

EFFICACY OF SUPEROVULATION AND INTRAUTERINE INSEMINATION
IN THE TREATMENT OF INFERTILITY

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ABSTRACT

Background Induction of superovulation with gonadotropins and intrauterine insemination are frequently used to treat infertility. We conducted a large, randomized, controlled clinical trial of these treatments.

Methods We studied 932 couples in which the woman had no identifiable infertility factor and the man had motile sperm. The couples were randomly assigned to receive intracervical insemination, intrauterine insemination, superovulation and intracervical insemination, or superovulation and intrauterine insemination. Treatment continued for four cycles unless pregnancy was achieved.

Results The 231 couples in the group treated with superovulation and intrauterine insemination had a higher rate of pregnancy (33 percent) than the 234 couples in the intrauterine-insemination group (18 percent), the 234 couples in the group treated with superovulation and intracervical insemination (19 percent), or the 233 couples in the intracervical-insemination group (10 percent). Stratified, discrete-time Cox proportional-hazards analysis showed that the couples in the group treated with superovulation and intrauterine insemination were 3.2 times as likely to become pregnant as those in the intracervical-insemination group (95 percent confidence interval, 2.0 to 5.3) and 1.7 times as likely as those in the intrauterine-insemination group (95 percent confidence interval, 1.2 to 2.6). The couples in the intrauterine-insemination group and in the group treated with superovulation and intracervical insemination were nearly twice as likely to conceive as those in the intracervical-insemination group.

Conclusions Among infertile couples, treatment with induction of superovulation and intrauterine insemination is three times as likely to result in pregnancy as is intracervical insemination and twice as likely to result in pregnancy as is treatment with either superovulation and intracervical insemination or intrauterine insemination alone. (N Engl J Med 1999; 340:177-83.)

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DEMAND for effective therapy for infertility has often led to practices that become accepted without the benefit of data from clinical trials. Two common treatments for infertility are induction of superovulation, in which the ovaries are stimulated with exogenous gonadotropins to develop several dominant follicles, and in-

trauterine insemination, in which motile sperm are suspended in culture medium and injected transcervically into the uterine cavity.

Superovulation and intrauterine insemination are used alone or in combination for the treatment of unexplained infertility, male-factor infertility, and other cases of infertility in which the woman has an unobstructed genital tract and some ovarian function and the man has motile sperm. Although national data on the cost of these procedures have not been compiled, costs of \$1,300 per cycle for superovulation and of \$500 per cycle for intrauterine insemination are typical.¹ The risks of superovulation include ovarian hyperstimulation,² multiple pregnancy,³ and possibly, an increase in the risk of ovarian cancer.⁴

We report the results of a large, randomized, controlled clinical trial of the efficacy of superovulation and intrauterine insemination.

METHODS**Centers and Subjects**

This study was conducted at 10 clinical sites and was approved by the appropriate institutional review committee at each site. All the couples gave informed consent to participate.

Before enrollment, each couple underwent a standard evaluation for infertility, including semen analysis in the man; endometrial biopsy, hysterosalpingography, and laparoscopy in the woman; and a test for serum antisperm antibodies in the couple. Semen analysis was performed according to standardized methods^{5,6} by trained technicians at each center, who followed common protocols and used the same types of supplies and equipment. The immunobead test used to detect antisperm antibodies was a modification of the test of the World Health Organization.⁶ The results of an endometrial biopsy were considered to be "in phase" if there was no more than a three-day lag in histologic dating according to the onset of the next menstrual period. Women who had received treatment for American Fertility Society stage I or II endometriosis⁷ were enrolled only if six months had elapsed after either surgical therapy or the return of ovulatory cycles after medical therapy. Detailed inclusion and exclusion criteria are listed in Table 1.

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TABLE 1. INCLUSION AND EXCLUSION CRITERIA.

