

CLINICAL EXPERIENCE WITH IMPLANT CONTRACEPTION

Elsimar Coutinho, M.D.

Maternidade Climerio de Oliveira
Federal University of Bahia, School of Medicine
Bahia, Brazil

ABSTRACT

Subdermal implants of polysiloxane (Silastic) capsules containing a number of synthetic progestagens have been studied in clinical trials to determine their contraceptive effectiveness and acceptability. The steroids studied include norgestrienone (R2010), gestrigone (R2323), megestrol acetate, d-norgestrel, norethindrone, ST-1435, lynestrenol and R-1364. With some of these steroids, studies have been undertaken with a varying number of implanted capsules. The estimated duration of use varies from 6 months to 6 years depending on dose and release rate of the individual steroid. The results of these studies involving about 5000 women in 8 years, indicate in general a high rate of effectiveness, as well as acceptability. Continuation rates at one year were generally 80% or greater. Abnormal bleeding patterns are the major disadvantage. Studies with implants containing a combination of estrogen and progestogen are being undertaken in an attempt to improve the bleeding pattern.

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INTRODUCTION

Most clinical experience with Silastic implants has been derived from trials carried out in Brazil, Chile and India (1-8). The earliest acceptability studies were conducted in Santiago and Bahia in 1967 and 1968, and the first reports published in 1969 (1, 2).

During the last 8 years, several compounds have been screened for their ability to be used in implant form. In order to qualify, the compound had to be active as a contraceptive at very low doses, be devoid of estrogenic or androgenic effects and be slowly and continuously released from the Silastic capsule. Most 19-norsteroids screened in pilot clinical trials qualified. Nevertheless, some of the compounds which have proven effective when administered through a Silastic capsule had to be discarded because their release rates were too rapid to provide a lasting effect. Chlormadinone acetate was one of these compounds. One of the first 19-norsteroids to be used successfully in an estrogen-free mini-pill, chlormadinone acetate was released so quickly from the Silastic capsule that adequate blood levels could be maintained for only two or three months. Another reason for exclusion of steroids with a potential for implant contraception was inflammation at the site of insertion. The progestin ST-1572 and progesterone itself are two such compounds which could not be used because of their tendency to produce inflammation at the site of implant insertion.

Following pilot clinical trials, eight compounds were selected for further clinical evaluation. The compounds selected, together with their expected duration of action when used in implant form, are listed in Table I.

MATERIAL AND METHODS

The studies carried out in Bahia have enrolled 4,752 women of reproductive age who bore implants containing one of the compounds listed in Table I for periods ranging from 6 months to 9 years. 67,807 woman-months of use were recorded. A total of 333 pregnancies occurred. Three of these were ectopic.

Capsules were hand-made with Silastic^(R) tubing (No.602-235 Dow Corning Corp. Midland, Mich.) and filled to capacity with the steroid. The capsules used in the studies with megestrol acetate and the early trials with norethindrone acetate were 2 cm in length. For the clinical trials with all the other compounds, a capsule of greater capacity, 3 cm in length, was used. The two extremities of the capsule were sealed with Silastic adhesive of medical grade. Sterilization was carried out by autoclaving for 20 minutes or by exposure to ethylene oxide. Irradiation, which was used for

Silastic^(R) is the registered trademark for Dow Corning Corp. brand of polydimethylsiloxane.

TABLE I: Steroids used in clinical studies of implant contraception

Compound	Release Rate μg/cm/day	Number of Capsules Proposed	Expected Life - Days	Effectiveness in Clinical Trials
Norgestrienone (R2010)	13	6	920 - 1470	18 months
Gestrigone (R2323)	20	6	400 - 640	12 months
Megestrol Acetate	14	4	600 - 960	15 months
Norgestrel	4	6	3000 - 4800	>5 years
Norethindrone	10	12	1700 - 2600	>3 years
ST-1435	40	1	300 - 480	6 months
Lynestrenol	60	5	200 - 320	8 months
R-1364	20	4	600 - 960	15 months

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the sterilization of a few batches, was found to reduce the release rates of several steroids, and for this reason was abandoned.

