Evaluation of Predictive Factors for Multiple Pregnancies During Gonadotropin/IUI Treatment

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Submitted: June 27, 1996

Accepted: September 27, 1996

Purpose: Our purpose was to analyze factors for their predictability of multiple pregnancies in patients treated with a combination of human menopausal gonadotropins (hMG) and intrauterine insemination (IUI).

Methods: The records of all patients conceiving through treatment with hMG/IUI were reviewed for factors predictive of multiple pregnancy.

Results: Ninety-one pregnancies reviewed included 78 singleton (86%), 8 twin (9%), and 5 higher-order pregnancies (5%). The total number of follicles >10 mm was greater in the multiple-pregnancy group and there was a decreased number of postwash sperm in the multiple-pregnancy group. Otherwise there was no significant difference in the factors analyzed.

Conclusions: No factor or combination of factors predicts multiple pregnancies to a degree that it would be helpful in managing or counseling patients.

KEY WORDS: human menopausal gonadotropins; intrauterine insemination; multiple pregnancy.

INTRODUCTION

The use of human menopausal gonadal (hMG) therapy has increased greatly, as indications for its use have expanded. Once used almost exclusively for treatment of anovulation, hMG is now used for the treatment of unexplained infertility and other nontubal causes of infertility, usually in conjunction with intrauterine insemination (IUI), and for in vitro fertilization (IVF) to produce multiple follicles. Undoubtedly, most large infertility centers now find the treatment of anovulation to be the indication for only a minority of hMG treatment cycles. With increased use of hMG has come

an increased concern regarding multiple pregnancies, arguably the major complication of hMG therapy. The need for minimizing multiple pregnancies, especially triplet and higher-order pregnancies, is obvious. Initial financial costs (maternal hospitalization for premature labor and neonatal intensive care costs) are extremely high. A recent survey of our IVF Program pregnancies showed unadjusted costs for hospitalization for premature labor and neonatal intensive care to be \$89,874 per triplet pregnancy ($n = 8$) and \$439,348 per quadruplet pregnancy ($n = 3$). This is in contrast to unadjusted costs of \$210 per singleton pregnancy ($n = 36$) and \$7,340 per twin pregnancy ($n = 27$) during the same period of time (1). Even more important is the ongoing morbidity of babies born very prematurely (2).

In view of these concerns, many suggestions regarding limiting the number of embryos replaced have been made for IVF treatment cycles (3). Additionally, much attention has been paid to hMG stimulation for non-IVF cycles to determine whether risk for multiple pregnancies could be determined, with the hopes of using this information to reduce the incidence of multiple pregnancies. Before the availability of ultrasound, hMG treatment cycles were generally monitored only by estradiol levels. There were some reports that indicated patterns of estradiol rise correlated with the frequency of multiple pregnancy (4), but most reports have shown no good correlation between the estradiol response and the occurrence of multiple pregnancy (5–7). When ultrasound began to be used to monitor hMG treatment cycles, there were initial reports of good predictability of multiple pregnancy based on the number of preovulatory follicles (8,9). However, further experience seemed to indicate that there may be little correlation of multiple pregnancy with the number of preovulatory follicles (7,10) or that multiple pregnancy might be correlated with the number of intermediate-size follicles rather than the number of preovulatory follicles (5,11).

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In view of our great concern regarding high-order multiple pregnancy and the conflicting data in the literature, we reviewed 2 years of our experience with hMG/IUI cycles, looking at estradiol levels and ultrasound findings, as well as etiology of infertility, number of days and dosage of hMG, age of the patient, and characteristics of insemination samples.

MATERIALS AND METHODS

The records of all hMG/IUI conception cycles at University Hospitals of Cleveland from January 1991 through December 1992 were reviewed retrospectively. The patients all had standard management with baseline estradiol levels and ultrasounds before initiation of medication. If estradiol levels were <50 pg/ml and there were no follicles >10 mm, hMG was begun. Ovarian stimulation was followed by serial estradiol levels and ultrasounds. Ten thousand units of human chorionic gonadotropin (hCG) was given in general when there was at least one follicle of 16-mm average diameter with an appropriate estradiol level. "Appropriate" estradiol levels were loosely defined. Generally if follicular development was borderline (e.g., only one follicle of 16-mm average diameter) and the estradiol level was low (e.g., <300 pg/ml), 1 additional day of hMG would be given before hCG was given. Conversely if the estradiol was high (e.g., >1200 pg/ml), hCG was considered even if the largest follicle was slightly <16 mm in average diameter. Approximately 36 hr after hCG injection, IUI was done. Luteal-phase support consisted of hCG, 2500 U, 1, 4, and 7 days after insemination. Quantitative hCG levels were drawn approximately 2 weeks following insemination. Positive hCG levels were followed with ultrasound approximately 2 weeks later. Conception cycles were evaluated for etiology of infertility, age of the patients, number of ampoules and days of gonadotropin therapy, estradiol levels, number and size of follicles, and semen parameters, both prewash and postwash. Data were analyzed using one-way ANOVA and Fisher LSD multiple-comparison test. A level of probability <0.05 was considered significant.

