Contraception—A Look Forward, Part II: Mifepristone And Gossypol

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Abstract: **Part II of this series examines two compounds that are or have been in use in countries other than the United States.**

Mifepristone (RU486) is the first of the clinically useful progesterone antagonists; it competes with progesterone for receptors in the uterus, ovary, and pituitary gland. When taken by women in the follicular phase, it might be capable of inhibiting folliculogenesis while still allowing endometrial proliferation for normal menstrual cycling. When the drug is taken in the late luteal phase, endometrial shedding can usually be induced even after nidation. Mifepristone could thus serve as an emergency postcoital agent. In principle, it could also be used as a monthly emmenagogue, but clinical trials have been unsuccessful due to disruption of the following cycle's length. Shorter-acting antiprogesterones now under development may overcome this difficulty. Political constraints ultimately may be more limiting than pharmacological ones.

Gossypol is a Chinese cottonseed derivative, which, taken orally, inhibits spermatogenesis in men. Its efficacy is very high, but use is presently limited by two adverse effects: occasional symptomatic hypokalemia and a 10 percent chance of irreversibility of aspermia. Current research is directed at understanding and overcoming these obstacles. (J Am Board Fam Pract 1991; 4:103-13.)

Mifepristone

Mifepristone (originally designated RU486) is a progesterone antagonist developed by the French pharmaceutical company Roussel-Uclaf while investigating the structure-affinity relations of steroid molecules.[1,2] It was designed as a glucocorticoid antagonist and only coincidentally found to possess progesterone antagonism. While not the first antiprogestin synthesized or clinically tested, it was the first with pure antagonist activity, a clinically important feature.[3] (To be precise, mifepristone's activity is not quite pure antagonism; in the absence of progesterone, it can display weak agonist activity.)[4,5] The drug is often described as a "contragestive,"[6] meaning that it acts to prevent or reverse implantation of the conceptus. (In addition to its effects on uterine progesterone receptors, mifepristone appears to act directly on ovarian steroidogenesis by inhibiting production of progesterone, but not estrogen.[7,8] The clinical significance of this finding is unknown.)

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The antiprogestin actions of mifepristone could act at two levels, either depriving the endometrium of the progesterone support needed to maintain early pregnancy or to interrupt the hypophyseal-ovarian axis. The antifertility effects could be used in three distinct time periods: (1) in the follicular phase to disrupt folliculogenesis; (2) in the luteal phase as an emmenagogue; (3) after a missed menstrual period, when pregnancy is suspected or diagnosed. The last of these uses, which has received the most political and journalistic attention, would be a substitute for surgical abortion[1,6,9] and is not addressed in this paper. The follicular and luteal phases are considered in turn.

Follicular Phase

Hermann, et al. reported that a short course of mifepristone in the first half of the menstrual cycle considerably delays, but does not prevent, ovulation, which is then followed by an apparently normal luteal phase.[10] This result was believed to be due to the drug's direct action on the ovary and its inhibition of gonadotropin release.

This phenomenon was confirmed by other investigators.[11-15] Compositely, these studies showed regression (or prevention of recruitment) of the dominant follicle, with consequent attenuation of the expected midcycle luteinizing hor-

mone (LH) surge, followed, after withdrawal of the drug, by apparently normal follicular and luteal phases, variously delayed. This effect was attributed to both the prevention of progesterone's stimulating action on gonadotropin release,[11] which was demonstrated in pituitary cell cultures,[16] and a direct effect of mifepristone on the ovarian follicle.[13]

A Finnish research team proposed a contraceptive regimen consisting of follicular-phase mifepristone followed by luteal-phase progesterone.[14] They suggested that a mifepristone dose could be achieved that would allow sufficient estrogenic support of endometrial proliferation for normal cycling yet suppress folliculogenesis and, consequently, ovulation. Their preliminary clinical results were published last year.[17] Seven women were treated with sequential low-dose mifepristone (25 mg) and norethisterone (5 mg) for a total of 11 cycles. Normal proliferative and secretory phase endometrium and menstrual bleeding were maintained despite significant suppression of estradiol and progesterone levels. Ovulation occurred in two cycles, but the authors conclude that consistent anovulation can be achieved by dosage adjustments.