CRITERIA	WOMEN	MEN
Inclusion	Age, ≤ 40 years Negative pregnancy test Normal pelvis and uterine cavity* "In phase" endometrial biopsy Negative serum antisperm antibody test Normal serum follicle-stimulating hormone and thyrotropin values on days 1–5 of cycle Length of 2 of the 3 most recent menstrual cycles between 24 and 40 days History of infertility for >1 year	Age, ≤ 55 years Negative serum antisperm antibody test Presence of any motile sperm on screening semen analysis History of infertility for >1 year
Exclusion	Previous use of in vitro fertilization or other assisted reproductive technology Previous treatment with gonadotropins Previous intrauterine insemination with current partner History of chronic disease History of chemotherapy or radiation to the abdomen or pelvis History of tubal surgery Extensive tubal adhesions Endometriosis of more than stage II† History of myomectomy, ovarian cystectomy, or unilateral oophorectomy‡	Previous use of in vitro fertilization or other assisted reproductive technology Previous intrauterine insemination History of vasovasostomy Varicocele within 6 months before study History of pelvic-node dissection

*Women with minimal or mild endometriosis (American Fertility Society stage I or II)⁷ were eligible six months after treatment.

†Endometriosis was classified according to the American Fertility Society revised classification.⁷

‡Women were eligible if subsequent laparoscopy revealed the absence of clinically important pelvic adhesions.

Hypothesis Tested and Design of the Study

The overall hypothesis of the study was that induction of superovulation or intrauterine insemination would result in a higher pregnancy rate among infertile couples than would no treatment. No treatment was defined as intracervical insemination timed to a surge in the urinary excretion of luteinizing hormone to ensure that sperm were present in the cervix and vaginal fornix at the time of ovulation. Eligible couples were randomly assigned to one of four groups: intracervical insemination timed to the surge in urinary excretion of luteinizing hormone (the control group), intrauterine insemination timed to the surge in urinary excretion of luteinizing hormone, superovulation and intracervical insemination, or superovulation and intrauterine insemination. Purified follicle-stimulating hormone (urofollitropin [Metrodin], Serono Laboratories, Norwell, Mass.) was used to induce superovulation.

Each couple received four treatment cycles unless pregnancy occurred. Rest cycles sometimes intervened between treatment cycles for either personal or clinical reasons. In superovulation cycles, treatment was canceled after day 3 if the serum estradiol concentration exceeded 3000 pg per milliliter (11,010 pmol per liter). Cycles were canceled in the intracervical-insemination and intrauterine-insemination groups if no surge in urinary excretion of luteinizing hormone was detected.

Procedures

After eligibility and informed consent were confirmed for each couple, randomization was carried out with use of a permuted-block procedure, stratified according to center.

Superovulation Protocol

Women assigned to one of the two superovulation groups were treated according to a standard protocol. Base-line pelvic ultrasonography was performed on day 1, 2, or 3 of the menstrual cycle. Then, 150 IU of follicle-stimulating hormone was administered

intramuscularly daily from day 3 through day 7. On day 8, ultrasonography was repeated and serum estradiol was measured. Daily administration of follicle-stimulating hormone was continued, with the dose adjusted if necessary, until at least two follicles reached ≥ 18 mm (average of two dimensions) and the serum estradiol concentration ranged from 500 to 3000 pg per milliliter (1835 to 11,010 pmol per liter). Once these criteria were met, treatment with follicle-stimulating hormone was discontinued and 10,000 IU of human chorionic gonadotropin (Profasi, Serono Laboratories) was administered intramuscularly. A single insemination was performed 36 to 40 hours later.

Spontaneous-Ovulation Protocol

Women who were not assigned to superovulation underwent insemination timed to spontaneous ovulation. Four days before the expected time of ovulation, the women began daily testing of their second morning urine specimen for luteinizing hormone, using a qualitative kit (OvuQuick, Quidel, San Diego, Calif.). Intrauterine insemination or intracervical insemination was performed on the day after the surge in urinary excretion of luteinizing hormone.