The compounds used, megestrol acetate (British Drug Houses), norgestrienone, gestrigone (R2323) R-1364 (Roussel UCLAF) norgestrel (Wyeth), norethindrone (Syntex), lynestrenol (Organon), and ST-1435 (Merck-Darmstadt) were supplied directly by the manufacturer or through the Population Council.

The capsules were inserted subcutaneously in the internal aspect of the anterior forearm or in the upper gluteal region through an 11-gauge trocar (Beckton Dickinson & Co., Rutheford, N.J.). At the end of the study, the capsule was removed through a small incision. Local anesthesia with 2% procaine was used for insertions and removals.

The women enrolled for the various trials were all volunteers of childbearing age to whom oral contraceptives were offered as an alternative to the implant. About two-thirds of the clinical population had taken oral contraceptives previously for periods ranging from 1 month to several years.

RESULTS

Norgestrienone

In the largest study, a group of 1,448 women bearing implants containing norgestrienone (R2323) were observed for 21,783 woman-months of use (6, 10). In this study, the women were implanted with one to six capsules, each containing 30 to 47 mg of steroid. At the calculated release rate of approximately 40 mcg per day per capsule, it was estimated that norgestrienone implants should last two years or longer. Preliminary trials with norgestrienone capsules indicated that a minimum of 4 capsules were necessary to provide protection lasting one year. With less than 4 capsules, the pregnancy rate at one year was too high. In a group of 103 women bearing 3 capsules for 1,019 woman-months, 9 pregnancies occurred after 11 months of use, indicating that the amount of drug being released from three capsules at the end of one year was insufficient to prevent conception. By increasing the number of capsules to four, effectiveness increased and the duration of the effect was extended to 13 months. In 249 women bearing 4 capsules for 1,570 woman-months, only one pregnancy was recorded. By increasing the number of capsules to six, a further extension of the contraceptive effect was obtained. Twenty pregnancies occurred in a group of 659 women bearing 6 capsules for 8,942 woman-months of use. Only four pregnancies occurred during the first year of use when 7,022 woman-months of exposure were recorded.

The Pearl Index for the first year was 0.6. For the period of eighteen months, the Pearl Index was 1.2 and for two years it rose to 2.6.

Of 86 pregnancies developing in women bearing from 1 to 6 norgestrienone capsules, two were ectopic. One of the ectopics occurred in a subject bearing one capsule and the other in a subject bearing three capsules.

Bleeding irregularities were common during the first six months of implant use. The greater the number of capsules, the higher the incidence of amenorrhea. In the six capsules group, 23% of the subjects missed the first expected period following the insertion of the capsules. At least one non-bleeding interval longer than 45 days was reported by 20% of the subjects during the period of implant use. The occurrence of amenorrhea diminished towards the end of the treatment. After one year of use, amenorrhea occurred in only 10% of subjects and at eighteen months the incidence was only 5%. The incidence of intermenstrual bleeding was low in the 6 capsule group, being reported by 8% of the subjects during the first month but by only 2% after the third month of implant use. In women bearing 3 or 4 norgestrienone capsules, the occurrence of breakthrough bleeding appeared to be more frequent in those who were receiving contraceptive steroid therapy for the first time. Forty per cent of the women reported one or more episodes of breakthrough bleeding during the treatment period whereas only 5% of the patients who had previously received oral contraceptives had developed this type of intermenstrual bleeding.

Most women maintained regular bleeding episodes similar to menstruation with a mean interval of 29.5 days (SD = 3.9) and a duration of 2-6 days with a mean of 4.0 days (SD = 1.9). Regular cycles throughout the duration of the treatment period were reported by 54% of the women bearing 6 capsules, 69% of those bearing 4 capsules and 76% of those bearing 3 capsules. In addition to the bleeding irregularities described above, a low incidence of acne, abdominal pain and loss of libido was found.

