PROSPECTS FOR THE PRACTICAL APPLICATION OF PROSTAGLANDINS

A PUBLIC HEALTH VIEW

by

J. F. MARTIN, M.D., M.S.P.H., D.T.M.

Introduction

The world has been experiencing a growing concern about population growth, both at the private and public level. The problem is particularly acute in the developing countries, but, even in the Western world, which shows only moderate demographic increase, the outstanding problem of pollution depends on both consumption and evidently numbers of people. At the private level, the burden of excessive fertility for the individual led to the emergence, since the beginning of this century, of private efforts to provide couples with the means to decide their family size. Women’s emancipation movements, both in the developed and developing world, emphasize the right to control one’s reproductive function. At the national and global level, concern over excessive fertility of the community has been increasing, especially during the last two decades. Asia and its “teeming millions” understandably was the setting where public action first took place. India has had a governmental family planning programme since 1951; other Asian countries followed suit in later years, particularly during the sixties. The movement has become really worldwide during the last five years.1

This paper, on the premises that “the opportunity to decide the number and spacing of children is a basic human right”2,3 and that the present demographic growth is one of the major problems facing mankind (second only to the search for peace4), examines the contribution that prostaglandins, as a new relevant tool, could make in this field. Although it recalls what the pharmacological and clinical sciences have demonstrated about prostaglandins, its outlook is more of public health.
Fertility Regulation—The Multiple Facets of the Task

In assessing what family planning programmes all over the world have accomplished, it has appeared with increasing strength that the problem is not only one of technology, or of diffusion of technology. What has been attempted is large scale action to change markedly the behaviour of people, in the very sensitive sphere of reproductive life. It implies a complex socio-cultural process. For any programme, Berelson thinks that the four basic elements which determine success or failure are the following: (1) the political will (at the leadership level) (2) the interest and motivation of the people (3) the contraceptive technology (4) the organization and administration of the programme.

The first, political will, is outside of the health field. The third is the one which comes to mind in the first place. The two others are very much of concern to the health/family planning workers, because the latter use or try to modify the interest and motivation of the population and because they are part of the programme organizational structure and, at various levels of responsibility, determine its performance.

An important point is that the foregoing are not independent variables. Even high interest and motivation will not lead to successful practice if the method offered (the technology) is a complicated one or if the organization does not communicate adequately with the client. On the other hand, family planning may be adopted in spite of a relatively low motivation when the method is easy to use, and/or when the service is delivered in a particularly convenient way. From these features, among others, can be evolved a number of conditions which a good fertility regulation method must fulfill. The most important are that it should be Safe, Effective, Acceptable, Easy to use, Cheap and Implementable on a large scale.

The first two characteristics don’t need particular comment. The acceptability issue deserves much emphasis. A 1969 Workshop said: “In the development of new methods of contraception it is acceptability, even more than effectiveness, that we are trying to improve,” and also social scientists, psychologists, and market research specialists should participate in the design of new contraceptive methods and in the improvement of current methods in order to maximize their acceptability.” In addition to the acceptability of a method for the patients, one has of course to consider its acceptability for the programme administrators, and for the community leaders, political, social and religious. Further, the ease of use requirement in self-explanatory, and depends partly on the acceptability (psychological ease of use). Finally, low cost and implementability are particularly imperative in poor countries with large populations, which are precisely the most concerned in trying to contain their numbers.

Prostaglandins and Human Reproduction

Discovered before World War II (in the semen of man and sheep) and the subject of research since then, prostaglandins (PG’s) have been showing increasingly in the scientific and medical literature in the last few years. A group of chemically related unsaturated hydroxy-fatty acids with 20 carbon atoms, they are widely distributed in the body of mammals (thirteen types have been found in the human semen). Among other properties, they appear to be nat-
PROSPECTS FOR THE PRACTICAL APPLICATION OF PROSTAGLANDINS

The practical application of prostaglandins has been explored in various clinical settings. They are endogenous regulators of reproductive function, with a potent oxytocic effect, inducing delivery as well as abortion, and are studied for their possible use to regulate menstruation.

Two types of prostaglandins have been mostly used for clinical experiments, PG E2 and PG F2 alpha. The latter is more stable but causes severe side-effects, especially nausea, vomiting, and diarrhea, as well as inflammation at the injection site. Prostaglandins have been administered by intravenous injection and later by intra-uterine infusion (either extrauterine or intra-amniotically), requiring a lower dose, and intra-vaginally. With both the latter routes, the side-effects are much reduced. Oral administration has been used recently for induction of labour. It should be mentioned also that a slow release of prostaglandins might explain the contraceptive action of the intra-uterine device.

