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Evaluation of luteal support therapy in a randomized controlled study within a gamete intrafallopian transfer program

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A randomized controlled study of luteal support therapy (using intramuscular injections of progesterone and/or human chorionic gonadotropin) was conducted in a trial designed to minimize variables that might adversely affect the chance of pregnancy. After applying rigid selection criteria, 207 women were recruited into one of four groups. Mathematical modeling was applied to the results to determine if there were degrees of improvement in uterine receptivity relative to various grades of embryo quality ("E" factor). Although the trial size was insufficient to enable the detection of significant improvements in the pregnancy rates that ranged from 27.5% for nontreatment to 41.2% for those receiving combined treatment, the birth rates were significantly better with luteal support (11.8% versus 29.4%). Similarly, the overall implantation rate just failed to reach statistical significance for luteal support, but the ongoing implantations were significantly better (3.6% versus 9.0%). Data modeling indicated that luteal support, particularly with the combined regimen, could improve the ongoing implantation rate by up to 2.5-fold when the E factor was poorest. Fertil Steril 55:131, 1991

Luteal support therapy using progesterone (P), progestogenic compounds, and/or human chorionic gonadotropin (hCG) has become a common component of infertility treatments involving ovarian stimulation, particularly where this is combined with assisted reproduction. There appears to be a reasonable rationale for luteal support in anovulatory women treated by human menopausal gonadotropins (hMG), as nonconception treatment cycles often display a markedly shortened luteal phase.[1] This has also been observed among cycling women treated by hMG for assisted reproduction, particularly those with a high estrogen output during the follicular phase;[2,3] hence luteal support is likely to be beneficial in hMG-stimulated cycles. This view is supported by a recently reported randomized matched study that examined hormonal and pregnancy data in a small series.[4]

However, cycles stimulated by clomiphene citrate (CC), with or without additional hMG, do not display shortened luteal phases.[3] Furthermore, published reports of randomized controlled trials assessing luteal phase treatments using P[5–7] or hCG support[8–10] fail to show significant improvements in pregnancy rates (PRs), although there is usually a trend implying a benefit. However, despite the careful methodology in these studies, they have all been far too small to enable the significant detection of even a 10% variation in the PR. Furthermore, they comprised a heterogeneous population of subjects within in vitro fertilization and embryo transfer (IVF-ET) programs that have usually been evolving through constant internal changes and that are generally reflected by inexplicable periods of poor PRs. One group attempting to study the effects of a progestagenic compound given during the luteal phase of IVF treatment cycles calculated that it would require two groups of 1,500 sub-

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jects in each category to significantly detect a 5% improvement in the PR, e.g., from 15% to 20%.[11]

To minimize the inherent problems in luteal phase supplementation studies, this relatively large randomized controlled trial was performed within a gamete intrafallopian transfer (GIFT) program beginning around 9 months after it was established and shown to be characterized by stable PRs. Subjects were carefully screened to include a single infertility subcategory and exclude all known factors that might adversely affect the chance of pregnancy.

MATERIALS AND METHODS

Trial Design and Treatment Regimens

The GIFT program was commenced at the PIVET Medical Centre in November 1985 and, from the outset, was shown to be effective for a range of nontubal causes of infertility. A modification of the methodology using increased sperm numbers enabled pregnancies to be achieved in male factor cases,[12] but pregnancy wastage appeared to be higher. Pregnancy rates with GIFT have been consistently higher than IVF-ET and not noticeably affected during fluctuations in results of the latter procedure. However, certain parameters such as underlying tubal disorders, antispermatozoal antibodies, high basal luteinizing hormone (LH) levels, and severe pelvic endometriosis were noted to influence the chance of pregnancy or its outcome in one or the other of the procedures;[13] therefore, the trial was designed to exclude any such influences.