Gestrigone (R2323)

The compound gestrigone, also called ethyl-norgestrienone or R2323 is an anti-estrogen anti-progesterone. The anti-estrogenic effect of R2323 is not well understood because the compound counteracts the effects of estrogen on the uterus and breasts without binding to estrogen receptors. On the other hand, gestrigone binds to androgen receptors without exerting any anti-androgenic effect. The compound was used successfully to suppress spermatogenesis in men. It has also been used as an oral weekly and midcycle contraceptive pill in women.

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Based on in vivo and in vitro release rates, it was calculated that 3 to 5 capsules of gestrigone should provide contraceptive protection for 9-12 months. Contraceptive clinical trials with 3, 4 and 5 implants of gestrigone confirmed that the contraceptive effect lasted 9 months or longer (11). In this first clinical effectiveness study, the lowest pregnancy rate was recorded in women bearing 3 capsules and the highest in those bearing 5 capsules. This apparent discrepancy was partly explained by the lower release of gestrigone from capsules of the batch used for the 5 implant group, as compared with those used for the women in the 3 and 4 implant groups. Differences in release rates of R2323 implants were found to be due to the differences in the sterilization procedure used for the various batches. Capsules sterilized by irradiation released less of the compound (17 mcg/cm/24hrs) than those sterilized by steam or ethylene oxide (23 mcg/cm/24hrs).

In the above mentioned study, the Pearl Index for women bearing 3, 4 and 5 capsules was 1.7, 2.3 and 4.9, respectively. However, in more recent studies in which 6 steam sterilized capsules of R2323 were used by 189 women for 2,199 woman-months, no pregnancies occurred.

Amenorrhea was the most conspicuous side effect of the R2323 treatment, occurring more frequently during the first 5 months of implant use. Between 44 and 50% of all women bearing 3 to 5 capsules of R2323 were amenorrheic by the end of the 3rd month following implant insertion. Many subjects remained amenorrheic following implant removal for as long as 8 months. Breakthrough bleeding and spotting were rare, being reported by less than 5% and 2% of cycles. Endometrial biopsies obtained from women bearing R2323 implants revealed varying degrees of endometrial atrophy.

Other side effects occurring in women bearing R2323 implants included decrease in breast size, acne, hirsutism and hoarseness. The incidence of these side effects was small, being reported by less than 5% of the subjects.

Megestrol Acetate (M.A.)

Megestrol acetate was the first compound to be selected for implant contraception because of its favourable release rates in vivo and minimum tissue reaction at the implant site. The compound was used in the early acceptability studies of implant contraception in Santiago and Bahia (1-4).

Clinical trials with M.A. in Bahia included 323 women. 6,443 woman-months were recorded. Twenty-one pregnancies developed. One of these pregnancies was ectopic.

Based on a release rate of 14 mcg/cm/day, the capsules of M.A. were calculated to have an estimated life of 600 to 960 days. On the basis of excretion studies however, the amounts of steroid released from the Silastic capsules were estimated to provide effective protection for only 12 to 15 months (9). The capsules of M.A. used in early trials were smaller (2 cm) than those used in clinical studies with other compounds. Capsules, containing approximately 18 mg of M.A. each, were inserted in batches of 4, 5 and 6 capsules. Clinical trials with 4 and 5 capsules indicated that the duration of effective protection was extended by increasing the number of capsules. With 4 capsules, protection lasted 9 to 10 months and with 5 capsules it lasted 12 to 15 months. With 6 capsules the effect was further extended to 18 months. The Pearl Index in a clinical trial with 5 capsules of M.A. was 3.1. In a group of 90 women inserted with 6 capsules of M.A. and observed for 2,813 woman-months, only two pregnancies were recorded, one of them with an ectopic implantation. For the six capsule regimen, the Pearl Index was therefore only 0.8. The incidence of menstrual irregularities in women bearing M.A. implants was approximately the same as in women on norgestrienone implants. Intermenstrual bleeding or spotting occurred in 6% of cycles. Hypermenorrhea was reported in 7.5% of cycles. The incidence of amenorrhea for women with 4 and 5 capsules was only 3.6%.

