progesterone IUD itself. Among the clinically recognized, predisposing causes of ectopic pregnancy, the one that has recently undergone explosive growth in certain countries, but has changed little from its historic patterns in others, is pelvic inflammatory disease (PID). PID is in turn related to the epidemics of sexually transmitted gonococcal and chlamydial infections occurring in certain countries but not in others.

It has long been clinically recognized that the once-infected fallopian tube may be either permanently occluded—causing infertility—or damaged in a fashion that subsequently predisposes the woman to tubal implantation. It is now known, on the basis of Weström's work [17], that the actual risk of subsequent ectopic pregnancy in women who have had salpingitis is about ten times greater than normal.

At the epidemiologic level, the association is strong between regions of high reported incidence of gonorrhea and the regions where ectopic pregnancy had its highest incidence in clinical studies with the progesterone IUD. Unfortunately, the clinical studies were not designed to exclude women who had previously had PID or to inquire with special vigor to make presumptive identification of women who had probably had PID; nor has it been possible to devise a way to establish these points retrospectively, several years after the fact. Thus, the association between previous PID and ectopic pregnancy cannot be said to have been proved in these studies at the level of individual patients. However, the preponderance of evidence—the large geographic variation in incidence, the recognized effect of salpingitis, and the well-documented, wide regional variability in veneral disease incidence—points to a patient-related rather than a product-related basis for the difference in the overall average incidence of ectopic pregnancy between the progesterone IUD and other IUDs. The lowest incidences of ectopic pregnancies with the progesterone IUD—0.06–0.08 per 100 women per year—are certainly comparable to the best figures reported with other IUDs. These rates occurred in Latin America and the Far East.

It is our recommendation that a woman with a history of pelvic inflammatory disease, or a sexual history that would make its occurrence likely, should use the progesterone or any other IUD only in full recognition that such contraception affords little protection against ectopic pregnancy, and that previous salpingitis has increased her risk to the point that ectopic pregnancy is nearly as likely to occur as is an accidental uterine pregnancy. On the other hand, by excluding such patients or by using IUDs in regions or countries where social mores are such that gonorrhea and other sexually transmitted diseases occur very infrequently, and where tuberculous salpingitis—the one recognized form of nonsexually transmitted salpingitis—is also infrequent, IUDs provide a low-risk form of contraception. The progesterone IUD provides, in addition, the benefit of reduced menstrual blood loss.

FUTURE DEVELOPMENT OF THE STEROIDAL IUD

The IPCS

The progesterone intrauterine contraceptive will probably attain its full potential in nonindustrialized nations only when certain problems are solved. One of these is intermenstrual bleeding, which usually subsides a few months after insertion. The problem is one of acceptability, since the amount of such bleeding appears too small to constitute a health problem [7]. One approach to dealing with it would be a change in the amount of progesterone released. For example, a slower rate of delivery might lessen intermenstrual bleeding; some of our studies indicate that less than 65 μg progesterone per day is needed to provide effective contraception [18, 19]. Another possibility, beyond the immediate reach of our technology, would be an altered delivery pattern for progesterone —*e.g.*, a pulsed pattern.

Duration represents another not-quite-solved problem. A three-years-plus functional lifetime may be too short for the needs of women in some areas; durations of greater than 3 years are currently under investigation. Five-year systems are a virtual certainty, and longer-duration systems are within reason. Unquestionably, more potent synthetic steroids are more adaptable than progesterone to extremely long-lasting systems, but they may lack the inherent safety of the physiologic hormone.

Intrauterine contraceptives using synthetic steroids

Among synthetic steroids under study for intrauterine contraception, those in the 19-nor category are in favor. Not only are they potent, but some believe they offer a balance of oestrogenic and proges-

tational activity, which may influence intermenstrual bleeding.

Laevo-norgestrel, the most potent, well-studied contraceptive steroid available, has been efficacious in the minipill at doses of 30 μg daily. Delivered to the uterus at a rate of 50 μg daily from silastic sleeves placed on a T, it has effectively inhibited ovulation without interfering with menstruation and with apparently little breakthrough bleeding [20]. For local action only, the release rate could be much lower and thus the functional lifetime of the intrauterine module could be many years.

In a study of five women, delivery of norethindrone from the vertical stem of a T unit did not suppress ovulation, but provided efficacious local contraception [21]. Authors state the bleeding patterns were favorable: 2 of the women had 9 or 10 spotting days during 80–114 days of treatment.

We will need, of course, much more work on use of various steroids in intrauterine contraception.

Intrauterine contraception in special populations

We also need extensive study of intrauterine contraception in special populations. These include postabortal and postpartum women. The WHO has programs under way in such populations.

Early studies of insertion of the Lippes Loop on days 2–8 of the puerperium resulted in a 30–40% expulsion rate by week 6. In a recent study [22], the fitting of three smaller intrauterine contraceptives within 20 minutes of delivery of the placenta gave 6-week retention rates exceeding 90%. The lowest expulsion rate—which occurred with the IPCS—was 2%, but the study was not of adequate size to draw firm conclusions. Data on immediate postabortal insertion of the IPCS have also been encouraging.

CONCLUSIONS

The steroidal IUD has some inherent advantages for use in populations of the nonindustrialized countries. Realization of these advantages, however, depends on rational development of hormonal units with the needs of such populations specifically in mind. To do this, we need more data with which we can define our developmental goals.

Even the issue of bleeding, generally conceded to be a major problem with IUDs, has not the same weight everywhere. Differing data from different clinical centres [4] on irregular bleeding suggest that women in some nations are under-reporting its occurrence because they wish to continue using the contraceptive. To them, this complication is apparently a minor concern compared with undesired pregnancy. Yet we know that in other societies, tabus make even slight intermenstrual spotting highly objectionable. Though a high enough delivery rate of progesterone could decrease bleeding to the point of producing complete amenorrhea, this is obviously no solution. To some women the absence of regular bleeding would be as alarming as slight metrorrhagia is to others. Therefore, before modifying our systems, we need to know what bleeding patterns, both menstrual and intermenstrual, are widely acceptable.

Likewise, we need to define our aims with respect to the functional lifetimes of intrauterine contraceptives. It may be that long-term residence of metal or steroid-releasing units could result in medical problems. While such problems have not as yet appeared in the literature, long-term monitoring for safety is an obvious necessity.

None of these problems is simple to solve, but neither are any of them insuperable. Their eventual working out—and an ability to match intrauterine steroidal contraception to populations having characteristics that would, on balance, tolerate its shortcomings—should place this mode of contraception in a better position to serve the urgent fertility control needs of the developing countries.

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