RESULTS

During the 2 years reviewed there was a total of 91 pregnancies resulting from 640 hMG/IUI treatment cycles: 78 singleton (86%), 8 twin (9%), and 5 higher-order pregnancies (5%). Of the higher-order pregnan-

Table I. Etiology of Infertility

	Single (n = 78)	Twin (n = 8)	High multiple (n = 5)
Unexplained	32	1	3
Endometriosis	5	0	0
Luteal-phase defect	4	1	0
PCOD	1	0	0
Cervical	2	1	0
Donor	14	4	1
Male	7	0	1
Anovulatory	12	1	0
Tubal	1	0	0

cies there were two triplet, two quadruplet, and one quintuplet pregnancy. The etiology of the infertility showed no difference among the three groups (Table I).

Although the age of the patients tended to be somewhat lower in the high-multiple pregnancy group, this was not of statistical significance. Similarly, the number of ampoules of hMG and days of hMG administration tended to be lower in the high-multiple pregnancy group, but this did not reach statistical significance. Estradiol levels in the 2 years reviewed were of no predictive value for multiple pregnancies; there were trends toward lower levels in twin pregnancies and higher levels in higher-order multiple pregnancies, neither of statistical significance. As far as follicular measurements, the high-multiple group did have a statistically significant larger number of total follicles >10 mm but did not have a statistically significant larger number of follicles >16 mm (Table II). Semen parameters both prewash and postwash were similar except for a decreased postwash number in the high-multiple pregnancy group (Table III).

DISCUSSION

In the 2 years reviewed in this paper, the multiple pregnancy rate of hMG/IUI cycles was 14%, which is at the lower limit of frequencies shown by others (8). The high-order multiple pregnancy rate (triplet or more) was 5%.

Similarly to Dodson *et al.* (7), we found no difference in etiology of infertility in the three groups. The tendency toward a higher multiple pregnancy rate in younger patients has been shown by others (7,12) and did reach statistical significance in a report by Navot *et al.* (5), where 51 singleton pregnancies were compared with 51 multiple pregnancies. However, even in their paper the difference in the age of the two groups was

Table II. Stimulation Data for Treatment Cycles

	Single (n = 78)	Twin (n = 8)	High multiple (n = 5)
Mean age	34.4	34.2	31.4
(Range)	(27-43)	(28-35)	(30-33)
Mean amps hMG	18.4	18.2	13.2
(Range)	(7-69)	(8-36)	(10-18)
Mean days hMG	8.0	7.6	6.8
(Range)	(2-14)	(5-12)	(5-9)
Mean maximum estradiol (pg/ml)	831	547	997
(Range)	(97-2790)	(180-760)	(666-1580)
Mean No. of follicles >10 mm	7.2	5.8	10.4*
(Range)	(1-18)	(2-10)	(8-12)
Mean No. of follicles >16 mm	3.0	1.8	4.0
(Range)	(0-10)	(0-3)	(1-6)

* $P < 0.05$ compared to single and twin groups.

Table III. Semen Parameters for Treatment Cycles

	Single (n = 78)	Twin (n = 8)	High multiple (n = 5)
Mean prewash Concentration (million/ml)	93.3	88.0	77.7
(Range)	(20-304)	(25-173)	(70-85)
Mean prewash motility (%)	59.1	55.5	58.3
(Range)	(31-91)	(33-75)	(45-74)
Mean postwash concentration (million/ml)	72.0	47.6	50.8
(Range)	(12-190)	(29-62)	(36-77)
Mean postwash motility (%)	69.1	63.8	52.0
(Range)	(25-93)	(41-83)	(37-71)
Mean total No. inseminated (millions)	21.9	14.3*	14.3*
(Range)	(1-85)	(5-26)	(8-26)

* $P < 0.05$ compared to single group.

only approximately 2 years, making the findings of questionable value when counseling patients. Multiple-gestation patients, in our own experience, showed a tendency toward a lower number of ampoules of hMG, which, although statistically not significant, is in contrast to the reports of others, who showed a tendency toward a higher number of ampoules of hMG used in their patients with multiple gestation (5,7,12). Likewise, we showed a tendency toward fewer days of hMG therapy in our multiple-gestation groups, whereas others did not (7,10,12). Our experience showing a correlation between multiple pregnancies and the total number of follicles, but not the number of follicles >16 mm, agrees with Navot *et al.*, who found a correlation with the number of intermediate-sized follicles and the number of implanted embryos (5).

In reviewing both prewash and postwash insemination parameters, interestingly the only significant finding was a lower number of motile sperm used for insemination in the high-multiple group. This undoubtedly was a fortuitous finding and of no clinical significance. In contrast, Sheldon *et al.*, (12) reported that

an increased sperm number in the inseminating sample was a major determining factor in the genesis of multiple gestation in their experience.

Our conclusion from reviewing 2 years of our experience and the experience of others (5,7,8,10,11) is that there is no parameter or combination of parameters that reliably predicts the relative risk of multiple pregnancy with hMG therapy other than possibly the total number of follicles and possibly a lower age of the patient. However, even if one accepts these parameters as being reliable for predictability, the magnitude of differences is not such that they would be particularly helpful in managing or counseling patients regarding the risk of multiple pregnancy.

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