The studies with megestrol acetate implants were discontinued because of the reported development of breast nodules in beagle bitches, following long term treatment with M.A.

d-Norgestrel

In view of its effectiveness as a low dose mini-pill, the use of d-norgestrel offered excellent prospects for implant contraception. It was hoped that the compound could be used in a single, very small capsule, which would remain effective for two or more years. Early pilot studies with small capsules containing less than 10 mg of d-norgestrel indicated however that the low in vivo release rates were insufficient to provide the minimum blood levels necessary to prevent conception. It became apparent from these early studies that in order to achieve adequate blood levels of d-norgestrel, one or more 3-cm capsules had to be used. Of all the compounds tested in implant contraception, d-norgestrel has the lowest release rate. In the human, only about 4 mcg/cm/day are released from the regular 3-cm Silastic capsules.

In the studies carried out in Bahia during the last five years, 115 pregnancies have occurred. None of these had an ectopic implantation. Table II shows the distribution of subjects, months of exposure, and pregnancies occurring in the various groups bearing d-norgestrel capsules. The largest single group of patients bore 6 capsules, and was exposed for 6,027 woman-months. In this group 47 pregnancies occurred for a Pearl Index of 9.0.

TABLE II: Clinical experience with different amounts of d-norgestrel implants

No. of Capsules	No. of Subjects	Woman-Months	Pregnancies	Pearl Index
1	38	202	2	11.8
2	228	2706	46	20.3
3	28	423	5	14.1
4	38	1063	2	2.2
5	65	2097	13	7.4
6	236	6027	47	9.3
12	49	853	0	0

The pregnancy rate observed in this group of subjects was probably due to a reduced release rate of d-norgestrel in capsules sterilized by irradiation. Irradiation was used to sterilize several batches of implants before it was found that exposure of Silastic to gamma rays reduced the release rates of compounds like d-norgestrel and R2323 through the Silastic. In a double blind study carried out by the ICCR, non-irradiated d-norgestrel capsules turned out to be more effective than R2010 when the same number of implants were used.

Because of its slow release rate, d-norgestrel implants should have the longest life among the various implants tested. It has been estimated that 6 d-norgestrel capsules should last 3,000 to 4,800 days at a constant release rate of 4 mcg/cm/day. In order to investigate the acceptability of a larger number of implants for a long lasting period of protection, 12 capsules of d-norgestrel were inserted in a small group of women in Bahia. This group of 49 women have been exposed for 853 woman-months and no pregnancies have occurred. This regimen should provide a long duration of contraceptive effectiveness.

Bleeding irregularities are the major concern of d-norgestrel implant users. Breakthrough bleeding and spotting are the most common side effect noted in studies with 6 capsules or less. Amenorrhea is more frequent in women bearing 12 capsules. Other side effects include acne, hirsutism and loss of libido.

Norethindrone (NET)

Norethindrone is one of the most widely used steroids in contraception. It has been used successfully for many years in combination with a synthetic estrogen in oral contraceptives. NET is also the active ingredient in a commercially available estrogen-free mini-pill with a daily dose of 350 mcg. In vivo release rates of NET from Silastic capsules are in the range of 7 mcg/cm/day. With these rates, 3-cm long implants of NET should last 1700 to 2600 days.

