CONTRACEPTION

PREGNANCIES ASSOCIATED WITH SPERM CONCENTRATIONS BELOW 10 MILLION/ML IN CLINICAL STUDIES OF A POTENTIAL MALE CONTRACEPTIVE METHOD, MONTHLY DEPOT MEDROXYPROGESTERONE ACETATE AND TESTOSTERONE ESTERS

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ABSTRACT

A potential male contraceptive approach was evaluated in clinical trials involving monthly injections of depot medroxyprogesterone acetate and either subdermal implants of testosterone propionate or monthly injections of testosterone enanthate. Pregnancies occurred in partners of 9 men with recent sperm counts of 10 million/ml or below. In 5 of the 9 instances, the sperm counts were less than 1 million/ml. It appears that male contraceptive methods involving spermatogenic suppression may require attainment and maintenance of azoospermia. The pregnancy rate cannot be calculated, because the extent of other contraceptive use is uncertain. There were no spontaneous abortions. 6 pregnancies were carried to term, and all progeny were normal, based on physical examination at birth or 3 months after birth.

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INTRODUCTION

In a group of clinical studies of monthly injectable regimens of depot medroxyprogesterone acetate and testosterone esters (1, 2, 3, 4, 5), it was found that sperm production was markedly inhibited in most men. However, azoospermia was not attained in all subjects. Moreover, even when azoospermia was attained, it was not always maintained during continued treatment. But, because sperm concentrations were often below 10 million/ml, it was hoped that many of these non-azoospermic subjects were actually infertile (2, 4). Subsequent data from these studies, as well as recent reports in the literature (6, 7), now indicate that fertility is more common at very low sperm concentrations than had been previously assumed (8).

METHODS

The details of treatment have been reported previously (1, 2, 3, 4, 5), and are only summarized here. 100 men received monthly intramuscular injections of depot medroxyprogesterone acetate, and either chronic testosterone propionate subdermal implants or monthly intramuscular testosterone enanthate injections.

Subjects were instructed to observe 3 days' coital abstinence prior to collection of semen samples at the monthly clinical visit. The sample was collected by masturbation before the next administration of treatment, and semen analysis was performed within 2 hours. Sperm counts were conducted in a hemocytometer. Depending on the sperm density under gross microscopic observation, specimens either remained undiluted or were diluted 1:10 or 1:20 in a white blood cell pipette, with a solution of either 5% sodium bicarbonate in 1% phenol (2, 5) or 0.9% sodium chloride (1,3,4). The pipette was thoroughly shaken, about 1/2 the volume was discarded, and the remainder was used to flood the counting chamber. Each count was done 1-4 times and the mean value was calculated. Although data were collected on sperm motility, they will not be considered because semen samples were not always received within 2 hours after collection. Sperm morphology was not examined.

In 2 clinics (2, 5), subjects were instructed to use other means of contraception during treatment and after discontinuation of treatment until sperm counts returned to pretreatment levels. In the other 2 clinics (1,3-4), they were instructed to use other methods until they were told that their sperm counts were less than 1 million/ml.

RESULTS

For interpretation of this section and of the subsequent Discussion it should be noted that, because variability in sperm counts is a normal occurrence, there could be a considerable difference between the sperm concentration at conception and that at a semen sampling.

9 pregnancies occurred in female partners of men whose recent sperm concentrations were below 10 million/ml. For each, the date of conception was estimated as 14 days after the female partner's last menstrual period. Table I presents the sperm concentrations for each subject for 6 months prior to and 6 months following the estimated date of conception. In 5 of the 9 pregnancies, conception probably occurred when sperm concentrations were at or below 1 million/ml. In the other 4, the pertinent sperm concentrations were probably below 10 million/ml. It should be noted, for the subject with azoospermic counts immediately before and after conception, that the postconception count was not truly azoospermic; 2 sperm were observed.

These studies were not expressly designed for testing contraceptive effectiveness, and the data are inadequate for calculating the pregnancy rate. However, many female partners were exposed to pregnancy because few men followed the instructions to use alternative methods of contraception.

Of the 9 pregnancies, 3 were terminated by induced abortion. The other 6 went to term, and the progeny were all found to be apparently normal, based on physical examination at delivery or within 3 months following birth. There were 3 males and 3 females. In the 2 instances in which blood group tests could be performed on the parents and the child, there was no evidence suggesting doubt of paternity. Unfortunately, tests to establish convincing evidence of paternity cannot be conducted in any of the cases.

DISCUSSION

For many years, a widely accepted standard for male subfertility was a sperm concentration below 20 million/ml. The criterion was based on the report by MacLeod and Gold (8) that sperm concentrations were below that level in only 5% of 1000 husbands of women in a prenatal clinic. Recently, downward revision of the standard has been suggested (9,10), because 19-20% of allegedly fertile men (men requesting vasectomy, usually after having fathered at least one child) were found to have sperm counts in this "subfertile" range. This finding was probably not due to inclusion of a large number of men whose sperm counts had declined since the last substantiation of their fertility; even when the data were subdivided according to time since the latest paternity (10), there were no differences among the subgroups in the percentages of sperm counts below 20 million/ml. (It should be noted that not all current data from vasectomy clinics support the idea that the subfertility definition should be lowered; in a recent sampling of the same geographical area as that of the original MacLeod and Gold study [8], only 7% of allegedly fertile vasectomy applicants had sperm counts below 20 million/ml [11]).