Intrauterine-Insemination Protocol

Semen specimens were collected by masturbation on site, evaluated according to standardized methods,^{5,6} and prepared for intrauterine insemination within one hour after collection. Semen was diluted 1:2 (vol/vol) with HEPES-buffered Ham's F10 medium containing 1.5 percent serum albumin (Albuminar, Bayer, Elkhart, Ind.). After centrifugation at $250 \times g$ for 10 minutes, the pellets were resuspended and combined in 3 ml of the medium. The sperm suspension was centrifuged for 10 minutes, and the pellet was resuspended in 0.35 ml of medium. Approximately 0.05 ml was used to determine the concentration and motility of the sperm. The remaining sample was drawn into a Shepard cath-

eter (Cook Ob/Gyn, Bloomington, Ind.) attached to a 1-ml syringe for intrauterine insemination, which was performed within 2½ hours after semen collection.

Intracervical-Insemination Protocol

Semen specimens were collected and evaluated as in the intrauterine-insemination protocol. Intracervical insemination was performed within 1½ hours after semen collection.

Definition of Pregnancy

Serum β-human chorionic gonadotropin was measured 15 days after insemination (luteal day 15). If the value exceeded 10 mIU per milliliter, the measurement was repeated on luteal day 17. Pregnancy was indicated by an increase in the serum β-human chorionic gonadotropin concentration between luteal days 15 and 17. We subsequently also recorded the outcome of pregnancy — spontaneous abortion, induced abortion, ectopic pregnancy, or live birth — and whether multiple pregnancy had occurred.

Data Management and Quality Control

Data were transmitted to the data-coordinating center before the enrollment of each couple and periodically thereafter. Research nurses and members of the data-entry staff attended two-day training sessions at the data-coordinating center. The technicians who performed semen analyses attended five-day training sessions at the University of California, Davis, and thereafter were tested for proficiency approximately twice each year with the use of unmarked specimens. All centers were audited on site by the study coordinator once a year for compliance with the protocol and the completeness and comparability of data with the master data base. Computerized checks of the validity of the data were performed. Quality-control analyses of serum β-human chorionic

gonadotropin and serum estradiol measurements were conducted annually by the central laboratory at Columbia University by having each clinical laboratory analyze unmarked samples containing various concentrations of each hormone.

Statistical Analysis

The pregnancy rates per couple were calculated for each of the four groups, and the results were compared with the use of chi-square tests with one degree of freedom. The Bonferroni correction⁸ for multiple comparisons was used to adjust the alpha level for statistical significance. These analyses were repeated after adjustment for clinical center. We also tested whether the fecundity rates at the centers were homogeneous.

The possible effects of rest cycles were accounted for by the use of stratified, discrete-time Cox proportional-hazards analysis.⁹ The results are presented for a model stratified according to center. However, results from an unstratified model, which included the center as a covariate, and from an unstratified model that did not include centers were similar, indicating that there was no interaction between treatments and centers.

The results of a planned interim analysis were reported to an independent data safety and monitoring committee but not to the investigators or other personnel. The alpha level was adjusted at the time of the interim analysis according to the method of O'Brien and Fleming.¹⁰

RESULTS

Characteristics of the Couples

The number of couples enrolled in each of the four treatment groups ranged from 231 to 234. The base-line characteristics of the couples in each group were similar (Table 2). Overall, the 932 couples en-

TABLE 2. BASE-LINE CHARACTERISTICS OF THE COUPLES.*

CHARACTERISTIC	INTRACERVICAL INSEMINATION (N=233)	INTRAUTERINE INSEMINATION (N=234)	SUPEROVULATION AND		P VALUE†
			INTRACERVICAL INSEMINATION (N=234)	INTRAUTERINE INSEMINATION (N=231)	
Age (yr)					
Women	32±4	32±4	32±4	32±4	0.73
Men	35±5	34±4	34±5	35±5	0.71
Duration of infertility (mo)	43±31	46±31	42±31‡	42±26	0.53
Bachelor's degree (%)					
Women	32	35	39	38	0.25
Men	36	31	33	38	0.28
White race (%)					
Women	87	90	87	88	0.67
Men	87	91	89	86	0.34
Nulliparous (women) (%)	61	61	57	59	0.66
Sperm count (×10 ⁶ /ml)					
Median	39	41	44	48	0.44
25th percentile	18	23	23	23	
75th percentile	74	70	74	80	
Sperm motility (%)					
Median	50	51	50	49	0.79
25th percentile	37	37	39	36	
75th percentile	57	59	60	59	

*Plus-minus values are means ±SD.