Clinical trials with NET capsules have been carried out in Bahia involving 290 women. 4,077 woman-months of exposure have been recorded. Pilot clinical trials with as many as 6 capsules indicated that the amounts of NET being released from the implants were inadequate to provide the blood levels necessary to prevent conception. In a group of 52 women bearing 3 capsules, 12 pregnancies occurred at the end of only 318 woman-months of exposure. In another group of 60 women bearing 4 capsules, 9 pregnancies developed during only 295 woman-months of exposure.

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In 50 women inserted with 6 capsules, 4 pregnancies occurred during 262 woman-months. As each capsule releases approximately only 20 mcg, the women on the 6-capsule regimen receive about 120 mcg of NET daily which is obviously inadequate to prevent conception effectively.

A larger group included 128 women bearing 12 capsules. This last group completed 3,202 woman-months. 9 pregnancies developed during this period resulting in a Pearl Index of 3. Bleeding irregularities in subjects bearing 12 capsules of NET are comparable to those described for patients on megestrol acetate.

ST-1435

The compound ST-1435 (16-methylene-17-alpha acetoxy-19 nor-progesterone) is a new 19-norsteroid devoid of androgenic and anti-androgenic activity. ST-1435 has a release rate in the range of 40 mcg/cm/day. This high release rate limits the life of ST-1435 implants to approximately 300 days. However, the contraceptive potency of ST-1435 when used in implant form was found to be higher than either norethindrone or norgestrienone, allowing the reduction in the number of capsules to only one or two per patient.

The first clinical trials were undertaken in Bahia in a group of 285 women who were inserted with 3 to 5 capsules of ST-1435 (7). A total of 3,174 woman-months of exposure were recorded. 52 women bearing 3 capsules completed 530 woman-months of exposure. No pregnancies occurred in this group. 48 women inserted with 4 capsules completed 502 woman-months of exposure. No confirmed pregnancy occurred in this group. In the largest group, consisting of 185 women bearing 5 capsules, 2,142 woman-months of use were recorded. Two pregnancies occurred, the first at the end of 11 months and the second at 19 months of use. It should be noted that both pregnancies occurred after the expected life of the implant, 10 months, had elapsed.

In more recent trials, a single capsule of ST-1435 has been inserted in each of 205 women who accepted short term implant treatment. The capsule had to be replaced at the end of six months of use for those who wanted to continue. 1,014 woman-months of exposure have been recorded. In the only pregnancy which occurred in this group of women, conception occurred prior to the insertion of the implant.

The most remarkable side effect with use of a single ST-1435 implant was amenorrhea. Amenorrhea occurred in 50% of the subjects and lasted as long as six months. The incidence of breakthrough bleeding and spotting was less in women bearing one implant than in those bearing 3 or more capsules.

Endocrine profiles of women bearing implants of ST-1435 show suppression of LH and absence of the progesterone rise typical of ovulation, indicating that even at the low levels of steroid release, ovulation is inhibited. Amenorrhea in women bearing ST-1435 implants seems therefore to result from ovulation inhibition.

Lynestrenol and R-1364

Lynestrenol and R-1364, a new norsteroid closely related to norgestrel, were also subjected to pilot clinical trials in implant form in Bahia. Both compounds revealed possibilities for relatively short term implant regimens. Capsules of lynestrenol with a release rate of 60 mcg/cm/day could last only 200 to 300 days. Four or five capsules of the compound would provide effective protection for approximately 6 to 8 months.

In a pilot study involving 60 women bearing 5 capsules of lynestrenol for 556 woman-months of exposure, no pregnancies occurred.

The calculated life of R-1364 was approximately 600 days, comparable therefore to that of megestrol acetate. However, the potency of M.A. is probably slightly higher than R-1364 since a greater amount of this latter compound was necessary to provide protection for an equivalent length of time.

Trials in Bahia with R-1364 involved 220 women divided into two equal groups. One-half of the women received 2 capsules and the other half four capsules. The first group completed 1,018 woman-months, whereas the second group involved 1,246 woman-months of exposure. Twelve pregnancies developed in the first group and only one in the second group.