Between August 1986 and July 1987, a total of 280 couples were recruited after fulfilling the following inclusion criteria: (1) age of woman between 22 and 39 years at time of procedure; (2) >3 years infertility; (3) regular menstrual cycles with hormonal and ultrasound (US) evidence of normal ovulatory pattern on cycle tracking; (4) no antispermatozoal antibodies in the woman's serum or cervical mucus; (5) no previous GIFT or IVF procedures; (6) no grade III or grade IV endometriosis; (7) husband normospermic with no antispermatozoal antibodies in his serum or semen; (8) GIFT treatment cycle involving stimulation with CC/hMG; and (9) only good responders accepted, i.e., with peak estradiol (E_2) at hCG trigger between 2,500 to 10,000 pM and at least two follicles $\geq$ 1.5 cm (i.e., both poor and excessive responders excluded)

Couples fulfilling the above criteria and providing informed consent were randomly selected by sequential allocation at the commencement of a treatment cycle into one of four groups: group 1, nil support; group 2, hCG support—1,000 IU hCG (Profasi; Laboratoires Serono SA, Aubonne, Switzerland) given by intramuscular (IM) injection on days 4, 7, 10, and 13 of the luteal phase with the day of oocyte retrieval nominated as day 0; group 3, P support—50 mg P in oil (Proluton; Schering AG, Berlin, Germany) given by IM injection on days 0, 1, 2, 3, and 4 (i.e., 5 days) beginning in theatre immediately after oocyte retrieval. This regimen follows an implied benefit reported in a previous study,[6] and group 4, combined hCG/P support—combines the aforementioned regimens, i.e., P 50 mg by IM injection days 0 to 4 inclusive followed by hCG 1,000 IU by IM injection days 4, 7, 10, and 13 of the luteal phase.

GIFT Treatment Protocol

All couples considered for assisted reproductive procedures including GIFT completed a full infertility investigation protocol before inclusion. This included a monitored cycle evaluation for ovulation defects; semen analysis; sperm/cervical mucus interaction assessed by a preovulatory postcoital test (PCT) performed in a standard prescribed manner;[14] the routine detection of antispermatozoal antibodies in the serum of both partners as well as the woman's cervical mucus and the man's semen (by immunobead test);[15] and a combined hysteroscopic/laparoscopic appraisal of the woman's pelvis that included dye pertubation of the fallopian tubes.

The 280 cases selected into this trial had completely normal investigations, mild pelvic endometriosis only (revised American Fertility Society classification* grades I or II only) or unexplained poor sperm/mucus interaction. They were therefore categorized as unexplained infertility. Such cases were usually treated by four cycles of ovarian stimulation therapy and, if PCTs were persistently negative, by additional intrauterine insemination of husband's washed, precapacitated spermatozoa[16] before inclusion in the GIFT program.

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* From American Fertility Society: Revised American Fertility Society Classification of Endometriosis. Fertil Steril 43:351, 1985

Table 1 Detailed Summary of GIFT Treatment Cycles With Respect to Oocytes Transferred and Luteal Support Therapy

	Age of patients	Pregnancies	Implantation sacs/oocytes transferred						Pregnancy rate		Implantation rate	
			1	2	3	4	5+	Total	Total	Ongoing	Total	Ongoing
	y											
NIL	30.92 ± 4.11 (22 to 39)	Singleton		5	3	38	5	51	14/51 (27.5)[a]	6/51 (11.8)	16/196 (8.2)	7/196 (3.6)
		ongoing		10	9	152	25	196				
		Twin		1	0	11		12				
		ongoing		0		5		5				
						2		2				
						1		1				
HCG	31.18 ± 4.15 (22 to 39)	Singleton	2	4	8	34	7	55	19/55 (34.6)	14/55 (25.5)	25/209 (12.0)	18/209 (8.6)
		ongoing	2	8	24	136	39	209				
		Twin	0	1	1	8	3	13				
		ongoing		0	1	7	2	10				
					1	4	1	6				
					1	2	1	4				
Proluton	31.18 ± 4.22 (22 to 39)	Singleton	1	3	7	38	1	50	16/50 (32.0)	13/50 (26.0)	24/185 (13.0)	17/185 (9.2)
		ongoing	1	6	21	152	5	185				
		Twin			1	9		10				
		ongoing			2	7		9				
		Quad			1	4		5				
		ongoing			0[b]	4		4				
						1		1				
						0[c]		0				
HCG/Proluton	31.33 ± 4.34 (22 to 39)	Singleton	1	6	9	30	5	51	21/51 (41.2)	15/51 (29.4)	27/187 (14.4)	17/187 (9.1)
		ongoing	1	12	27	120	27	187				
		Twin	0	1	3	10	2	16				
		ongoing		0	2	9	2	13				
		Triplet			1	3		4				
		ongoing			1	1		2				
					0	1		1				
						0[b]		0				

