Outcome comparison of in vitro fertilization treatment with highly purified subcutaneous follicle-stimulating hormone (Fertinex, a urofollitropin) versus intramuscular menotropins

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OBJECTIVE: The aim of this study was to investigate various outcome measures of stimulation with highly purified subcutaneous follicle-stimulating hormone (Fertinex, a urofollitropin) compared with first- and second-generation urinary human menopausal gonadotropin standards (Pergonal, Metrodin).

STUDY DESIGN: Retrospective analysis was restricted to our most efficient in vitro fertilization age group (23-34 years). Data from Institute for Assisted Reproduction in vitro fertilization cycles 1 through 11 with Pergonal, Metrodin, or both were tabulated for hormonal values, oocyte quality, and embryo outcome as baseline data. Patients in cycles 12 through 13 were treated with Fertinex and Pergonal or Fertinex alone and then reviewed for the same parameters.

RESULTS: Two hundred thirty-eight in vitro fertilization records with embryo transfer were analyzed. Clinical pregnancy rates per embryo transfer in an optimal age group were similar despite use of first- through third-generation urinary gonadotropin preparations: Pergonal and Metrodin, 67%; Metrodin, 64%; Fertinex and Pergonal, 62%; and Fertinex, 54%. There were no discernible differences in hormonal response, oocyte recovery, or embryonic growth.

CONCLUSION: Administered subcutaneously, the third-generation urinary gonadotropin preparation Fertinex is effective in in vitro fertilization treatment in young women. (Am J Obstet Gynecol 1998;179:299-307.)

Key words: In vitro fertilization, third-generation menotropin

In 1961 human menopausal gonadotropins (hMGs) in conjunction with human chorionic gonadotropin were shown to induce ovulation, with resultant pregnancy and delivery. These hMG preparations, which contained both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), were only 5% pure.[1] In the 1980s protocols with pharmacologic doses of hMG were developed to obtain multiple follicular growth yielding sufficient eggs for in vitro fertilization (IVF). With polyvalent antibodies, a relatively pure FSH extract (Metrodin) was developed but still contained 95% urinary protein. More recently, specific monoclonal antibodies have been used to selectively bind FSH in the urinary bulk material, producing a highly purified FSH preparation (Fertinex, a urofollitropin) with <0.1 IU LH/75 IU FSH and <5% urinary protein.

IVF at the Institute for Assisted Reproduction in Charlotte, North Carolina, has maintained consistent clinical pregnancy rates through the transition from a urinary hMG preparation (Pergonal) to a urofollitropin preparation (Metrodin) for women ≤34 years old with or without intracytoplasmic sperm injection. Our infertility practice had previously used subcutaneous Fertinex in controlled ovarian hyperstimulation and intrauterine insemination cycles without apparent change in pregnancy rates. In our practice subcutaneous administration of Fertinex was preferred by most patients who had previously received intramuscular preparations. Concern that the change in hormonal stimulation might have adversely affected egg quality and IVF outcome prompted this retrospective review.

Studies comparing first- and second-generation intramuscular urinary gonadotropin preparations[2-4] show no disadvantages of relatively LH-free products. Reports of the effectiveness of highly purified urinary FSH in IVF[5-9] have come from European centers, where legislation regulates embryo use after reduced-dosage stimulation protocols more than at our center.

Estradiol levels have been used as an endocrine marker of follicular development in IVF. When recombinant FSH preparations with no LH concentration are used after down-regulation, LH levels may be suboptimal to drive thecal androgen synthesis.[10] Estradiol levels have been reported to be higher during the first 7 days of stimulation with intramuscular hMG than with subcutaneous

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highly purified urinary FSH.[6, 9] Such differences might alter step-down stimulation. Westergaard et al[6] demonstrated greater FSH concentration across the follicular phase with subcutaneous highly purified urinary FSH than with intramuscular hMG. Fleming et al[9] then found significantly higher circulating concentrations of FSH with subcutaneous highly purified urinary FSH than with intramuscular highly purified urinary FSH.