Information on occurrence of pregnancy in previously infertile couples shows clearly that men with sperm counts below 20 million/ml often are actually fertile when the female partner has no fertility impairment (6, 7, 12, 13). In the following list, these findings are presented in terms of pregnancy rates within particular oligozoospermic subgroups (rather than in terms of pregnancy rates of oligozoospermic

Table I. Sperm concentrations (in millions/ml) in men treated with depot medroxyprogesterone acetate (DMPA) and testosterone enanthate (TE), for 6 months prior to and 6 months following the estimated date of conception (= 14 days after the female partner's last menstrual period).

ESTIMATED DATE OF CONCEPTION

Monthly Treatment	MONTHS BEFORE CONCEPTION 6	5	4	3	2	1	MONTHS AFTER CONCEPTION 1	2	3	4	5	6
150 DMPA 500 TE	0	0	0	0	0	0	0 ②	0 ①	2	1	34	91
100 DMPA 250 TE	<1		<1	<1	<1	<1	<1	<1				
100 DMPA 250 TE	<1		<1		<1	<1	<1	1		1	5	<1
100 DMPA 250 TE	1	5	<1		2	<1	<1	2	<1	1	2	2
100 DMPA 250 TE		<1	1			<1	1					
100 DMPA 250 TE	80	20	10	3	<1	2						
100 DMPA 250 TE	<1		40	20	15		4	2	1	<1		3
100 DMPA 250 TE	80	20		20	15	4	3	<1				
150 DMPA 250 TE	<1	<1	2	5	3	4	8	28	34	30	17	21

▬ Treatment (month following injection)
② Two sperm; nonprogressive motility
① One sperm; slow, coordinated zigzag motility

subgroups in relation to the total population). Since the durations for these observations were not reported, the rates cannot be expressed according to a standard interval.

Oligozoospermic Subgroups, Based on Ranges of Sperm Concentrations (millions/ml)

	20-0	10-0	5-0	1-0
Pregnancy rates within subgroups	8 (10)	7 (10,12)	20* (6)	22 (6)
	16 (12)	15 (10)	42 (7)	
	18 (10)	31 (14)		
	37 (14)	45 (7)		
	48 (7)	52 (6)		
	50 (14)			
	61 (6)			

*estimated

(parentheses enclose reference numbers)

It can thus be seen that reported rates for impregnation have gone as high as 61% (6) within groups of men with sperm counts below 20 million/ml. In groups with sperm counts below 10 million/ml, rates up to 52% have been obtained (6). Even in groups of men with sperm counts below 5 million/ml and 1 million/ml, there have been rates of 42% (7) and 22% (6), respectively. This last rate is of particular interest for the current study, in which there were 5 pregnancies with sperm counts below 1 million/ml within the total of 9 pregnancies at sperm counts below 10 million/ml.

It has been specifically recommended several times (6, 10, 12) that the definition of subfertility, or oligozoospermia, be reduced to the level of sperm counts below 10 million/ml. However, our data and those from the other reports suggest that this level of oligozoospermia is far from equivalent to infertility. Even if as many as half of the reported pregnancies are attributable to another male partner, the fertility at this level of oligozoospermia is considerable. A male contraceptive method based on suppression of spermatogenesis seems to require an end point of sustained azoospermia.

Effectiveness is only one of several relevant issues in male contraception. Another concern in this field has been the possibility of adverse effects on subsequent progeny, due to sperm or semen defects. Steroidal suppression of spermatogenesis might result in such defects because of direct steroidal action on the sperm, support cells or semen, or because of changes in sequence and/or duration of the spermatogenic steps. Men could expose female partners to increased numbers of abnormal sperm during the decline prior to azoospermia, in periods of partial suppression, or during post-treatment recovery. In fact, there are some specific data for sperm changes associated with use of progestins. Shifts toward more sperm abnormalities in seminal cytology have been reported for treatment with either depot medroxyprogesterone acetate or testosterone enanthate (15). Chromosomal damage has been detected in precociously pubertal boys after long-term depot medroxyprogesterone acetate treatment (16), and in dogs immediately following testicular progesterone infusion (17). However, a recent review of the outcomes of pregnancies for men treated with compounds affecting spermatogenesis (18) has indicated that there is not a high risk of problems associated with such treatments. There were no increases in problems of pregnancy, abnormalities of birth, or abnormalities of early development. In the present studies, all 6 progeny from conceptions at sperm counts below 10 million/ml appeared to be normal. Although it is reassuring that there do not appear to be high risks to progeny associated with suppression of spermatogenesis, the data are still inadequate for detection of low level risks (18). Moreover, when more effective means of spermatogenic suppression are found, they too will require extensive evaluation.

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