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A conservative treatment protocol with human menopausal gonadotropins aimed at reducing multiple births

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Abstract

In multicenter studies involving 3002 courses of human menopausal gonadotropins (hMG) therapy in 1286 patients, 20% of the patients who delivered had multiple gestations; 75% of these were twins and 25% were triplets or higher parity. Our stimulation regimen is very conservative in that we 1) try to allow a female with LPD and regular cycles but not reaching a mature follicle to first select her dominant follicle and wait until the serum E_2 reaches approximately 100 pg/mL then add the hMG. With anovulatory women we frequently begin with only 75 IU hMG and gradually increase the hMG dosage. Using this approach we have usually attained at least a 70% pregnancy rate in six months. A study was

performed to see if this conservative approach resulted in a decreased multiple birth rate percentage especially with triplets or more. The study was to evaluate the outcome of 241 consecutive pregnancies in which hMG was the sole therapy. There were 203 with one gestation and 38 with multiples. Twins – 32; triplets – 6. Thus 15% (38/241) had multiple births; six of 38 (15%) of the multiples had triplets or more. Though our multiple birth rate and especially higher parity rate appears to be lower than average no statistical difference was found. Thus even with conservative use of hMG multiple births cannot be easily avoided.

Keywords: Conservative protocol, high order multiples, human menopausal gonadotropins, multiple births.

1 Introduction

Human menopausal gonadotropins (hMG) are used for a number of clinical circumstances including ovulation induction in anovulatory women with hypogonadotropic hypogonadism [8], polycystic ovarian syndrome [17] and even in patients with hypergonadotropic amenorrhea [4]. Also, the drug may be used for luteal phase defects (LPD) related to release of oocytes from immature follicles [2].

Gonadotropin therapy is known to increase multiple gestation [13]. The multiple birth rate has varied according to the published series from 11 to 42% [1, 6, 9, 14, 15]. A decreased multiple gestation rate occurred once monitoring with ultrasound and rapid serum estradiol (E_2) levels commenced [3, 16, 17]. The most common use for hMG is anovulation related to polycystic ovarian syndrome (PCO). WANG and GEMZELL reported a 27.6% multiple birth rate in hMG treated PCO patients using rapid serum estradiol (E_2) levels for measurement [17].

LOUCOPOULOS and JEWELWICZ reported in 1982 that 66% of high order multiple gestations occurring between 1965 and 1981 were due to hMG therapy [7] and RON-EL et al similarly reported 64% related to hMG therapy [12]. Recently, however, REIN et al evaluating high order multiple gestations at Brigham and Women's Hospital from 1983 to the end of

1986, found that only 18% were related to hMG therapy [11].

The Serono company revised its statements in the physicians desk reference on the incidence of multiple gestations from hMG and now claims is 20% with 75% of them twins. These data were based on multicenter studies involving 3002 courses of hMG therapy in 1286 patients. The present study was aimed at determining whether the use of a conservative hMG treatment protocol might result in an even lower multiple birth rate that could be achieved by merely using E_2 and ultrasound monitoring alone.

2 Materials and methods

A prospective analysis was performed on 250 consecutive pregnancies in which hMG therapy was the exclusive ovulation inducing drug employed. Besides strict monitoring with sera E_2 and progesterone (P) and luteinizing hormone (LH) levels and sonographic monitoring certain conservative treatment modalities were used to try to reduce the risk of multiple gestation and ovarian hyperstimulation syndrome (OHSS). These included: 1) when using hMG to treat LPD related to immature follicles the hMG was not given on day 5 of the menstrual cycle as is traditionally done, but not started until the serum E_2 reached 100 pg/mL; 2) for eues-

trogenic anovulatory patients who failed to conceive with clomiphene citrate, they were treated with only 75 IU hMG daily and were only switched to 150 IU if the serum E_2 levels were not rising after seven days of therapy. The majority of these patients had elevated LH levels and usually had an LH level at least twice the follicle stimulating hormone (FSH) level; 3) for hypogonadotropic women 75 IU hMG was started on day 5 for three days then increased to 150 IU daily and, in general, the attempt was made to stay with this dosage unless there was an inadequate rise in serum E_2 .

The objective in each case was if possible to attain only one mature follicle. Human chorionic gonadotropin (hCG) 10,000 units would be given when there was at least one mature follicle attained by pelvic sonography using an abdominal transducer (ATL ultramark with 3.5 MHz transducer) of 18–24 mm with a serum E_2 of 200 pg/mL. If the LH had not doubled the baseline value and the P level was not approaching 1 ng/mL then hCG would not be given until the serum E_2 level attained a value equal to 200 pg/mL for each follicle 16 mm or more in average diameter. A rising LH or P level might prompt the use of hCG before the E_2 reached the aforementioned level as long as it reached a minimum of 200 pg/mL.

No patient was included in this study where hMG was used for hypergonadotropic amenorrhea, nor cervical factor. Furthermore, no one was included where purposeful hyperstimulation was used e.g. pelvic adhesions, or unexplained infertility [5].

Each patient was required to have a pelvic ultrasound eight weeks from conception to determine fetal viability and numbers. Only those pregnancies demonstrating a viable fetus were included. Thus the incidence of multiple births may have been slightly less at birth since all numbers were based strictly on the number of viable gestations at eight weeks.

3 Results

The ultrasound results of nine patients were unavailable related to long distance so they

were eliminated from the study. Single gestations were found in 203 patients and 38 with twins or higher order gestational number. Twins were found in 32 women and six had triples. Thus 15.7% (38/241) had multiple births; of which six (15.8%) were higher order gestations.