A recent American report[11] in a small series found improved egg quality and IVF outcome with Fertinex administration, despite reduced cytoplasmic maturation. A Swiss report[8] concluded that a highly purified urinary FSH protocol synchronizes oocyte maturation better than does hMG. The objective of this study was to analyze retrospective data comparing highly purified subcutaneous monoclonal derived FSH (Fertinex) with various intramuscular gonadotropins.

Material and methods

Between January 1, 1995 and September 15, 1997, 279 patients between 23 and 34 years old initiated IVF treatment at the Institute for Assisted Reproduction. This group represented 48% of cycle 1 through 13 starts. Infertility factors included tubal factor, male factor, endometriosis, and unexplained infertility. All factors other than these 4 were categorized as unexplained because of small subgroups.

Male factor selection for intracytoplasmic sperm injection was made if any of the following criteria were met: Kruger strict-criteria morphologic characteristics ≤3% normal forms, 24-hour sperm motility at 37°C <20%, antisperm antibody level by direct Immunobead (Irvine Scientific, Santa Ana, Calif) testing was ≥80%, or total motile sperm population was <1 million. Intracytoplasmic sperm injection was also performed when couples had previous failure of conventional fertilization at other centers despite normal seminal parameters.

Ovarian reserve assessment was performed in screening cycles by determination of day 3 FSH (Immulite, DPC Cirrus Inc, Diagnostic Products Corporation, Randolph, NJ) values and ultrasonographic vaginal probe (EUB-405 6.5 MHz; Hitachi Instruments Inc, Danbury, Conn) assessment of visible ovarian follicles <10 mm. Patients were excluded from this protocol if basal FSH values were >10, screening follicle count was <6, or the patient had previous poor response to gonadotropin stimulation. Such patients were treated with a microdose flare[12] leuprolide acetate (Lupron) and high-dose gonadotropin protocol or with donor-egg IVF as appropriate.

All patients gave written informed consent to use these Food and Drug Administration–approved drugs for an appropriate indication: IVF, intracytoplasmic sperm injection, coculture, and assisted hatching. These consent documents had been approved by the Presbyterian Hospital Institutional Review Board.

All patients included in this report had luteal phase down-regulation for 10 days with subcutaneous Lupron; the gonadotropin-releasing hormone agonist dosage was decreased by 50% at the start of gonadotropin stimulation.

Three hMG products were used during the 2.5-year period, Pergonal, Metrodin, and Fertinex. Their selection paralleled the change in availability of gonadotropins from the manufacturer (Serono Laboratories, Inc, Norwell, Mass) during this time. Lot variations were not controlled. Mixing and administration followed Serono Laboratories recommendations.

Before stimulation ovarian inactivity was confirmed according to the following criteria: endometrial thickness <5 mm, no ovarian cyst >3 cm, and a serum estradiol value <50 pg/mL. For all the follicular stimulation protocols a step-down controlled ovarian hyperstimulation regimen was initiated with 4 ampules of the gonadotropin type or a combination thereof. In all instances dosage was reduced to 3 ampules when estradiol levels were >200 to 250 pg/mL and was maintained at 2 ampules/d when the mean diameter of the lead follicle was 14 mm. In the Fertinex-Pergonal combination stimulation group, Pergonal was deleted when the mean diameter of the lead follicle was 14 mm. Similarly, Metrodin was deleted from the Pergonal-Metrodin group once the aforementioned follicular criteria were achieved. Human chorionic gonadotropin (Profasi) at 10,000 U was administered 36 hours before oocyte retrieval when ≥2 follicles had achieved a mean diameter of 16 to 18 mm. Embryo transfer was performed under abdominal ultrasonographic guidance (GE RT-3200, 5 MHz; GE Medical Systems, Waukeesha, Wis) with a Wallace (Marlow Surgical Technologies, Inc, Willoughby, Ohio) catheter. Additional luteal-phase support was provided through intramuscular injection of 50 mg progesterone in oil starting the day of oocyte retrieval.