†The chi-square test was used for categorical variables, and the F statistic from an analysis of variance was used for continuous variables.

‡Data were missing for one couple.

rolled in the study were observed for 4676 cycles (Table 3), of which 57 percent were treatment cycles, 18 percent were clinically mandated rest cycles, 18 percent were rest cycles requested by the couples, and 6 percent were cycles in which treatment was canceled. Most clinically mandated rest cycles in the superovulation groups were the result of the detection of ovarian cysts at the beginning of a cycle. The number of cycles of canceled treatment was higher in the groups that did not involve hormone therapy, largely because of the failure of the women to detect a surge in urinary excretion of luteinizing hormone. The rate of withdrawal from the study was higher among the couples in the superovulation groups (Table 3).

The pregnancy rates per couple in the four groups are shown in Table 4. The overall pregnancy rate was highest (33 percent) in the group treated with superovulation and intrauterine insemination. The rates in the intrauterine-insemination group and the group treated with superovulation and intracervical insemination were higher than the rate in the intracervical-insemination group. The results were similar when the pregnancy rates were analyzed according to the number of insemination cycles.

The pregnancy rates according to prerandomization characteristics of semen for each treatment group are shown in Table 5. In general, pregnancy rates increased with increasing numbers of sperm in the ejaculate, increasing sperm counts, and increasing motility. For the two lowest quartiles with respect to total sperm in the ejaculate and sperm count, the pregnancy rates were highest for the two groups in which intrauterine insemination was part of the treatment. Moreover, for the lowest quartile of sperm values, treatment with superovulation and intracervical

insemination did not appear to be associated with significantly higher pregnancy rates than treatment with intracervical insemination alone. The pregnancy rates per couple in the four groups were not affected by the woman's age or the man's age. The rates decreased with increasing duration of infertility: the rate was 28 percent with 12 to 23 months of infertility, 20 percent with 24 to 35 months of infertility, and 17 percent with ≥ 36 months of infertility. The rates were higher among women with a previous pregnancy (23 percent) than among those who had never been pregnant (18 percent).

Couples in the two superovulation groups remained in the study longer than those in the other two groups because they had more rest cycles. After adjustment for the number of rest cycles, the couples in the group treated with superovulation and intrauterine insemination were estimated to be 3.2 times as likely to become pregnant as those in the intracervical-insemination group (95 percent confidence interval, 2.0 to 5.3; $P=0.008$) and 1.7 times as likely to become pregnant as the couples in the intrauterine-insemination group (95 percent confidence interval, 1.2 to 2.6; $P=0.002$). The results did not change after adjustment for the women's age, duration of infertility, and semen characteristics (data not shown). The couples in the intrauterine-insemination group and the group treated with superovulation and intracervical insemination were 1.9 times as likely (95 percent confidence interval, 1.1 to 3.2; $P=0.007$) and 1.8 times as likely (95 percent confidence interval, 1.0 to 3.0; $P=0.02$), respectively, to become pregnant as those in the intracervical-insemination group.

We also compared the number of liveborn infants in each of the treatment groups (Table 6). Liveborn

TABLE 3. SUMMARY OF CYCLES AND WITHDRAWAL RATES.

VARIABLE	INTRACERVICAL INSEMINATION (N=233)	INTRAUTERINE INSEMINATION (N=234)	SUPEROVULATION AND		ALL GROUPS (N=932)
			INTRACERVICAL INSEMINATION (N=234)	INTRAUTERINE INSEMINATION (N=231)	
Cycles (no.)					
Total	997	1002	1378	1299	4676
Insemination	706	717	637	618	2678
Rest for clinical reasons	28	27	413	387	855
Rest for personal reasons	144	160	285	262	851
Canceled	119	98	43	32	292
Withdrawal (no.)*	30	22	65	50	167
Total (%)	13	9	28	22	18
Treatment-related (%)	1	0	4	4	2
Not related to treatment (%)	12	9	24	18	16

*Twenty-one couples withdrew for reasons related to treatment, such as the absence of a response to superovulation and intracervical insemination for two consecutive cycles, ovarian hyperstimulation for two consecutive cycles, and two consecutive anovulatory cycles. A total of 146 couples withdrew for reasons not related to treatment, including other medical problems, desire to adopt a child, and the cost of treatment.