[a] Values in parentheses are percents.

[b] Signifies that pregnancy reverted to singleton after early scans demonstrated twins or triplets. Subsequently categorized with ongoing singleton group.

[c] Scan at 8 weeks showed four clear sacs with embryos but only two ongoing by 16 weeks. Subsequently categorized as ongoing twin.

The protocol for ovarian stimulation involved a set schedule of CC (Clomid; Merrell Dow, French's Forest, NSW Australia) 50 mg twice a day on days 2 to 6 of the cycle and a flexible schedule of hMG (Pergonal, 75 IU hMG/ampule; Laboratoires Serono SA) commencing with two ampules per day on day 3. This was increased every 4th day, if required, up to 6 ampules per day to achieve a continuing E_2 rise (measured daily along with serum LH and P) above a baseline for 6 consecutive days, when an hCG trigger of 10,000 IU was given. In the vast majority of cases, this was day 11 ± 1 of the cycle. Cases were canceled if E_2 failed to reach 1,500 pM and were excluded from the trial if peak E_2 was outside the range of 2,500 to 10,000 pM or an LH surge occurred before the hCG trigger. This trial precedes our current routine of transvaginal US-directed oocyte recovery, hence all cases had laparoscopic aspirations using a double-lumen flushing needle.[17] In all cases, oocytes were graded according to established criteria,[18] and the highest graded oocytes were selected for transfer to the woman within the GIFT treatment cycle. Current protocol firmly dictates that a maximum of three oocytes are transferred (usually into 1 tube), but during the trial period the routine was for four (2 into each tube) and sometimes a fifth, or even a sixth, was transferred, generally in older women and those couples who indicated that only a single attempt was feasible for them. Only clinical pregnancies were recorded in the trial, i.e., those demonstrating a rising β-hCG after day 16 of the luteal phase and the subsequent demonstration of a pregnancy sac(s) on US, performed routinely in the 7th week