Oocytes were placed into microdroplets (30 to 50 μL) of human tubal fluid culture medium supplemented with 6% human serum albumin (Plasmanate; Cutter Biological, Miles, Inc, Covina, Calif). After 4 to 6 hours oocytes were inseminated in microdroplets containing concentrations of 100,000 to 300,000 sperm cells/mL. If clinically pertinent, cumulus cells were enzymatically removed and intracytoplasmic sperm injection was performed, as previously described by Palermo et al.[13] Oocytes were considered dysmorphic if the following observations or characteristics were observed: presence of vacuoles, lack of cytoplasmic integrity within the body of the oocyte (loose center), grainy or contracted cytoplasm, and the presence of refractile bodies or inclusions.

In our laboratory embryos are routinely cultured by 1 of 2 methods. In most instances embryos are cultured in petri dishes containing microdroplets (30 to 50 μL) of

Table I. Evolution of urinary gonadotropin preparations

Name	*Technique*	*Nonspecific protein (%)*	*LH (IU)*
Pergonal	Extraction	95	75
Metrodin	Polyvalent antibody	95	1
Fertinex	Monoclonal antibody	<5	0.1

Table II. Patient inclusion data

Patient demographics	*Pergonal and Metrodin*	*Metrodin alone*	*Fertinex and Pergonal*	*Fertinex alone*
No.	55	119	21	43
Age (y)				
Mean	30.8	30.5	32	30.8
Range	23–34	23–34	29–34	27–34
Infertility factor (%)				
Tubal	40	40	38	21
Male	29	29	10	36
Endometriosis	15	8	24	17
Unexplained	16	23	28	26

human tubal fluid covered with equilibrated paraffin oil. This human tubal fluid is supplemented with 15% maternal serum. In some instances cultures are performed on partial monolayers of bovine oviductal cells with serum-supplemented human tubal fluid. Patient selection criteria and procedures for coculture have been previously described in detail by Wiemer et al.[14, 15]

Regardless of culture technique used, embryos remained in culture for 48 to 52 hours. On the morning of day 3 (day 0 was the day of oocyte retrieval), embryos were individually assessed for morphologic qualities. All embryos had zona measurements to determine whether assisted hatching was indicated. This zona drilling procedure has previously been described in detail by both Cohen et al[16] and Wiemer et al.[14] The number of embryos selected for transfer was based on morphologic criteria. Additional factors, such as duration and cause of infertility, were used to guide embryo replacement number.

Outcomes were grouped by stimulation protocol and subgrouped by intracytoplasmic sperm injection or IVF. Stimulation characteristics of Pergonal and Metrodin, Metrodin only, Fertinex and Pergonal, and Fertinex only were assessed. Response was evaluated by total gonadotropin dose, duration of stimulation, estradiol level on the day of first dosage reduction, estradiol level on the day of human chorionic gonadotropin administration, and cancellation rate. Oocyte quality was evaluated by determining the mean number of oocytes retrieved and the percentage of mature (according to gross morphologic evaluation). In addition, fertilization rates and frequency of dysmorphic oocyte characteristics, as previously described, were established. Resulting embryos were graded according to number of blastomeres and level of fragmentation present at the time of replacement. The mean number of embryos transferred, clinical pregnancy rate, and implantation rate for each treatment group were established. Frequency of multiple pregnancies with more than twins was determined.

FSH and estradiol were measured by chemiluminescent enzyme immunoassay (Immulite; DPC). The sensitivity of the FSH assay was 0.1 mIU/mL. The intra-assay and interassay coefficients of variation were 6.4% and 7.5%, respectively. The estradiol assay had a sensitivity of 12 pg/mL; intra-assay and interassay coefficients of variation were 9.3% and 10.6%, respectively. Clinical pregnancy was defined as the presence of a gestational sac with a visualized yolk sac between 3.5 and 4 weeks after embryo transfer.

Sample size calculations were based on the number of patients achieving a clinical pregnancy after embryo transfer. Our established rate for cycles 1 through 11 was 65%; European reports[6-10] with highly purified urinary FSH listed rates of approximately 30%. Assuming Fertinex is 20% less effective, on the basis of a type I error of 0.05% and a type II error of 0.2%, a sample size of 36 patients would be needed for a 2-tailed test with unpaired data.