Studies with both lynestrenol and R-1364 were discontinued because other compounds such as R2010, R2323, norgestrel and ST-1435 offered more favourable release rates. However, these two compounds hold potential as implants for implant contraception of relatively short duration.

Progestin-Estrogen Combinations

In order to oppose possible androgenic side effects associated with the prolonged use of estrogen-free implant contraception, combination treatment in which implants of estrogen have been inserted along with the capsules containing the progestin have been studied.

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The compounds megestrol acetate, norgestrienone (R2010) and gestrigone were used in association with estrogen. In all cases the estrogen used was estradiol, whose release rate from Silastic implants is of the order 2 to 5 mcg/cm/day, one 3-cm long capsule supplying 6 to 15 mcg of the steroid daily. In view of its very low release rates, estradiol capsules containing 5 to 7 mg of the steroid were expected to last up to three years. However, studies in post-menopausal women carried out in Bahia have indicated that their clinical effectiveness lasted not more than two years (17).

Clinical trials with the combination treatment were carried out in Bahia involving 320 women who were inserted with one capsule of estradiol in addition to 3 or 4 capsules of the progestin. 4,976 woman-months of observation were recorded. In order to evaluate the influence of estrogen on effectiveness and incidence of side-effects, each estrogen-implanted group had a corresponding estrogen-free progestin implant group against which it could be compared. Table III shows the distribution of subjects, length of observation and incidence of pregnancies for the various groups.

These studies show that the pregnancy rate is higher in all estrogen implanted groups as compared to the progestin-only groups. These differences are statistically significant for R2323 and megestrol acetate.

The most interesting differences in performance were recorded in women bearing R2323 capsules. During the first six months of R2323 implant use, the incidence of amenorrhea was lower in the group of women bearing one estrogen capsule than in those bearing capsules of the progestin without estrogen. On the other hand, during the last six months of use, the incidence of amenorrhea was higher in the group bearing R2323 plus estrogen than those on R2323 alone. The incidence of spotting was higher in women on R2323 plus estrogen than in those on R2323 alone. Differences in duration or intensity of the bleeding episodes was not statistically significant for the two groups of patients.

Although these differences in performance are undoubtedly small, they suggest that the contraceptive action of the progestin implant is due in part to its anti-estrogenic effect. The small amounts of estrogen released by the capsule of estradiol probably counteract the anti-estrogenic effect of the progestin at the target organs, thereby reducing its contraceptive action.

TABLE III: Comparison of implants containing various progestins with progestin-estrogen combination

Compounds	Subjects	Woman-Months	Pregnancies	Pearl Index
Norgestrienone (4)	453	7830	28	4.2
Norgestrienone (4) Estradiol (1)	183	3485	16	5.5
Megestrol Acetate (4)	102	1474	11	8.9
Megestrol Acetate (4) Estradiol (1)	55	496	9	21.7
Gestrigone (R2323) (3)	179	2209	4	2.1
Gestrigone (R2323) Estradiol (1)	82	995	6	7.2

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Because of the potential benefit of estrogen in reducing the incidence of androgenic side effects which may result from long term use of progestins, expanded clinical trials with combined estrogen-progestin implants are necessary to allow the several years exposure necessary for a meaningful assessment of the effect of additional estrogen.

COMMENTS

Clinical trials carried out with several implant regimens during the last 8 years show that implant contraception has high acceptability and efficacy. Side effects resulting from prolonged implant use appear also to be acceptable, as suggested by the continuation rates of 80% or higher at one year for most implant regimens.