Delay in folliculogenesis in monkeys by mifepristone was confirmed by Danforth, et al.[18] They did not propose a specific contraceptive regimen from their results but seemed to support the conclusions of the Finnish team. Alternatively, though these authors did not suggest it, one could argue for a trial of weekly (or daily) low-dose mifepristone, taken continuously, to suppress folliculogenesis. The user would, in essence, be suspended in a persistent follicular phase. Obviously, the consequences of such a major alteration from the natural hormonal pattern would require substantial assurance of long-term safety.

Luteal Phase

The antifertility use of mifepristone in the luteal phase theoretically could be either as a monthly routine or as a postcoital contragestive taken only in cycles with risk of pregnancy.

Early Luteal Phase

Mifepristone administration in the early luteal phase failed to induce menses immediately and, in fact, delayed onset of menses by several weeks.[10]

Li, et al. administered a wide range of mifepristone doses to normal fertile women between 2 and 6 days after the midcycle LH surge.[19] The likelihood of inducing complete luteolysis increased independently with both increasing dose and increasing time from ovulation, but their data did not allow more detailed analysis of these relations (e.g., threshold dates or dose for this phenomenon to occur). In rats, mifepristone given immediately after mating caused more rapid transport of the conceptus from oviduct to uterus, delay in endometrial and embryonic development, and reduced likelihood of nidation.[20] It is not yet known whether analogous changes would occur in humans or if such effects could be exploited for contraceptive use.

Midluteal Phase

The midluteal phase seems a logical time for administration of a progesterone antagonist, because its events include the peaking of progesterone levels and the beginning of nidation. Mifepristone given either as a single dose or as multiple doses produced two different patterns of response in a number of studies (Table 1).[10,13,21-26] Compositely, about one-third of the women had a normal menstrual period induced within 48 hours of treatment, followed by a normal or somewhat lengthened subsequent cycle. In these women, complete luteolysis appears to have occurred. Overall, about two-thirds experienced light menstrual bleeding, caused by the direct antiprogesterone effect on the uterus, followed by normal menses several days later that were at or near the expected time; induced luteolysis therefore was incomplete. The subsequent cycle in these women was typically of normal duration. It is impossible to determine from these studies whether an early pregnancy would have been terminated with either response pattern, but it may be that failure to achieve luteolysis would also mean failure to disrupt nidation in spite of light uterine bleeding.

Late Luteal Phase

A normal menstrual period can certainly be induced in nonpregnant women by a dose of mifepristone in the late luteal phase.[10] Furthermore, it appears that this pattern of use can be continued by nonpregnant women in consecutive cycles without disruption of regularity.[26,27] But

Table 1. Results of Eight Studies of Mifepristone Administration to Normal Nonpregnant Women in the Midluteal Phase.

Reference	Number of Women	Complete Luteolysis (Percent)	Incomplete Luteolysis (Percent)	Other Patterns (Percent)*
Hermann, et al. 1985[10]	2	0 (0)	2 (100)	0 (0)
Schaison, et al. 1985[21]	32	13 (41)	16 (50)	3 (9)
Nieman, et al. 1985[22]	8	6 (75)	1 (13)	1 (13)
Shoupe, et al. 1985[23]	20	0 (0)	20 (100)	0 (0)
Nieman, et al. 1987[24]	6	3 (50)	3 (50)	0 (0)
Shoupe, et al. 1987[25]	26	9 (35)	16 (62)	1 (4)
Garzo, et al. 1988[26]	10	2 (20)	8 (80)	0 (0)
Swahn, et al. 1988[13]	9	5 (56)	4 (44)	0 (0)
Total†	113	38 (34)	70 (62)	5 (4)

*A small number of women experienced bleeding patterns that are not well described by the other two categories. The most common of these was failure of mifepristone to induce any immediate bleeding.