The data were analyzed comparing the 2 intramuscular protocols, Pergonal with or without Metrodin versus Fertinex alone; the combination protocol of Fertinex and Pergonal was then compared with Fertinex alone. Means of various outcomes were compared with the z test.[17] Pregnancy rate data were analyzed with the χ^2 test (Kwikstat; Texasoft, Cedar Hill, Texas). Differences with $P < .05$ were considered to be significant.

Table III. Controlled ovarian hyperstimulation response

Criterion	*Pergonal and Metrodin (mean ± SEM)*	*Metrodin alone (mean ± SEM)*	*Fertinex and Pergonal (mean ± SEM)*	*Fertinex alone (mean ± SEM)*
Dose total (ampules)	30	31	30	34
Duration (d)				
Day of first dose reduction*	4.6 ± 1.69	5.0 ± 1.88	4.9 ± 1.31	5.4 ± 1.7
Day of human chorionic gonadotropin*	9.7 ± 0.98	9.4 ± 1.27	9.5 ± 1.26	9.9 ± 1.99
Estradiol (pg/mL)				
Day of first dose reduction	276	385	379	391
Day of human chorionic gonadotropin	2446	2001	2500	2494
Cancellation rate (%)	15	10	16	14

*Intramuscular medication alone versus subcutaneous Fertinex alone, not significant; Fertinex and Pergonal versus Fertinex alone, not significant.

Table IV. Oocyte quality after 4 controlled ovarian hyperstimulation protocols

Criterion	*Pergonal and Metrodin*	*Metrodin alone*	*Fertinex and Pergonal*	*Fertinex alone*
No./retrieval (mean ± SEM)				
TOTAL*	13.6 ± 5.77	13.7 ± 6.41	16.0 ± 9.84	16.7 ± 9.71
Mature (intracytoplasmic sperm† injection only)	12.5 ± 4.62	10.3 ± 4.95	11.7 ± 6.25	11.9 ± 5.80
Fertilization rate after intracytoplasmic sperm injection† (%)	67	69	68	71
Mature oocytes dysmorphic at intracytoplasmic sperm injection*				
No.	61/236	163/654	50/115	162/375
%	26	25	43	43

*Intramuscular medication alone versus subcutaneous Fertinex alone, $P < .001$; Fertinex and Pergonal versus Fertinex alone, not significant.
†Intramuscular versus subcutaneous or Fertinex and Pergonal versus Fertinex alone, not significant.

Results

Overall the clinical pregnancy rate per embryo transfer for patients undergoing IVF at the Institute for Assisted Reproduction in Charlotte, NC, from January 1, 1995, to September 15, 1997, in women between 23 and 34 old was 63% (149 pregnancies among 238 transfers). In concept, the controlled ovarian hyperstimulation protocol for this age group did not change during this period; however, the urinary gonadotropin preparations available from Serono Laboratories did change. Table I presents the first- through third-generation evolution of menotropins.

Table II is an overview of patient demographics. The mean age of treated patients was 30.8 years. Seventy-five percent of patients were in their first IVF attempt. Metrodin alone was the most common gonadotropin used in 1995 and 1996. Combinations of new and older preparations were selected as each new generation of drug was marketed. One third of the patients during the transition from Pergonal to Metrodin received a combination of both drugs; a similar percentage of patients were treated with both Fertinex and Pergonal when Fertinex was first released. The 2 most common causes of infertility treated were tubal factor (36%, 86/238) and male factor (29%, 69/238).

As presented in Table III, the total dose, duration of treatment, peak estradiol level, and cycle cancellation rate appear similar with the 3 gonadotropin preparations or combinations.

Oocyte quality is reviewed in Table IV. We increased our average total recovery of eggs in 1997; however, the number mature at intracytoplasmic sperm injection did not change with any of the gonadotropin protocols. Fertilization rates were consistent. Dysmorphic eggs were found more often in subcutaneous Fertinex cycles.