TABLE 4. PREGNANCY RATES PER COUPLE.

TREATMENT GROUP	No. OF COUPLES	No. OF INSEMINATION CYCLES	No. OF PREGNANCIES	PREGNANCY RATE PER COUPLE* %	PREGNANCIES DURING INSEMINATION CYCLET no. of pregnancies/ no. of insemination cycles (%)
Intracervical insemination	233	706	23	10	14/706 (2)
Intrauterine insemination	234	717	42	18	35/717 (5)
Superovulation and intracervical insemination	234	637	44	19	26/637 (4)
Superovulation and intrauterine insemination	231	618	77	33	54/618 (9)

*The results of chi-square tests of a priori comparisons, adjusted for center, are as follows: intracervical insemination as compared with superovulation and intracervical insemination, P=0.006; intracervical insemination as compared with intrauterine insemination, P=0.01; intracervical insemination as compared with superovulation and intrauterine insemination, P<0.001; intrauterine insemination as compared with superovulation and intrauterine insemination, P<0.001; superovulation and intracervical insemination as compared with superovulation and intrauterine insemination, P<0.001. The P value that indicates statistical significance after the Bonferroni correction is 0.01.

†The results of chi-square tests of a priori comparisons, adjusted for center, are as follows: intracervical insemination as compared with superovulation and intracervical insemination, P=0.024; intracervical insemination as compared with intrauterine insemination, P=0.003; intracervical insemination as compared with superovulation and intrauterine insemination, P<0.001; intrauterine insemination as compared with superovulation and intrauterine insemination, P<0.001; superovulation and intracervical insemination as compared with superovulation and intrauterine insemination, P=0.005. The P value that indicates statistical significance after the Bonferroni correction is 0.01.

TABLE 5. PREGNANCY RATES ACCORDING TO CHARACTERISTICS OF SEMEN.

VARIABLE	SUPEROVULATION AND INTRACERVICAL INSEMINATION		SUPEROVULATION AND INTRAUTERINE INSEMINATION		ALL GROUPS
	INTRACERVICAL INSEMINATION	INTRAUTERINE INSEMINATION	INTRACERVICAL INSEMINATION	INTRAUTERINE INSEMINATION	
	pregnancy rate/100 couples				
Total sperm in the ejaculate (×10 ⁻⁶)*					
Quartile 1 (0.4–53)	8	18	6	24	14
Quartile 2 (53.1–126.9)	5	21	16	31	18
Quartile 3 (127–225)	17	14	24	42	23
Quartile 4 (225.1–1400)	11	20	28	36	25
Sperm count (×10 ⁻⁶ /ml)*					
Quartile 1 (0.2–21.8)	8	16	6	26	14
Quartile 2 (21.9–43.4)	7	24	26	34	23
Quartile 3 (43.5–75.2)	11	9	22	32	19
Quartile 4 (75.3–700)	14	23	20	40	25
Motility (%)					
Quartile 1 (4.5–37)	11	17	10	24	16
Quartile 2 (37.1–50)	8	15	12	30	17
Quartile 3 (50.1–59)	10	15	29	44	24
Quartile 4 (59.1–85)	10	23	22	36	23

*Data were missing for six couples who were enrolled early in the study because of late delivery of the equipment to some of the sites. Data were missing for one couple in the group treated with superovulation and intrauterine insemination and for one couple in the group treated with superovulation and intracervical insemination and for two couples in each of the other two groups. In addition, one couple with a pregnancy in the group treated with superovulation and intracervical insemination did not have valid data for total sperm in the ejaculate.

infants were more common in the groups treated with superovulation and intracervical insemination ($P=0.01$) and superovulation and intrauterine insemination ($P<0.001$) than in the intracervical-insemination group and were more common ($P=0.01$) in the group treated with superovulation and intrauterine insemination than in the group treated with intrauterine insemination alone.