†Totals are shown only to establish general trends. As the studies vary in methodological details, no formal statistical combination is attempted here.

the use of mifepristone as a monthly contragestive at the end of the luteal phase would require its ability to induce menses even when nidation has occurred, without disrupting the rhythmicity of the cycles.

Croxatto, et al. tested the ability of mifepristone to induce menstruation in women with pseudopregnancy simulated by increasing daily doses of exogenously administered human chorionic gonadotropin (hCG) starting in the midluteal phase.[28] Mifepristone was given in the last 4 days of the expected cycle length. An average of 2.5 days of bleeding quickly ensued, followed by an average of 2.2 more days of bleeding 9 days after the first bleeding began, as progesterone levels fell with the regression of the corpus luteum. If this pattern held for true pregnancies as well, the regularity of the menstrual cycle would be seriously disrupted every time an early pregnancy was present, thus making mifepristone unacceptable as a monthly contragestive. But a subsequent pseudopregnancy study reported induction of apparently normal menses, with no abnormality of the following cycle.[26] The reasons for the discrepant results are not clear.

A small trial of mifepristone as a late luteal regimen was conducted in which the drug was used only in cycles in which intercourse occurred.[29] Seven women were observed for a total of 28 cycles, with mifepristone given starting on day 27 of each of the 21 cycles at risk for pregnancy. (Apparently, no schedule adjustment was made for women with normal cycle lengths of other than 28 days.) Of these 21 cycles, three were positive for hCG. Two of these pregnancies continued in spite of mifepristone treatment. Each of these therapeutic failures followed two consecutively medicated but hCG-negative cycles. One appeared to have been due to wrongly timed administration of mifepristone, an error caused by delayed ovulation, a side effect of the previous mifepristone doses. This is consistent with the conclusion that mifepristone interruption of very early pregnancy can significantly disturb cyclic regularity.[28] These results are not encouraging for the monthly use of mifepristone in the late luteal phase.

It is possible that the method failure rate presumably due to such disruptions is related to the duration of effect of mifepristone in vivo. The drug's elimination half-life has been variously reported as 10–20 hours,[30] 24 hours,[25,31,32] 34 hours,[33] and 53.7 hours.[34] In addition, some of mifepristone's metabolites also display antiprogestin activity and are present for many days in serum and body tissues, including the myometrium and follicular fluid.[31,33,35,36] One can speculate that a progesterone antagonist with more rapid elimination might not be as likely to disrupt the postadministration cycle.[37] However, even short-lived compounds may disrupt the following cycle if circulating hCG continues to sustain the corpus luteum for a day or two after ingestion of the pill, thus delaying the onset of folliculogenesis.[38] Furthermore, simple month-to-month variation in cycle length may make regular menses induction a practical impossibility.[39]

Emergency Postcoital

While the disruption of cyclic regularity will probably prevent the use of mifepristone in consecutive months, it might still prove useful given only occasionally as a postcoital contragestive.

van Santen and Haspels tested this use of mifepristone in 62 women at risk for pregnancy.[40] After treatment, only one pregnancy remained. Because of inconsistent use of hCG testing, it is not known how many of these women were actually pregnant, and an effectiveness rate cannot be calculated. One pregnancy remaining in 62 women at risk is undoubtedly lower than would have been found without the mifepristone. The authors reported no side effects. They did not comment on the effects on post-treatment cycles.

Two subsequent studies reported effectiveness of 94.4 percent (17/18)[41] and 81.3 percent (39/48)[42] among women in whom conception and nidation had been confirmed by a sensitive hCG test. Treatment in both studies was a single oral 600-mg dose of mifepristone administered the day before expected onset of menstruation. Induction of bleeding did not always indicate successful termination. A minority of women experienced bleeding of more than 2 days longer than usual, but mean bleeding time was not increased. Other side effects were minor.

The pregnancy rates for all women enrolled and treated (who had engaged in unprotected intercourse) were 3.3 percent (1/30)[41] and 6.5 percent (9/139).[42] By comparison, postcoital contraception with IUD insertion, high-dose estrogens, combination oral contraceptives, or danazol result in pregnancy rates of approximately 0.1 percent, 0.6 percent, 1.8 percent, and 2.0 percent, respectively.[43] These results indicate that mifepristone was less effective as a postcoital agent than other currently available regimens, but it could be used in the large number of patients who present too late for these other methods to be employed. Such use would prevent surgical abortion in many cases.