Table V addresses embryo quality and transfer efficiency. The mean number of embryos transferred ranged from 3.7 for Pergonal and Metrodin to 4.3 for Fertinex and Pergonal. Any difference in embryo performance needs correlation with patient categories, as noted in Table II; Pergonal with Metrodin and Metrodin alone have 31% endometriosis or unexplained infertility; these 2 diagnoses were increased with Fertinex with Pergonal (52%) and Fertinex alone (43%). Our historically most favorable group is that with tubal factor; the Fertinex groups thus had more patients with poor prog-

Table V. Embryo evaluation after 4 controlled ovarian hyperstimulation protocols

Criteria	*Pergonal and Metrodin*	*Metrodin alone*	*Fertinex and Pergonal*	*Fertinex alone*
No. of embryos transferred* (mean ± SEM)	3.7 ± 0.99	3.8 ± 0.99	4.3 ± 1.42	4.1 ± 1.09
Mean blastomeres or embryos	8.4	8.4	8.8	8.6
Mean fragmentation rate* (%)	7.0	7.3	9.2	7.7
Implantation rate* (%)	30	32	23	26

*Intramuscular versus subcutaneous or Fertinex and Pergonal versus Fertinex alone, not significant.

Table VI. Pregnancy rates per embryo transfer

Outcome measured	*Pergonal and Metrodin*	*Metrodin alone*	*Fertinex and Pergonal*	*Fertinex alone*
Clinical pregnancy (%)				
Overall*	67	64	62	54
Intracytoplasmic sperm injection*	63	63	60	59
No. of multiple pregnancies (more than twins)	4	21	3	6
Number of clinical pregnancies	37	76	12	22
Patients delivered†				
No.	29/53	65/110	NA	NA
%	55	59	NA	NA
No. of singletons	15	33	NA	NA
No. of twins	10	24	NA	NA
No. of triplets	4	6	NA	NA
No. of quadruplets	0	2	NA	NA
No. of multiple reductions	1	0	NA	NA

*Intramuscular medication alone versus subcutaneous Fertinex alone, not significant; Fertinex and Pergonal versus Fertinex alone, not significant.
†Cycles 1 through 10, proportion of transfers.

noses. Couples undergoing IVF for the first time had the same success rate (62%, 116/187) as patients undergoing repeated IVF (65%, 32/49) from our programs and others. Patients treated with coculture had a 65% clinical pregnancy rate (90/138), compared with a 60% rate (61/100) for conventional culture. Patients undergoing intracytoplasmic sperm injection fertilization had a 62% clinical pregnancy rate (78/126), compared with a 63% rate (73/112) for standard insemination.

Table VI presents pregnancy rates per embryo transfer by clinical pregnancy rate for cycles 1 through 13 and patients delivered of infants for cycles 1 through 10. Overall, transfer of ≤3 embryos resulted in a clinical pregnancy rate of 58% (51/88), compared with 65% (98/150) for ≥4 embryos. Clinical pregnancy rate rates across the stimulation protocols (intramuscular or subcutaneous) for ≤3 embryos did not differ ($P \geq .510$).

Multiple pregnancies with more than twins occurred in 23% of successful transfers (35/149). Couples who had transfers of ≤3 embryos had 6 triplet pregnancies and 1 quadruplet pregnancy. With ≥4 embryos transferred there were 20 triplet pregnancies and 8 quadruplet pregnancies.

Conception occurred for 3 of 6 couples who requested day 5 embryo transfer limited to 2 or 3 blastocysts in an effort to avoid a multiple pregnancy. Of interest, we noted that 11 of 16 couples (7% of this age group) with supernumerary embryos cocultured to blastocysts that were appropriate for clinical cryopreservation had a clinical pregnancy rate of 69% after day 3 transfer.

Comment

Success of IVF depends on multiple variables. An age-related decline in fertility is apparent with all infertility therapies. Aneuploidy is increased in unfertilized oocytes in older women.[18] The meiotic spindle in 79% of oocytes in natural cycles of women between 40 and 45 years old show chromosome displacement from the metaphase plate during second meiotic division, compared with 17% in younger women, between 20 and 25 years old.[19] Oocyte chromosome degeneration, characterized by chromosomes splitting into unassociated chromatids, was found in 24% of failed fertilization oocytes in women ≤34 years old, 52% in women between 35 and 39 years old, and 96% in women ≥40 years old.[20] As a result of this information, we decided to reduce the influence of age-related oocyte decline in assessing controlled ovarian hyperstimulation response when comparing subcutaneous Fertinex with the traditional intramuscular menotropins by selecting an optimal pregnancy rate age group ≤34 years old.