Induction of Labour: A number of studies have shown that prostaglandins are effective in the induction of labour. The most impressive series to date is Karim's (Makerere Medical School, Uganda) who, over two years, treated about 1500 women. In spite of gastrointestinal side-effects, he tends to consider PG E2 as the drug of choice for labour induction. His double-blind study shows that PG E2 is superior to PG F2 alpha in this respect. Craft et al. arrive at a similar conclusion, but Beazley and Gillespie did not find marked differences. Some do not see why one should discard the long-used and satisfactory oxytocin. However, prostaglandins seem to have some advantages over oxytocin: prostaglandin-induced contractions, as spontaneous ones, are inhibited by the intravenous injection of ethyl-alcohol (oxytocin induced are not); as prostaglandins have no antidiuretic effect, they can be used even in cases of toxemia; unlike oxytocin, prostaglandins are active during the entire pregnancy, and have successfully been used in cases of missed abortion, missed labour, and hydatidiform mole.

Termination of Pregnancy: Early work in this respect stems from Sweden and Uganda, and a growing number of clinical studies are going on all over the world. There are significant side-effects, but, as mentioned above, these are diminished by the local routes of administration. Also, the number of incomplete abortions has been found high in certain series. However, prostaglandins certainly appear to represent a valuable additional means to induce abortion, especially in the second trimester. Although Swedish investigators found prostaglandins F2 alpha suitable for induction of abortion in the early weeks of pregnancy, the current prevailing opinion is that prostaglandins are less satisfactory than other methods (vacuum aspiration particularly) for pregnancies of less than 12 weeks.

Regulation of Menstruation: Few human studies have been carried out. Although prostaglandins have a lutolytic effect in some animal species, the induction of menses in the human seems to be due more to the stimulation of the myometrium.

Prospects for the Large Scale Routine Use of Prostaglandins

Leaving aside their use to induce labour at term, since the need for new drugs in this respect is not paramount,
the most interesting prospects opened by prostaglandins relate to fertility control, and developments are keenly awaited by those concerned with population and family planning programmes. Their major potential contributions are based on one established feature, that they are post-conceptive birth control agents, and on one possibility, that research may evolve compounds easier to use and less troublesome in terms of side-effects than those used presently, which will eventually allow for self-administration, or at least prescription by paramedics and on an outpatients basis. Practically, the developments hoped for, on the basis of the work done to date, are:

Prostaglandin as an abortifacient, administered as vaginal suppository or oral tablet, useable during the first and second trimesters of pregnancy (preferably early).

Prostaglandin as a “once-a-month” pill, regulating the menstruation when it is delayed—in fact, emptying the uterus regardless of whether or not conception has occurred.

Prostaglandin as a “morning-after” pill, making sure that earlier sexual intercourse will not result in a pregnancy. Some studies already have shown that prostaglandins stimulate markedly the motility of the non-pregnant human uterus.

The following discussion, out of necessity, will be based on the assumption that the developments just outlined will take place. If they do not, if prostaglandin use remains burdened with relatively frequent and bothersome side-effects, if their administration continues to require close medical supervision, they will not add much to the armamentarium of those in charge of family planning programmes. As a matter of fact, there is a consensus that significant progress, in terms of slowing down the planet’s demographic growth, will be achieved only by providing acceptable and effective means of fertility control at the periphery (which is to be short of hospitals for a long time still in most parts of the world), and through auxiliary personnel. Self-administration would be of course even preferable, and Karim thinks that the problems in this respect will be overcome.

With this assumption in mind, let us look how close these three prostaglandin-based birth control means would be to the essential characteristics of the “ideal contraceptive”:

Safety: The evidence gathered so far is still insufficient, but many clinical workers have been impressed by the overall safety of the prostaglandins. No life-threatening incidents have been recorded. As mentioned above, side-effects have clearly diminished with the local routes of administration. One would suggest that the fact that side-effects appear readily with doses close to or above the therapeutic dose might act as a relative protection. Even if prostaglandins become freely available, there is little doubt that this risk will rapidly become notorious (it is the type of information that spreads most rapidly in this kind of situation, as evidenced by the backlash effect, on the Indian IUCD programme around 1968, of rumours about side-effects of the device). However, one certainly might consider that an unsatisfactory safeguard, and the very potency of the drug is a drawback as far as the possibility of administration without medical supervision is concerned. Further, more studies are needed about possible long-term undesirable effects (e.g.,
effects on the fetus in the event of failed abortion\textsuperscript{48,53,60}, no matter how unlikely they appear to be.