These two studies also incidentally shed more light on the question of whether mifepristone could be used as a monthly late-luteal-phase pill. In the first of these trials, the post-treatment cycle length was extended an average of 4 days in both groups (hCG positive and negative).[41] In the second, the post-treatment cycle was 32 days in the hCG-positive group and 30 days in the hCG-negative group.[42] This difference was not statistically significant, but the important comparison, for the question here, is between the treatment cycle and the post-treatment cycle. Mifepristone appears to have extended the latter by 2 days for each group. These observations add to doubts that mifepristone would prove successful as a monthly late-luteal-phase pill.

Teratogenesis

Teratogenesis is a matter of concern for any pharmacologic contraceptive. Mifepristone has been reported to induce fetal abnormalities in rabbits, but this merely duplicates the effect of progesterone deficiency and may be species-specific.[44] Subtherapeutic doses in a relatively small number of rats have shown no embryotoxicity.[45] It is known, though, that mifepristone crosses the human placenta, probably by active transport, and may concentrate into fetal tissues from maternal circulation.[46] To date, no birth defects have been found among the few children born after failure of mifepristone treatment in the first trimester.[1] However, one fetus surgically aborted after mifepristone treatment had limb reduction defects,[47-49] a fact which has been seized upon by J.C. Willke, president of the National Right to Life Committee, to declare mifepristone "another thalidomide."[49]

Other Uses

In addition to its contragestive and abortifacient potential, preliminary studies hint of other possible values for mifepristone. These include the expulsion of a dead fetus,[50] cervical dilation and labor induction,[51] chemotherapy of progestin-supported breast cancers,[52-56] and the treatment of hepatoma,[57] meningioma,[39] Cushing syndrome,[3] and endometriosis.[39] Such investigations are currently too limited to allow prediction of clinical applicability. On theoretical grounds, it has also been suggested that the drug may be useful for estrogen-dependent breast and endometrial cancers.[58]

Mifepristone has consistently failed to disrupt ectopic pregnancies.[6,10,59,60] The reasons for this disappointing and rather surprising finding are unknown.

Politics

Because of its ability to interrupt early pregnancy, mifepristone has been targeted for attack by anti-

abortion groups in the United States. They argue that any pharmacologic or mechanical agent acting after conception is the moral equivalent of surgical abortion (in any trimester) or of murder.[61] Abortion advocates, on the other hand, welcome the drug's potential both as a monthly contragestive[62] and as a replacement for surgical abortion.[63] Cahill has cogently analyzed the rhetoric of the debate, finding both sides equally guilty of hiding important moral assumptions and conclusions in their choice of terminology.[64]

Neither Hoechst (Roussel-Uclaf's parent company) nor any other pharmaceutical firm has publicly expressed interest in developing or licensing mifepristone for clinical use in this country. Reasons for such lack of interest undoubtedly include legal liability, questionable profit potential, and the possibility of adverse publicity. Advocates of the drug have made explicit their step-by-step strategies for gaining eventual FDA approval and U.S. availability (Bass, Howes, and Falkenburg: "A report on RU486 and its prospects for use in the U.S." Unpublished.), while opponents have announced their plans to halt its development and licensing[65] and have already called for a boycott of Hoechst's products.[49] It has been speculated that U.S. licensing might be accomplished by a small venture firm, with few assets to attract liability suits and no other products to boycott.[66,67] (This would be in the pattern of GynoPharma, established for U.S. marketing of the copper T380A intrauterine device.)