A luteal-phase gonadotropin-releasing hormone ana-

log down regulation followed by moderate dose step-down gonadotropin protocol is efficient in properly screened young women. An early report[21] of a step-down regimen comparing Pergonal with Pergonal and Metrodin without Lupron pretreatment found increased success with FSH enrichment of the then-standard Pergonal therapy. We found no significant differences in total dosage, duration of therapy, estradiol level, and cancellation rate with phasing out of Pergonal (Fertinex and Pergonal), phasing out of Metrodin (Pergonal and Metrodin), Metrodin only, or Fertinex only. We believe that stimulation success depends on routine ovarian reserve screening and adequate gonadotropin starting dosage. Typical oocyte recovery with a starting low dose (2 or 3 ampules) ranges from 3 to 9 oocytes[2, 4, 10]; moderate dosage, similar to that we use, yields between 9 and 12 oocytes per retrieval.[3, 7] This parallels our yield of between 13 and 16 oocytes/retrieval in 2.5 years.

Maturity of oocytes after retrieval can be estimated by rate of cumulus expansion. However, a more precise evaluation of nuclear maturity is possible after cumulus removal. Dark oocyte cytoplasm was more frequent in hMG-treated patients than in those treated with highly purified urinary FSH,[8] but no other differences were noted in the frequency of cytoplasmic anomalies and granulations. Oocyte anomalies at the time of intracytoplasmic sperm injection have been reported to decrease in conjunction with increased ongoing pregnancy rates with Fertinex only[11] compared with the combinations of Pergonal and Metrodin or Pergonal and Fertinex. We found a significant difference in dysmorphic oocytes at the time of performing intracytoplasmic sperm injection with the Fertinex stimulation protocols. However, pregnancy rates did not appear to be compromised by these morphologic abnormalities.

Fertilization rates in comparative trials[8, 11] of subcutaneous highly purified urinary FSH alone versus intramuscular preparations were 75% with the highly purified urinary FSH group and 69% for the intramuscular groups. We found no difference in intracytoplasmic sperm injection fertilization rates across the 4 stimulation protocols reviewed.

Pregnancy rates with a subcutaneous highly purified urinary FSH[4-8] ranged from 19% to 41%, with a mean of 28%, when transferring 2 or 3 embryos. With an intramuscular protocol, pregnancy rates in those same reports ranged from 16% to 38% with a mean of 24%. Our overall clinical pregnancy rate per transfer for this age group ≤34 years old was 63%. No statistical difference in rates were seen with subcutaneous Fertinex; however, a trend toward lower numbers warrants reassessment as additional cases are completed with Fertinex only.

One of the risks of this level of success is high-order multiple pregnancy. Limiting embryo transfer to 3 embryos in this age group was suggested at the Fifty-ninth Annual Meeting of The South Atlantic Association of Obstetricians and Gynecologists last year.[22] Day 3 transfer of ≤3 embryos reduced our clinical pregnancy rate to 58% and decreased the high-order multiple rates to 14%. Blastocyst transfer of 2 or 3 embryos after "optimized" culture conditions results in a 38% ongoing pregnancy rate.[23] However, only 55% of those patients had embryos develop to the blastocyst stage. In our program progression of supernumerary embryos on coculture to cryopreservation for later clinical use was correlated with day 3 embryo transfer success. Fresh blastocyst transfer (2 or 3 embryos) was inferior to day 3 transfer of ≥4 embryos but did not result in high-order multiple pregnancy in a limited number of patients. Culture techniques will require improvement before blastocyst use can routinely offer optimal pregnancy rates without high-order multiple pregnancy.

Recombinant FSH was offered on the US market in October 1997 by 2 pharmaceutical firms (Organon Inc, West Orange, NJ; Serono Laboratories, Inc, Norwell, Mass). Recombinant FSH was said to be more potent than Metrodin[10, 24] or highly purified urinary FSH in oocyte recovery.[25] We anticipate studies similar to this report on Fertinex will demonstrate the IVF effectiveness of the recombinant products; urinary gonadotropins will then be of historical interest only.