There were 34 patients (14.1%) using the hMG with hypogonadotropic hypogonadism and 207 (85.9%) were euestrogenic; 83 of the 207 (40.1%) had at least a 2 to 1 LH to FSH ratio and either clinical hirsutism or a mild increase in serum testosterone (T) so that a diagnosis of polycystic ovarian syndrome was made.

All of the hypogonadal patients were anovulatory; some degree of ovulation as evidenced by a serum P level that exceeded 8 ng/mL in untreated patients occurred in 112 of the 207 (54.1%) euestrogenic women; hMG was given in this group for luteal phase defects related to releasing an oocyte from an immature follicle [2].

4 Discussion

Though the multiple birth rate, especially higher order parity rate in the study presented herein, appears to be lower than the average for multicenter studies, no statistical difference was found. Power analysis finds that 696 patients would be needed to demonstrate that the 15.7% higher order gestation rate is different than the 25% rate; similarly 1538 patients would be needed to show a 5% decrease with 95% confidence between the 20% and 15% multiple birth rate.

These data demonstrate that even with a very conservative approach of using hMG, multiple birth rates are still higher than women not taking fertility drugs. Certainly, the wide range in multiple birth rate may relate to the method of employing the drug. However, it is clear that even with meticulous monitoring with frequent sonography, and rapid sera hormone assays for E_2 , P and LH, and a very conservative dosage schedule, there is still an increased risk for multiple gestation and patients should be so warned.

Recently, some data was published suggesting that pulsatile subcutaneous administration of hMG would result in a low incidence of multiple pregnancy [10]. This awaits confirmation by other studies.

5 Conclusion

Despite the conservative use of human menopausal gonadotropins and careful follicular monitoring the risk of multiple gestation was only slightly reduced.

References

- [1] CASPI E, S LEVIN, I BUKOVSKY, Z WEINRAUB: Induction of pregnancy with human menotropins after clomiphene failure in menstruating ovulatory infertility patients. *Isr Med Sci* 10 (1974) 249
- [2] CHECK JH: Ovulation inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. *Int J Fertil* 33 (1988) 252
- [3] CHECK JH, BB GOLDBERG, A KURTZ, HG ADELSON, C DIETTERICH: Serum estradiols versus pelvic sonography in monitoring hMG therapy. *Int J Fertil* 30 (1985) 61
- [4] CHECK JH, K NOWROOZI, JS CHASE, A NAZARI, D SHAPSE, M VASE: Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropin amenorrhea. *Fertil Steril* 53 (1990) 811
- [5] DODSON WC, DB WHITESIDES, CL HUGHES, HA EASLEY, AF HANEY: Superovulation with intrauterine insemination in the treatment of infertility: a possible alternative to gamete intrafallopian transfer and in vitro fertilization. *Fertil Steril* 48 (1987) 441
- [6] HACK M, M BRISH, D SERR, V INSLER, B LUNENFELD: Outcome of pregnancy after induced ovulation. Follow-up of pregnancies and children born after gonadotropin. *JAMA* 211 (1970) 791
- [7] LOUCOPOULOS A, R JEWELWICZ: Management of multifetal pregnancies: Sixteen years' experience at the Sloane Hospital for Women. *Am J Obstet Gynecol* 143 (1982) 902
- [8] LUNENFELD B, V INSLER: Classification of amenorrhoeic states and their treatment by ovulation induction. *Clin Endocrinol (Oxf)* 3 (1974) 223
- [9] MARSHALL JR, SA WIDER: Results of human menopausal gonadotropins (hMG) therapy for anovulatory infertility using a nonvariable treatment schedule comparison with previous reports. *Fertil Steril* 22 (1971) 19
- [10] NAKAMURA Y, Y YOSHIMURA, H YAMADA, Y UBUKATA, K YOSHIDA, Y TAMAOKA, M SUZUKI: Clinical experience in the induction of ovulation and pregnancy with pulsatile subcutaneous administration of human menopausal gonadotropin: a low incidence of multiple pregnancy. *Fertil Steril* 51 (1989) 423
- [11] REIN MS, FL BARBIERI, MF GREENE: The causes of high-order multiple gestation. *Int J Fertil* 35 (1990) 154
- [12] RON-EL R, E CASPI, P SCHREYER, Z WEINRAUB, S ARIELI, MD GOLDBERG: Triplet and quadruplet pregnancies and management. *Obstet Gynecol* 57 (1981) 458
- [13] SCHWARTZ M, R JEWELWICZ: The use of gonadotropins for induction of ovulation. *Fertil Steril* 35 (1981) 3
- [14] SCHWARTZ M, R JEWELWICZ, I DYRENFURTH, P TROPPER, RL VANDE WIELE: The use of human menopausal gonadotropins for induction of ovulation. Sixteen years' experience at the Sloane Hospital for Women. *Am J Obstet Gynecol* 138 (1980) 801
- [15] SPADONI LR, DW COX, DC SMITH: The use of menopausal gonadotropin for the induction of ovulation. *Am J Obstet Gynecol* 120 (1974) 988
- [16] STONE SC, M SCHIMBERNI, PA SCHUSTER, LB WERLIN, P WEATHERSBEE: Incidence of multiple gestations in the presence of two or more mature follicles in the conception cycles. *Fertil Steril* 48 (1987) 503
- [17] WANG CF, R GEMZELL: The use of human gonadotropins for the induction of ovulation in women with polycystic ovarian disease. *Fertil Steril* 33 (1980) 479

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