Because of political protests, Roussel-Uclaf halted production of mifepristone only days after its public debut. At the time of this writing, mifepristone is being used in France only because the Minister of Health ordered the manufacturer to continue distribution. (In February 1990, the French government went further and announced its intention to provide the drug free of charge to abortion-seeking women unable to purchase it themselves.) The company has announced that it will no longer supply the drug to other countries that have been using it, such as China.[67] Regardless of the progress of scientific research on mifepristone, its future in the United States is, at best, uncertain. The U.S. government during the Reagan years was openly hostile to mifepristone,[67] but proponents in California are exploring using the state's regulatory authority to import the drug for in-state use only, bypassing the FDA's interstate jurisdiction.

At least two other pharmaceutical firms (Schering and Organon) are known to be developing mifepristone-like antiprogestin steroids, some of which are at the level of efficacy trials in animals.[68-73] It is believable that one or more of these products eventually will find a place in the world's pharmaceutical market, even if legal and political obstacles prevent its use in the United States.[74]

Gossypol

In sharp contrast to the technological laboratory invention of mifepristone stands gossypol, a naturally occurring substance with humble origins. Gossypol is a yellowish, polyphenolic pigment compound found in plants of the family Malvaciae, most commonly in the seeds of the genus *Gossypium* (cotton), from which it is routinely removed during the processing of cottonseed oil. It was identified and purified in the nineteenth century, but discovery of its potent antifertility effects came many years later in China. The story, as related by the traditional doctor who observed the events, deserves retelling:

> Around 10–25 years before the outbreak of Japanese aggression of China in 1937, a village situated at the juncture of Wu-xi, Jiang-yin and Chang-shu counties in the Jiang-su province was called the Wang Village. In the spring of 1929, I accompanied my school mate Wang Yin-min to pay a visit to that village. I discovered that the 30-some families in that village were quite well to do owing to their diligence and thriftiness. All the people there ate and clad economically. They chose to consume cotton seed oil as their cooking oil because it was much cheaper than other kinds of cooking oil. As a result, within the 10–15 years while taking cotton seed oil, not a single child, be it a boy or a girl, was born to any of the 30 families. For quite a period of time, no-body knew what was the matter, why all the families that were quite wealthy had had no childbirth? Many farmers tried to take a concubine, but still got no childbirth. Some farmers even tried to marry women who had given multiple births in the past, but when these women emigrated to Wang Village, they immediately became unable to conceive. After some time, some farmers became impatient and sent their concubines away to some neighboring villages. To their surprise, these women promptly got pregnant when married to men in other villages. This puzzling phenomenon certainly made the farmers of Wang Vil-

lage furious. They thought the almighty God was trying to exterminate the people in Wang Village on purpose.

So, for at least 10 years, people in Wang Village were horrified because they thought they were going to be extinguished and did not know what to do.

But the tragedy did not last indefinitely, up until the early forties. The mass production of soya-bean in the North-eastern provinces made the price of soya-bean oil so much cheaper than cotton seed oil.

So the farmers in Wang Village quickly shifted from cotton seed oil to soya-bean oil for daily cooking. Quite unexpectedly, many of the wives in the 30 families began to conceive and have children. . . .

I hope our scientists can strive to investigate . . . because based on the experience in Wang Village, cotton seed oil is definitely effective in preventing conception. And whenever childbirth is desired again, just cease to take cotton seed oil. . . . This looks to me a very simple and convenient way of contraception.[75]

Animal studies in the early 1970s duplicated the antifertility effect. Clinical trials were able to begin relatively quickly because safe limits of gossypol ingestion had already been determined (for cottonseed oil purity standards) and because the compound previously had been clinically tested as a remedy for bronchitis.[76] Pilot studies confirmed the observations of Wang Village and found low incidence of subjective side effects.

Phase III Clinical Trial

A multicenter trial was undertaken in China, enrolling 8806 men. This trial reported an impressive 99.07 percent rate of successful induction of oligospermia (sperm count less than 4×10^6/mL) and presumed infertility. Effective dosage was established to be 20 mg per day for 60 to 70 days of loading (during which time the sperm count gradually fell, although motility was significantly impaired before density) and 40 to 50 mg per week maintenance. Subjective side effects were again not prohibitively frequent or severe. However, this trial confirmed the presence of one previously suspected serious adverse effect (irreversibility) and revealed another unsuspected one (hypokalemic paralysis).