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Discussion

Dr Barry S. Verkauf, Tampa, Florida. Dr Crain and associates compared highly purified urinary FSH, in the form of Fertinex, with earlier urinary gonadotropin products, marketed as Pergonal and Metrodin, that were less pure with respect to the presence of LH and urinary protein. They did this as a consequence of changing market conditions and product availability during a 21-month interval. Although retrospective in nature, this study design is quite crisp. Other than the drug used, widely accepted clinical methods during that interval were held constant. The group wisely limited observations to an optimized group of younger patients among whom pregnancy rates are known to be better, thus increasing the efficiency of data extraction. Observations were made on a number of important issues related to the stimulation outcome itself (total drug dosage, duration of treatment, peak estradiol levels, and cancellation rates), oocyte quality, fertilization rates, and pregnancy rates. They compared outcomes according to etiologic groups; they also compared subgroups who underwent coculture with those undergoing traditional culture techniques and compared those undergoing intracytoplasmic sperm injection with those undergoing standard insemination. They applied statistical methods not only to compare differences but to ascertain the number of patients required for the comparisons to be of appropriate power. With the exception of the number of oocytes retrieved and the number of dysmorphic oocytes at intracytoplasmic sperm injection with Fertinex alone, no statistically significant differences were found in any comparative outcome categories as a consequence of stimulation with any of these first-, second-, or third-generation hMG products or combinations. From the practical outlook of the patient, pregnancy rates were similar.

Dr Crain, I have 4 questions regarding the study. (1) Were patients who underwent assisted hatching or 5-day transfers equally distributed among all groups? (2) Were responses in patient groups controlled for weight or body mass index? (3) How did you select patients for coculture? (4) To what do you attribute the higher proportion of oocytes retrieved with subcutaneous Fertinex compared with intramuscular Pergonal, Metrodin, or both?

In closing, there was reference to even newer gonadotropin products. Recently available on the market are Gonal F and Follistim, produced by recombinant gene technology. If new preparations are already available, are Dr Crain and associates' observations passé? I think not. According to data in this article, Dr Crain and associates perform in vitro fertilization in almost 300 patients/y and have done so for some time, with admirable success rates. Their current conclusions regarding their past observations could foretell the future!

A pharmaceutical representative came to my office to discuss his new recombinant product and gave me a report that included a picture of an elderly nun shaking hands with the gentleman who picks up her urine collection bottles. I inferred Dr Crain's closing statement, "Urinary gonadotropins will then be of historical interest only." I remember having ambivalent feelings recognizing this as another example of the relentless trend of scientific technologic advance replacing human interaction and collaboration of the past. However, crisp intellectual analysis takes precedence over nostalgia. The pharma-

ceutical representative pointed out that changing technology has resulted in reduction of nonspecific proteins, theoretically reducing the risk of allergic responses. It has also resulted in reduction of contaminating LH that some believe to reduce oocyte quality and limit fertilization and live births. In addition, recombinant deoxyribonucleic acid technology has the advantages of unlimited supply of product through a different and perhaps simpler, more efficient process.

Clearly, new biotechnologic methods will improve our world in many important ways. However, today in medicine and certainly as far as I can see into the future, cost will be a fourth dimension that physicians will hear about in addition to the classic triad of patient care, teaching, and research.

If we are to embrace a new product, it should add value to what we do for our patients. In economic terms, *value* is defined as quality divided by cost. Quality is usually associated with improved satisfaction or a more desirable outcome. Value can be enhanced by improving quality, lowering cost, or—the best of both worlds—combining better quality with lower cost.

Controlled pharmacokinetic studies suggest that the new recombinant FSH products will behave similarly to earlier ones.[1] If I read the recent literature correctly, like Dr Crain's study early reports regarding recombinant gonadotropins suggest that in terms of pregnancy rates they are certainly as good as, but probably not significantly better than, earlier products used for years. However, a recent article applying the statistical method of meta-analysis concluded that recombinant FSH has superior—though not dramatically so—pregnancy rates, particularly when pregnancies from subsequent frozen embryo replacements derived from that cycle are included.[2] Time will tell.