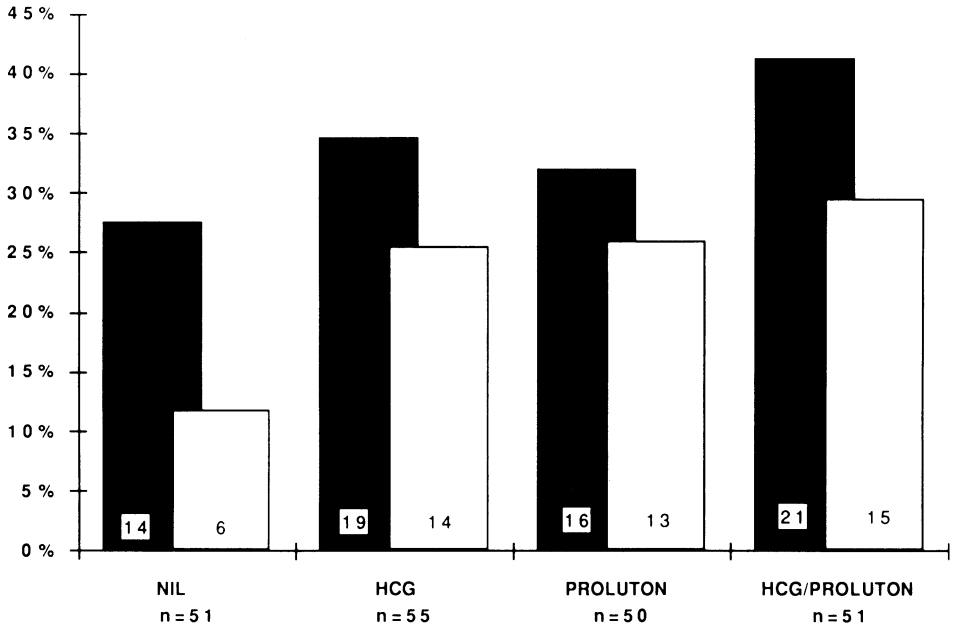

Figure 1 Pregnancy rates and birth rates (>20 weeks) after GIFT procedures with randomized allocation of luteal support regimens. Birth rates were significantly higher for combined treatment groups compared with nontreatment ($P < 0.05$). ■, pregnancy rate; □, birth rate.

or histologically if an ectopic occurred. Pregnancy losses were diagnosed as blighted ovum if a viable fetus was not shown within the sac or spontaneous miscarriage if a viable fetus subsequently was lost before the 20th week. All first trimester pregnancy losses were classified as having single sacs. Those pregnancies progressing beyond 20 weeks were classified as ongoing or births.

Data Handling and Statistics

Case inclusions were decided each day by the research group acting in liaison with the co-ordinating nurse who maintained the register of cases. The trial was continued until at least 50 cases had completed luteal support therapy in each treatment group or a benefit was demonstrated. Pregnancy rates and implantation rates (pregnancy sacs diagnosed per total oocytes transferred) were recorded. Pregnancy outcomes were also determined as well as subcategories of pregnancy wastage. Respective outcomes from each group were compared by χ^2 analyses in contingency tables and Yates correction factor applied where indicated. The age of women was calculated at the date of oocyte retrieval and for each group the mean age ± SD and age range were recorded.

The overall implantation rates and ongoing implantations were further examined within a binomial distribution with respect to the two, presumably independent, variables: uterine receptivity ("U") and embryo viability ("E"). The probability of pregnancy is given by the formula $U(\binom{n}{r})E^r(1 - E)^{n-r}$ where n is the number of embryos transferred and r is the number of embryos implanting.[19–21] Iterative procedures seeking minimum χ^2 values were applied to arrive at the best fit between observed and predicted distributions. This enabled calculations of: (1) the probability that an egg will fertilize and implant and (2) the probability that an egg will fertilize, implant, and continue to an ongoing pregnancy. In the former, a U factor for implantations ("UI"), and in the latter, a U factor for ongoing pregnancies ("UO") was determined by iterative "best fit" procedures for a range of embryo viability factors (0.05 to 0.25).

RESULTS

Of the 280 couples accepted for randomized luteal support therapy, 207 completed their GIFT treatment cycles within the criteria of the trial. The majority of exclusions were from canceled cycles because of poor responses or the occurrence of spontaneous LH surges before the hCG trigger. The comparative groups ranged from 50 to 55 subjects in each and showed very similar profiles with respect to the range and means of the women's ages. A detailed summary of their treatments and outcomes is shown in Table 1. The PRs ranged from 27.5% for nil treatment to 41.2% for the group treated with combined hCG/Proluton, but the differences were not significant. However, the on-