Irreversibility

The problem of irreversibility of infertility had been expected on the basis of case reports of some of those who had ingested unpurified cottonseed oil. The incidence of irreversibility after cessation of gossypol treatment, based on semen analysis, was found in the multicenter study to be about 10 percent.[76] Other controlled trials have found it to be as high as 49 percent.[77] (Even the lower figure would likely make gossypol an unacceptable contraceptive choice for many potential users.) Furthermore, some men with apparently normal sperm counts had persistent residual defects in sperm morphology, motility, and enzymatic function.[78] The incidence is statistically correlated with both high dosage and prolonged (more than 2 years) use and is more likely to occur in men who become aspermic (rather than oligospermic) during treatment. Even with these risk factors known, success at predicting irreversibility has been poor.

The complication seems to be related to induced atrophy of seminiferous epithelium.[76] There is damage to both Leydig and Sertoli cells, with consequent derangements of hormonal levels.[79]

Lei has suggested that measurement of blood gossypol concentration may allow identification of those in whom the drug accumulates to toxic levels before irreversible atrophy occurs.[80] Others have proposed monitoring the lactate dehydrogenase-X activity of spermatozoa to individualize dosage.[76] Neither strategy has been clinically tested to show its ability to reduce the incidence of permanent impairment of fertility.

Hypokalemic Paralysis

This side effect was an unexpected finding of the large clinical trial of gossypol. Its incidence was 0.75 percent. In all cases, the paralysis was preceded by a prodrome of muscular weakness or severe fatigue, which then progressed to flaccid paralysis of the lower limbs and thence upward, though usually sparing the respiratory muscles. The syndrome included typical hypokalemic electrocardiogram changes and increased urinary potassium. Recovery was usually uncomplicated, but is some cases it was prolonged. The incidence was increased in regions and seasons of low potassium intake.

No laboratory animal species has been found to model this adverse effect, so the details of its pathophysiology remain unclear; nevertheless, the mechanism appears to be a direct toxic effect

of gossypol on the renal tubules.[81] Qian and Wang report that indomethacin promptly alleviated symptomatic hypokalemia in two subjects and argue for the centrality of excessive prostaglandin E activity in the etiology of this problem.[76]

An early report claimed that paralysis could be prevented by administration of potassium salts during the prodromic stage,[76] but a controlled study failed to reduce the incidence of hypokalemia by use of a potassium supplement or a potassium-sparing diuretic (triamterene) administered with gossypol.[82-84] On the basis of a very small study, Liu, et al. suggest that a slight reduction in dose and length of loading period (to 15 mg per day for 60 days) will decrease the incidence of hypokalemia while maintaining adequate inhibition of fertility.[77] Lei suggests that titrating the dose according to blood gossypol levels may reduce the incidence.[80]

Because the paralytic stage is preceded by, first, asymptomatic hypokalemia and, second, prodromal symptoms, it may be possible to use a combination of periodic serum potassium checks and patient education to prevent paralysis, at least in developed countries, where such monitoring for drug effects is commonly a part of clinical practice.

Other Clinical Trials

Liu, et al. carried out an important double-blind trial for evaluation of side effects and contraceptive efficacy.[85] They enrolled 152 volunteers, men of proven fertility (at least 1 child and normal semen analysis), and randomized them to 75 days of gossypol loading dose (20 mg per day) or placebo, during which time other contraception was continued. After this phase, the subjects were unblinded, and the placebo group loaded with gossypol and added to the efficacy study.

Overall effectiveness (defined as sperm count less than 4×10^6/mL) was 87 percent at the end of loading and 97 percent after an additional 3 months of treatment. At least 85 percent remained aspermic until the end of the 12-month maintenance phase. No pregnancies occurred among the subjects' wives. There was no change in body weight, hemoglobin concentration, or blood pressure. Serum potassium levels declined from a mean of 4.3 to 3.8 mEq/L during the 14 months of treatment.