Of the 186 pregnancies that occurred during the study, 72 percent resulted in live births, 20 percent resulted in spontaneous abortion, and 4 percent resulted in ectopic pregnancy (Table 6). Two pregnancies ended in induced abortions; one of the aborted fetuses had Down's syndrome, and the other was a partial hydatidiform mole. There were three quadruplet pregnancies, one in the group treated with superovulation and intracervical insemination and two in the group treated with superovulation and intrauterine insemination. One pregnancy was reduced to triplets, and the other two were reduced to twins. There were four sets of triplets, one in the group treated with superovulation and intracervical insemination and three in the group treated with superovulation and intrauterine insemination. Seventeen of the 18 sets of twins were in the superovulation groups. Six women had ovarian hyperstimulation requiring hospitalization; three of them were pregnant.

DISCUSSION

Induction of superovulation and intrauterine insemination are common treatments for couples with unexplained infertility and those with infertility associated with specific diagnoses in which no pregnancy has occurred despite standard diagnosis-directed treatments. We studied only couples in which evaluation of the woman revealed no abnormalities and that therefore would be considered to have either unexplained

infertility or male-factor infertility. In these couples, the combination of the induction of superovulation with follicle-stimulating hormone and intrauterine insemination was associated with a likelihood of pregnancy that was more than three times as high as that for intracervical insemination alone.

Although to our knowledge there have been no previous large-scale, randomized comparisons of these treatments in couples with unexplained or male-factor infertility, a recent randomized trial comparing superovulation and intrauterine insemination with no treatment among women with minimal or mild endometriosis revealed that the use of superovulation and intrauterine insemination was associated with a birth rate that was 5.6 times as high as the rate in the absence of treatment.¹¹ A combined analysis of the literature on unexplained infertility¹² yielded estimated pregnancy rates of 4 percent per cycle for control cycles and intrauterine-insemination cycles, 8 percent per cycle for superovulation cycles, and 18 percent per cycle for cycles of superovulation and intrauterine insemination. We expected somewhat lower rates in our study, because we included men who had any motile sperm in their ejaculates. Some provocative results from this study regarding characteristics of semen were that intrauterine insemination had more of an effect on the likelihood of pregnancy for couples in which the man's semen values were in the lower quartiles and that superovulation had less of an effect for these couples.

The apparent variations in the rate of miscarriage among the groups deserve comment. The miscarriage rate was highest in the group treated with superovulation and intrauterine insemination, but the numerator was small. The fact that the rates of miscarriage were not lower in the group treated with superovulation and intracervical insemination and the

TABLE 6. PREGNANCY OUTCOMES.

OUTCOME OF PREGNANCY	INTRACERVICAL INSEMINATION	INTRAUTERINE INSEMINATION	SUPEROVULATION AND		ALL GROUPS
			INTRACERVICAL INSEMINATION	INTRAUTERINE INSEMINATION	
	no. of pregnancies				
Live birth					
At term	17	28	31	41	117
Preterm	1	2	5	9	17
Stillbirth	0	1	0	0	1
Spontaneous abortion	4	6	5	22	37
Ectopic pregnancy	0	2	1	4	7
Induced abortion	1	1	0	0	2
Unknown or lost to follow-up	0	2	2	1	5
Total	23	42	44	77	186

intrauterine-insemination group than in the intracervical-insemination group suggests that there is nothing about superovulation or intrauterine insemination itself that leads to an increased likelihood of miscarriage. Moreover, there is no evidence or theoretical basis to suggest that superovulation and intrauterine insemination interact synergistically with respect to miscarriage.

We conclude that for infertile couples in which the woman has no identifiable infertility factor and the man has motile sperm, the combination of superovulation and intrauterine insemination is an effective means of achieving pregnancy. Moreover, the effects of superovulation and intrauterine insemination on pregnancy appear to be independent and additive. In recommending treatment options to couples, physicians should weigh these results against those for in vitro fertilization; they should also consider the costs of the various procedures, the results of semen analyses, the woman's age, and the incidence of ovarian hyperstimulation and high-order multiple pregnancies. At present, no rigid algorithm can be constructed. We recommend that couples be informed of all their options, be given realistic information about the chances of success as well as the costs and complications, and be involved in the final decision about which treatment method to use.

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APPENDIX

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