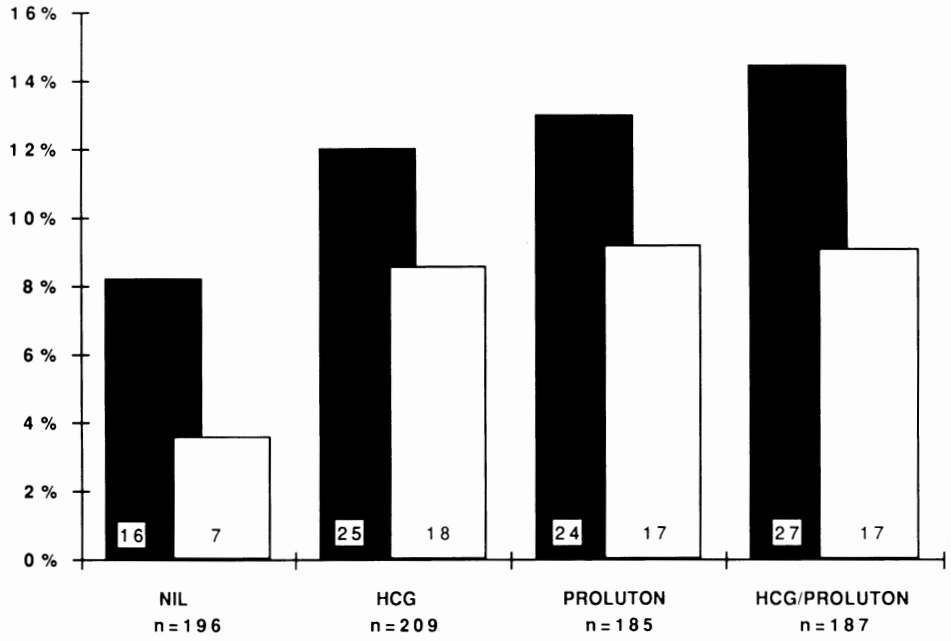

Figure 2 Gestational sacs identified in early pregnancy (implantations) and infants delivered (>20 weeks) after GIFT procedures with randomized allocation of luteal support regimens. Because of limitations of trial size, only borderline significance was reached for luteal support treatment relative to total implantations ($P = 0.07$) but significantly improved the chance of progression to births ($P = 0.02$). ■, implantations; □, infants.

going PR showed a wider variation from 11.8% in the nil treatment group to 29.4% of GIFT treatments supported by hCG/Proluton. This was significant for all groups having luteal support therapy compared with nil support (Fig. 1; $P < 0.05$).

Two of the pregnancies were shown to be multiple on first trimester scans, but subsequent resorption of one sac in a twin and two sacs of a triplet pregnancy meant they were subsequently categorized as ongoing singleton pregnancies. A third multiple pregnancy revealed four gestational sacs containing fetuses with identifiable heart beats at the 8-week scan, but only two were viable at 16 weeks. The pregnancy was subsequently categorized as an ongoing twin pregnancy. In each group, most pregnancy losses were of the blighted ovum category, and there were no unusual patterns of loss, e.g., the number of ectopics in each group ranged from nil (hCG support) to two (none support and Proluton support). Of the 59 infants, there were three congenital abnormalities detected (1 female infant with multiple congenital abnormalities in the none support group and 2 infants with cardiac abnormalities in the Proluton support group). One was a female infant with a patent ductus arteriosis requiring surgery, the other a male infant with hemitruncus and patent ductus requiring surgery.

Similar numbers of oocytes were transferred in each group (185 to 209), further indicating homogeneity among the groups relative to selection criteria. Analysis of the results relative to oocytes implanting (Fig. 2) showed a similar pattern to the pregnancy data. Overall implantation rates ranged from 8.2% of oocytes in the nil support group to 14.4% of oocytes in the group supported by hCG/Proluton. These differences approached statistical significance ($P = 0.07$) for the combined groups receiving luteal support but, assuming the ratios were maintained, the series would have required a further 182 oocytes transferred (25% increase) to have reached the 5% level of significance. Of greater variation was the ongoing implantation rates that ranged from 3.6% in the nil support group to around 9.0% (8.6% to 9.2%) in each of the luteal support treatment groups. There was a significant difference indicating the ongoing implantation rate was better in the combined luteal support groups compared with no treatment ($P = 0.02$).