**Effectiveness**

It was mentioned that the number of therapeutic failures has been high in certain series. However, most researchers think that the performance on this score is, or will become, satisfactory. As regards second trimester termination of pregnancy, several authors\textsuperscript{44,49} think that prostaglandins are already now the method of choice. Further, prostaglandins being a post-conceptive means, a hundred per cent effectiveness is of less psychological importance (for the patient), as they can be backed up by other methods. The proportion of cases requiring medical treatment (e.g., evacuation curettage) should however remain small enough, if one wants to use the drug routinely. About post-coital and “once-a-month” use, clinical trials are just beginning.

**Acceptability**

We insisted earlier on the importance of that aspect, in regard to which it appears that prostaglandins have much to offer. For the patient, a very appealing factor will be the post-conceptive administration, freeing the sexual relations from any disturbing manipulation, and from the fear of contraceptive failure attached to many of the pre-conceptive methods (the so-called traditional and conventional means especially, but also, to a clearly smaller extent, the IUCD and the pill). As a matter of fact, experience shows that post-conceptive control of fertility has often been more widely used (which, practically, means more widely acceptable,\textsuperscript{44} at least at the level of the individual) than conception prevention (viz., the incidence of induced abortion all over the world, in spite of its illegality in many places). Another significant advantage is that it will not need co-operation (nor consent) of the partner. It could hopefully be used in strict privacy. The reversibility would be complete.

One most acceptability enhancing feature, it seems to us, is offered by both the “morning-after” and the “once-a-month” pills. In one way or another, they would act, if “needed”, by preventing what would have been otherwise the development of a pregnancy. But, taking them (shortly after either intercourse or the expected date of menstruation), one would never know! . . . whether there was actually a conception (except in the case of very early subjective symptoms of gestation). To our mind, this uncertainty would act powerfully to allay any guilt feeling with which termination of pregnancy might be associated (“deculpabilization”), and would make it much more acceptable than abortion at a later stage.

As far as society is concerned, prostaglandins and their mode of action may seem of questionable acceptability by today’s standards. A number of countries and religions are still reluctant to allow fertility control, especially termination of pregnancy. However, the experience of the last ten years has shown how rapidly attitudes can change.\textsuperscript{6} If prostaglandins confirm their great convenience for individual patients, it seems unlikely to us that political, legal, cultural or religious considerations will hinder much their progress (As regards induced abortion, the patent inefficacy of societal interdictions in diminishing its incidence is a matter of record). In this respect, the great discrepancies one finds between public and private opinion (public opinion being more “restrictive”, private opinion
and behavior more “permissive”) need to be recalled.63

**Ease of Use**

This would be very good with vaginal suppositories or oral tablets. Also, as a post-conceptive method, prostaglandins would not require the sustained motivation and the regular use that the pre-conceptive methods (except IUCD’s and sterilization) require. In most cases, they would not need to be used more than three or four times a year.60

**Cheapness**

It is too early yet to estimate their cost; should prostaglandins become an extensively used method, with the possibilities of cheaper manufacturing, it implies.

**Implementability**

Self-administrability, or prescription by auxiliaries in peripheral health units, would be a great advantage in this sense. We may here draw a parallel with the orals. In numerous family planning programmes (as in Thailand, Indonesia, Sri Lanka, Nepal, Malaysia, South Korea, Tunisia, Chile, Puerto Rico, to name a few), pills are now distributed by paramedicals at the periphery. Further, be that authorized or not, they have become increasingly self-administered all over the world—the need for a physician’s prescription has often come down to a mere matter of form. In many developing countries, even where family planning is still frowned upon, as in certain parts of Latin America and Africa, pills are sold freely over the counter. This explains in part their increasing popularity and, in practical terms, this means easy implementability. Within or outside organized programmes, and still assuming that safe, “easy-to-use,” prostaglandins will become available, similar developments may be visualized for them. However, one problem worth mentioning here, is the likely resistance of administrators, and especially doctors, to the free (or almost free) availability of a drug like prostaglandins: “... if prostaglandins are ever to be made available without medical supervision, it will require a degree of courage and realism on the part of administrators and the medical profession which they have not shown previously.”64

Table I summarizes how prostaglandins, if the assumptions we have made above are verified in the future, would compare with the major contraceptive means presently in use:

**Concluding comments**

“The Prostaglandin era is dawning; but there remain many clinical, social and ethical considerations which deserve the closest scrutiny.”60

Before prostaglandins can become a routine fertility control method, a certain number of questions need to be answered. First, it is too early to say whether compounds useable without medical supervision will eventually become available. Would the present constraints on their use remain the same, we have seen that their contribution could only be modest, particularly in the less developed part of the world. Possible long-term side-effects need to be studied. The number of therapeutic failures (or, rather, incomplete successes) should diminish. One does not know what the cost of prostaglandins would be in the event of widespread use. Their acceptability for the individual patient seems excellent, and societal resistance should not prove to be too difficult an obstacle, but it has not been possible to date to gather mass scale evidence of it. Last, but not least, doctors would need
### TABLE I

**Relative Advantages and Limitations of Prostaglandins as Compared With the Major Contraceptive Methods Presently Used**

<table>
<thead>
<tr>
<th>Basic Requirements</th>
<th>Condoms</th>
<th>Orals</th>
<th>IUCD's</th>
<th>Sterilization</th>
<th>Prostaglandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety of regular use</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+ +</td>
</tr>
<tr>
<td>Effectiveness, if used consistently</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Acceptability</td>
<td>Variable</td>
<td>Good</td>
<td>Variable</td>
<td>Variable</td>
<td>Good</td>
</tr>
<tr>
<td>Ease of regular use</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Cheapness</td>
<td>Variable</td>
<td>Good</td>
<td>Variable</td>
<td>Variable</td>
<td>NA</td>
</tr>
<tr>
<td>Implementability</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>(large scale programme)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Limitations**

- Need for sustained motivation: +++
- Need for action at time of coitus: +
- Need to replenish supplies: +++
- Need for services by trained personnel: +
- Need for careful instruction: +
- Possibility of troublesome initial side effects: +
- Possibility of rare but serious side effects: (+)

---

*The improved prostaglandins compounds which will be hopefully developed in the future and which were discussed above.*

*The consistent use of condoms being admittedly difficult.*

*Low (but improving) acceptability in many Moslem, Buddhist, African and Latin American countries.*

*Low acceptability in South Asia presently, particularly India (mostly because of earlier inadequate implementation of programmes and follow-up).*

*Acceptability of male sterilization roughly similar to the one of condoms. Acceptability of female sterilization depends much in the availability of the necessary operative facilities.*

*In fact, they would not need regular use _stricto sensu._*

*In family planning programmes, all services are often free. But then the cost has to be borne by the state, of course. Also, according to the time scale one is considering, the cost of using contraceptive methods varies much. If it prevents conception for 20 years, sterilization becomes a cheap method. On the other hand, the cost of buying 100-150 condoms a year during 20 years may not be negligible.*

*As far as vasectomy is concerned, the recent Indian experience (camps) may point otherwise.*

*As far as family planning programmes are concerned, sterilization is still to be considered an irreversible method, in spite of the notable successes in recanalization of the vas.*


*We consider that there is no such need because of the post-conceptive use.*

*Once only in principle (in a number of countries, especially trained paramedicals are authorized to insert IUCDs).*
to be convinced that prostaglandins could be used without their supervision.

The very potency of these drugs, at any time of the gestation, through a single administration, seems to us a potential drawback, if they are to become freely (or almost freely) available. A woman would be able, at any time, to trigger the emptying of her uterus, would that mean early abortion, late abortion, premature labour, or delivery at term. At both ends of the pregnancy this might not be a problem. During the late second and early third trimesters however, it would involve serious risks, both physically (e.g., bleeding) and psychologically (e.g., the late abortion of an almost viable product is likely to be a traumatizing experience). Also, the imposition of the hazards of prematurity on a possibly surviving foetus would be indefensible. The ease of the procedure (admittedly single intake) might prompt termination of pregnancy for trivial reasons, and give rise to more later regrets about it than is presently the case. In this regard, the suggestion could be made to the biomedical scientists to develop a “two-shot” prostaglandin, with which, in one way or another, the administration of the same or different drugs, at a one-or two-day interval, would be necessary to terminate the pregnancy.

In spite of these reserves, it remains that prostaglandins offer promising prospects for improved fertility management in the future, both as regards the individual desirous of deciding responsibly her reproductive and family life, and the community concerned about its excessive demographic growth and the “tragedy of the commons.” Further research and experimentation are undoubtedly warranted.

References