Subjective reports of fatigue and libido decrease were more frequent during gossypol loading than with placebo, but the differences failed to reach statistical significance. Before completion of the maintenance phase, 40 percent of the subjects had discontinued gossypol use: 15 percent for medical reasons (side-effect intolerance, including two cases of symptomatic hypokalemia), 16 percent for use-related reasons (inconvenience of pills), 10 percent for personal reasons (planning pregnancy, moving, loss of spouse). These rates should reasonably reflect clinical reality.

A long-term study (6 to 10 years of use) of 32 men found persistent subjective side effects as described above, lowered but stabilized serum potassium, 3 cases of persistently elevated serum alanine aminotransferase, decreased IgG levels, and decreased ability of peripheral lymphocytes to form erythrocyte rosettes.[86] There was no loss of the antispermatogenic effect. It is noteworthy that immunodepressive effects similar to these are seen in laboratory mice treated with very high doses of gossypol.[87] The clinical significance of these changes is unknown.

Teratogenicity

Clinical doses in humans and tenfold clinical doses in laboratory animals produce no chromosomal alterations, but 30-fold doses can induce such changes.[76] High doses of gossypol given to female rats before and during pregnancy produced no adverse effects (compared with control) on the offspring in terms of fetal death rates, birth weight, testis weight, or subsequent fecundity.[88-91] Considerably higher doses produced dose-dependent embryotoxicity in mice, with up to 94.5 percent fetal deaths, although no malformations were noted.[87] (It is not clear that this observation has clinical relevance, because gossypol is not proposed to be administered to women.) Offspring of male rats treated with high-dose gossypol had abnormalities no more frequently or of different types than did controls.[89-91]

Mechanism of Action

Many sites of inhibition have been proposed and confirmed. These are reviewed by Qian and Wang,[76] with several additional observations by White, et al.[92] Probably the most important

targets are the sperm midpiece mitochondria, which are impaired by the decoupling of oxidative phosphorylation.

Gossypol as a Spermicide

Because of its ability to inhibit sperm motility by contact *in vitro*, it has been proposed that gossypol be used as a vaginal spermicide. A clinical trial of a gossypol gel was performed using 15 surgically sterilized women.[93] Postcoital collection of semen from the vaginal fornix showed greatly reduced sperm density and motility compared with use of the inert carrier gel alone. The investigators reported "no side effects" and "no irritation" in their subjects and point out that the additional advantages of gossypol are its antiviral and antigonococcal properties.

On the negative side, it has been reported that gossypol is irritating to mucosa and stains skin and clothing.[80] Of greater concern are the possible tumor-promoting properties of topical gossypol.[80] No mutagenicity was found in the standard Ames test, but there is tumor-inducing potential when gossypol is applied to the skin of mice.[76] Further, murine bone marrow is found to contain cytogenetic alterations within 24 hours of vaginal application of gossypol.[94] These results necessarily cast suspicion on the safety of gossypol as a vaginally applied spermicide.

Future

Gossypol as a pill for men has many potential advantages: high efficacy, easy administration (one pill weekly for maintenance), reasonably low incidence of unpleasant side effects, low manufacturing costs, and no known induction of birth defects in case of failure. Clearly, the primary obstacles are the irreversibility of the antifertility effect in a substantial fraction of users and the occasional case of hypokalemic paralysis.

Because natural gossypol is a racemic mixture, it was hoped that one enantiomer would be found to be active and the other toxic, thus allowing easy separation of the effects. However, the (–) enantiomer is responsible for both efficacy and toxicity; the (+) enantiomer is apparently inactive.[80] Similarly, there is hope that an analogue of gossypol can be found that maintains its efficacy without toxicity. To date, though, every analogue synthesized lacks antifertility effect.[80,95,96]

If no chemical modification of gossypol proves satisfactory, it is still possible that gossypol itself could be widely used, but this will require extensive clinical testing of protocols to reduce the incidence of irreversible damage and hypokalemic paralysis.

For now, clinical trials in China have been suspended, and the research focus has reverted to questions within the laboratory domain, especially the mechanisms of efficacy and toxicity.[97] Elucidation of these properties may lead to development of analogues with more clinically acceptable side-effect profiles.

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