The expected impact of luteal support treatment in any given program has been calculated relative to the embryo quality E factor. Table 2 shows the best fit UI and UO rates for embryo viability ranging from 5% to 25% of oocytes that covers likely values in assisted reproduction,[21] assuming that approximately 70% to 75% of oocytes will fertilize. These calculations indicate that UI is only marginally improved overall by luteal support therapy (10% to 50%; Fig. 3), but the benefit is maximal when the E factor is lowest and luteal support is by hCG/Proluton (50% improvement). However, a marked improvement in

Table 2 Modeling Technique Using Iterative Procedures Based on Binomial Formula to Show "Best Fit" Relationship Between Embryo Quality E and Uterine Receptivity U From Observed Data

U estimates[a]	Range of values for E factor[b] 0.05	0.1	0.15	0.2	0.25
Nil					
Best UI[c]	1.71	**0.88**	0.64	0.54	0.49
χ^2	4.96	**3.72**	4.22	5.36	6.94
Best UO[d]	0.79	**0.41**	0.30	0.25	0.22
χ^2	2.50	**1.74**	1.90	2.38	3.07
HCG					
Best UI	2.60	1.27	0.85	**0.68**	0.59
χ^2	17.45	6.94	3.88	**3.20**	3.83
Best UO	2.20	0.95	0.64	**0.51**	0.45
χ^2	13.42	5.86	3.67	**3.26**	3.83
Proluton					
Best UI[e]	3.04	1.29	0.83	0.64	**0.54**
χ^2	21.21	9.42	5.22	3.52	**3.11**
Best UO	2.22	0.98	0.65	**0.52**	0.44
χ^2	12.43	5.48	3.29	**2.65**	2.80
HCG/Proluton					
Best UI	4.00	1.53	1.00	**0.79**	0.75
χ^2	27.57	7.68	3.15	**2.30**	3.18
Best UO	2.17	1.07	**0.75**	0.63	0.57
χ^2	7.59	4.30	**4.16**	5.11	6.75

[a] Best estimates based on minimum χ^2 value for difference between observed and predicted pregnancy distribution.
[b] Bold numbers signify optimum E and U factors for observed data.
[c] UI, uterine receptivity factor for all implantations.
[d] UO, uterine receptivity factor for ongoing gestational sacs.
[e] Best fit estimates based on treating quad as twin pregnancy.

UO rates is shown for all luteal support therapies (80% to 250%; Fig. 4), and again this is maximal with hCG/Proluton.

The only significant side effects noted among the women during the study were two cases of ovarian hyperstimulation syndrome requiring hospitalization for 4 and 6 days, respectively. One woman required paracentesis to relieve respiratory embarrassment from ascites. She had hCG/Proluton luteal support (final 2 injections of hCG withheld) and progressed to a singleton, ongoing pregnancy. The other woman had hCG alone for luteal support (final injection withheld) and progressed to a twin, ongoing pregnancy. These cases represent 1.3% of the treated group or 1.9% of those receiving hCG.

DISCUSSION

The data presented indicate a significant benefit for luteal support therapy in GIFT treatment cycles after stimulation by CC/hMG. The benefit is clearly shown relative to ongoing pregnancies and is apparent for individual implantations, particularly those that proceed to births.

As with previously reported studies, absolute clarification of what we suspect to be the full benefits of luteal support is limited by the trial design and the number of patients recruited into the treatment groups. Apart from randomization and a control group, an ideal research trial requires a double-blind method of treatment so that patient and therapist are unaware of the case category. This was not possible to achieve in the study trial given the various treatment methods that were being evaluated. In retrospect, a study comparing hCG/Proluton with nonsupport may have been more valuable but would require both an ethical and a logistic consideration regarding the use of placebo injections for the control group. Although it was intended, we were unable to expand the study after this trial because it proved impossible to achieve unbiased randomization of subjects once the therapists (co-ordinating nurses, medical, and counseling staff) became aware of the benefits in this study.