Although recombinant products are more pure and may therefore be useful in patients hypersensitive to urinary gonadotropins or other urinary protein, such patients are quite uncommon. Urinary gonadotropins are bioequivalent by the subcutaneous and intramuscular routes,[3] and recombinant FSH has been found to be not only equally efficacious but also similarly tolerated from the point of view of symptoms when given either subcutaneously or intramuscularly.[4]

If various gonadotropin preparations are similarly tolerated and pregnancy rates do not really differ significantly, if new products are not provided to us and our patients with easier access and at cheaper price, where is the value added? In the Tampa Bay, Fla, area, whether bought singly or in bulk, at nationwide chains or independent pharmacies, new products (with the exception of recently introduced generic equivalents) have consistently increased rather than decreased in cost. We surveyed all patients in our IVF program during the past year who have experience with both subcutaneous and intramuscular gonadotropins and, like Dr Crain and associates' patients, almost all preferred the subcutaneous route. But if the expectancy of pregnancy were the same, none would be willing to pay more than a 10% premium for the simplicity of subcutaneous access (Verkauf BS, Bernhisel MA, Tarantino S. Unpublished observations, 1997.).

Are we looking in the right place? Like most physicians who frequently stimulate ovulation, I have been puzzled, humbled, and on occasion defeated by patients with either poor response to gonadotropin stimulation (chronic poor responders) or variable and unpredictable response. This leads me in closing to add another observation and ask an additional question of Dr Crain. First, perhaps the advantage of recombinant technology, offering highly reproducible, highly specific, and highly purified gonadotropins, will eliminate a variable, allowing better focus on other areas of research, implied by Dr Crain's reference to screening for ovarian reserve, into intraovarian and endometrial factors in our quest to find the reproductive endocrinologist's "holy grail"—a pregnancy at the end of every stimulation. Finally, it is frustrating that it takes so long for clinical answers to come into clear perspective. It may be true that multiple investigators working independently at distant sites better elucidate population dissimilarities and through differing perspectives lead to more unique breakthroughs in research. Dr Crain, I congratulate you on your intellectual curiosity and the effort expended in relating the results of a well-done study to us today, but I wonder whether you agree that in a medical world with increasingly limited resources future research will be best served by large, collaborative studies allowing even greater statistical power marshaled across shorter periods of time, giving clinicians quicker access to information approximating scientific truth to apply to our patients' needs?

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Dr. Crain (Closing). The technique of assisted hatching was equally distributed among all treatment groups. Day 5 blastocyst transfers were offered only to 2 groups of patients: (1) those who for personal reasons would

not consider an elective fetal reduction procedure under any circumstance and (2) those who had uterine abnormalities related to diethylstilbestrol exposure, multiple intramural uterine myomas, or unicornous uterine cavity.

We did not control patient assignment for body weight. Patients who weighed ≥200 lb receiving intramuscular medication used 2-inch 21-gauge needles for injection. Obese patients treated with the subcutaneous preparation were treated in the same fashion as slender patients.

Patients were selected for coculture in this age group if they had (1) previous IVF failure associated with poor embryo quality, (2) baseline FSH values >7.2 (by Immulite), (3) either polycystic ovary syndrome with estradiol level >5000 pg/mL on the day of human chorionic gonadotropin or ≥20 oocytes at retrieval, or both, and (4) blastocyst transfer.

We believe that the increased number of oocytes retrieved in 1997 was a reflection of increased retrieval experience in 3 years. A small number of patients treated in 1997 with intramuscular medications had more eggs retrieved than with similar preparations in 1995. The numbers of mature oocytes retrieved remained similar across the 3 years and the 3 drug preparations. We cited a report of improved oocyte harvest with recombinant FSH preparations. Whether that can be documented in this country remains to be proved.

Dr Verkauf in closing suggested initiation of collaborative research in assisted reproductive technology. The Southeastern Reproductive Medicine Association was organized in 1995 to allow multicenter trials. This organization consists of reproductive medicine practices in North Carolina, South Carolina, and Georgia. We hope that group effort, with industry support, can quickly provide clinical answers with statistical power.