Alterations in bleeding patterns are probably the major side effect of implant contraception. Some regimens (e.g., R2323, ST-1435) tend to induce prolonged amenorrhea whereas some of the others may increase the frequency of bleeding episodes or spotting (e.g., norgestrel 4). In our clinic population, amenorrhea is very well accepted and even desired by some patients. It may also be advantageous for the undernourished, anemic women of under-developed areas, who will certainly not miss the sometimes incapacitating monthly blood loss. Frequent spotting or prolonged bleeding, on the other hand, may be more difficult to tolerate and have no medical justification. However, it should be noted that even with those implant regimens in which prolonged bleeding episodes and spotting predominate, there are women who retain their regular bleeding patterns or develop amenorrhea.

The early reports of an increased incidence of ectopic implantations in pregnancies occurring in implant users was not confirmed by the more recent studies. Out of 334 unintended pregnancies occurring as a result of contraceptive failure in 4,863 implant users exposed for 68,456 woman-months, only three ectopic implantations occurred. According to Tietze, 0.8 to 1.2 ectopic gestations per 100 woman-years should be expected in unprotected women exposed to pregnancy (18). On the basis of these calculations, more than 50 ectopic pregnancies should have occurred in this group of women if the treatment were ineffective in preventing them. The study therefore shows that the contraceptive implant protects women not only against intrauterine but also against ectopic pregnancies.

Some of the women bearing progestin implants develop adnexal masses which are usually discovered during routine examinations. Reports of occasional abdominal pain have also been recorded in almost all clinical trials with the various implant regimens. Both adnexal masses and abdominal pain were thought to be related to ectopic pregnancies (5). However,

the low incidence of confirmed ectopic pregnancies in the larger studies and the clinical evolution of patients complaining of abdominal pain do not support this view. The adnexal masses disappear spontaneously without implant removal, becoming undetectable during follow-up examinations.

Other side effects occurring in women bearing progestin implants are listed below with their reported range in various groups of norgestrienone and gestrigone implant users.

Headache	5 to 24%
Nervousness	1 to 14%
Dizziness	0 to 14%
Acne	4 to 16%
Hypertrichiosis	1 to 12%
Hoarseness	0 to 4%
Breast hypotrophy	1 to 12%
Chloasma	1 to 14%
Jaundice	1 to 12%
Loss of libido	4 to 18%
Nausea	0 to 10%
Pruritus	1 to 8%
Rash	0 to 5%
Inflammation at the site of insertion	0 to 3%
Depression	2 to 6%

Some of these symptoms such as headaches seem to have a lower incidence in treated women than in non-treated controls. The androgenic side effects seem to develop more easily in older women with low endogenous estrogen or after prolonged treatment.

Because the treatment in most regimens is estrogen-free, it is expected that none of the estrogen-dependent undesirable side effects associated with use of combination oral contraceptives will develop in implant users. Serum alkaline phosphatase, SGOT, SGPT, cholesterol and triglycerides remained within normal limits in patients bearing M.A., norgestrienone, gestrigone and norgestrel implants. A lowering of blood cholesterol and triglyceride levels has been observed in approximately 50% of the patients bearing norgestrienone capsules but the significance of this finding, if any, remains to be established.

Another potential advantage of implant contraception in addition to being estrogen-free, may be the fact that the steroid does not reach the liver as a bolus as is the case with oral contraceptives. It has been pointed out that the high concentration of both estrogen and progestin of the contraceptive pill, reaching the liver through the portal system on a daily regimen, may be an excessive load on the liver cell, leading to hepatic pathology (12, 13). Moreover, changes in liver enzymes, induced by oral contraceptives, appear to be responsible for the increase in plasma lipoproteins and triglycerides which is a nearly universal feature of pill users. The suggestive relationship between increased

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serum triglycerides and premature coronary heart disease has become during the last few years a major cause of concern to pill users (14, 15, 16).

Studies with norgestrel, norgestrienone, norethindrone and ST-1435 are being continued in Bahia. Some of the successful regimens are being expanded at the present time in view of their demand by our clinic population. The method is well known in the city, where it has been in use by almost 5,000 women during the last 8 years. Among these women it is rated one of the best methods of contraception, being second in preference only to the intrauterine devices.

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