As indicated in the preamble concerning the trial design, this study focused on those patients receiving infertility treatment by assisted reproduction who were least likely to require luteal support therapy. It attempts to exclude any known or suspected variables that may adversely affect the chance of implantation or development of an implanted conceptus. Furthermore, the trial is set in the GIFT program, which universally has relatively high and stable PRs without luteal support. It considers only those cases having ovarian stimulation by a regimen (CC/hMG) that is not associated with evidence of luteal deficiency. The rationale for applying the selection criteria described was twofold. First, it reduces the effects of confounding variables that would otherwise require an enormously large series to cover for the appropriate case matches, and second, it enables any conclusions regarding benefits of therapy to be extrapolated as being of greater relevance when luteal disorders may be suspected.

From the above comments, we believe this trial establishes the case for luteal support therapy, which should therefore be considered as a routine in all assisted reproduction programs. The benefits will be most marked in those circumstances in which the E factor is lower (Figs. 3 and 4), and although treatment may not be necessary in many

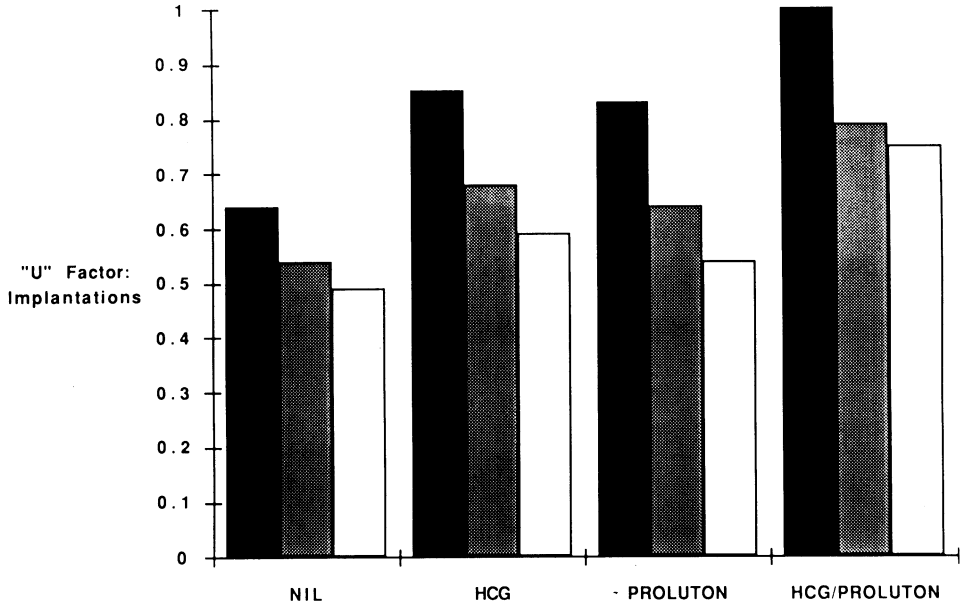

Figure 3 Uterine receptivity levels (U) for all implantations set against various embryo quality levels (E). Applies best fit from observed data to show the probability that an egg will fertilize and implant. E Factor: ■, 0.15; □, 0.2; and □, 0.25.

cases if the E factor is very high, the treatment does not appear to cause any adverse effects such as early embryo wastage or congenital abnormalities. On the contrary, pregnancy wastage was significantly lower with luteal support. The two infants with cardiac abnormalities from the Proluton group can be added to a total series of 290 infants delivered to the end of 1989 at PIVET after Proluton in the luteal phase without any further cases of cardiac abnormalities. However, the two cases of ovarian hyperstimulation therapy raise the question of a possible adverse effect of luteal support therapy. The common factor was hCG, but the incidence was not higher than that expected among patients receiving hMG for ovarian stimulation[22] nor was it a statistically significant observation. However, from an extensive clinical experience, the protocol of management for ovarian hyperstimulation syndrome includes the withholding of hCG because abdominal girth measurements of the women and other clinical features show an immediate worsening of the condition after the hormone is injected (within hours). On the positive side, the majority of patients (>75%) developing the condi-

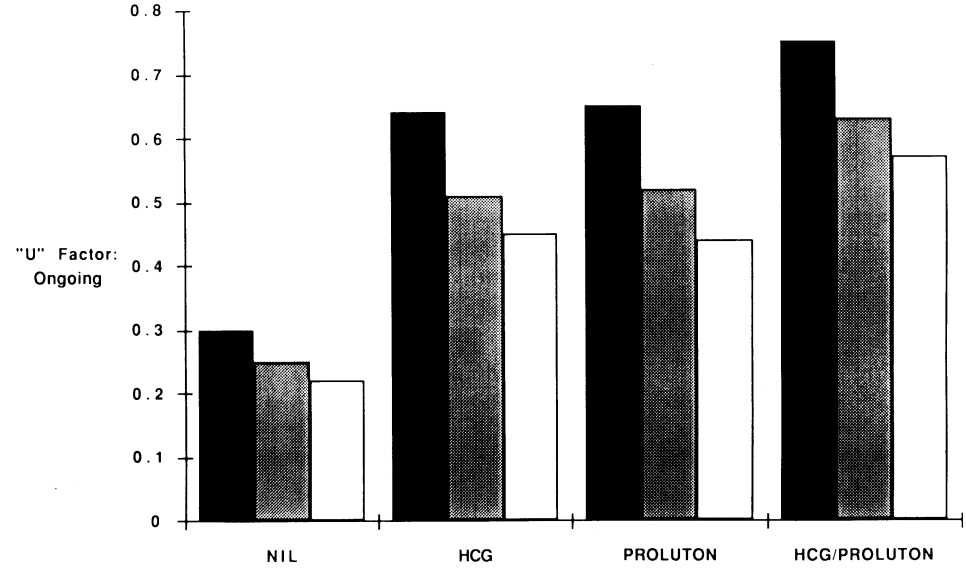

Figure 4 Uterine receptivity levels (U) for ongoing implantations set against various embryo quality levels (E). Applies best fit from observed data to show the probability that an egg will fertilize, implant, and subsequently proceed to the delivery of an infant (>20 weeks). E factor: ■, 0.15; □, 0.2; □, 0.25.

tion have progressed into clinical pregnancy,[23] suggesting some factor from the implanting embryo may be responsible.

The modeling technique using iterative procedures based on the binomial formula provided two interesting extrapolations from the observed data. First, it demonstrated the relationship between embryo quality and uterine receptivity in a manner that enabled the relevance of luteal support to be seen in perspective. That is, the poorer the quality of the embryo, the greater the benefit of improvements in uterine receptivity. This is best shown in Figures 3 and 4. Second, there appears to be an interdependence of uterine receptivity to embryo quality. From Table 2, it can be seen that the optimum U and E factors (shown in bold numerals) both tended to be high when the outcome was best and both were low when the outcome was poorest. This latter observation assumes the mean embryo quality was similar in all groups before the embryos reaching the uterus. It was not possible to measure embryo quality in this trial, but it was designed to exclude every known bias. We therefore believe the observation to be real and that it supports the concept of preimplantation embryo-endometrial interactions whereby quality factors in one can benefit the other and vice versa.

The study does not enable conclusions to be drawn regarding the best regimen of luteal support, but we believe the hCG/Proluton regimen provides the optimum cover during the luteal phase and this is apparent from the results. The regimen is now incorporated as a routine at PIVET and is a contributing factor to the higher pregnancy and live-birth rates recorded overall during 1988 and 1989. Of 212 GIFT transfers during that period, 88 pregnancies arose (41.5%) and 57 (26.9%) proceeded through to birth. It is also applied routinely in all IVF-related treatments and during the same period 166 pregnancies arose after 566 embryo transfer procedures (29.3%) with 111 (19.6%) proceeding to births. These results are a significant improvement on our own data from the years preceding this trial and from that reported nationally in Australia.[24] Although other beneficial factors have been identified,[25] luteal support therapy is believed to be a major contributor to the improvement.

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