Female and male partner age and menotrophin requirements influence pregnancy rates with human menopausal gonadotrophin therapy in combination with intrauterine insemination*

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This study analyses the influence of female and male patient age and human menopausal gonadotrophin (HMG) requirements on clinical pregnancy rates and live birth rates with ovulation stimulation using HMG in combination with intrauterine insemination (IUI). In this study, 363 consecutive HMG/IUI treatment cycles in 184 patients carried out at a university fertility centre were analysed in a retrospective fashion. The main outcomes measured were clinical pregnancy rates and live birth rates. Increased female partner age (>35) and male partner age (>40) were found to negatively influence pregnancy rates with HMG/IUI therapy. In addition, this study demonstrated a critical threshold of HMG requirements beyond which pregnancy did not occur. No pregnancies occurred in treatment cycles requiring >25 ampoules (1875 IU) of menotrophins to achieve follicular maturity, irrespective of patient age. In conclusion, female partner age, male partner age, and HMG requirements all significantly influence pregnancy rates with HMG/IUI therapy.

Key words: HMG/intrauterine insemination/patient age/pregnancy rates

Introduction

Controlled ovarian stimulation with human menopausal gonadotrophins (HMG) with intrauterine insemination (IUI) is an established treatment regimen for patients undergoing infertility therapy. This ovulation stimulation protocol has been shown to be an effective treatment regimen for patients with a variety of infertility diagnoses (Dodson and Haney, 1991). Despite the broad acceptance of this treatment modality, there are limited data assessing HMG requirements and pregnancy rates in women receiving HMG/IUI therapy.

Human reproductive capacity is known to decline with increasing female chronological age (Gindoff and Jewelewicz, 1986; Menken et al., 1986; Pearlstone et al., 1992; Magarelli et al., 1996). Previously, we reported a dramatic decline in both clinical pregnancy rates and live birth rates in women receiving clomiphene citrate (CC)/IUI (Agarwal and Buyalos, 1996) and sequential CC/HMG therapy (Brzechffa et al., 1996). However, there are minimal data assessing the impact of female partner age on clinical pregnancy rates and live birth rates with HMG/IUI therapy; particularly for women aged >35 years. Furthermore, there are conflicting data on the impact of male partner age on pregnancy rates with infertility therapy (Galle et al., 1990; Piette et al., 1990; Mathieu et al., 1995). There are no data examining the effect of male partner age and pregnancy rates with HMG/IUI treatment. The objectives of this study were firstly, to examine the relationship of female and male partner age on clinical pregnancy rates and live birth rates with HMG/IUI therapy and secondly, to determine whether a critical threshold exists between menotrophin requirements and clinical pregnancy rates with this therapy.

Materials and methods

Subjects

The study population consisted of women aged 25–46 years and their male partners aged 26–71 years undergoing ovulation induction with HMG in combination with IUI at the Fertility Center of the University of California, Los Angeles, CA, USA, between August 1988 and July 1995. A total of 363 consecutively completed treatment cycles in 184 patients were evaluated in a retrospective manner. Informed written consent was obtained prior to initiating therapy as part of an institutional review board approved protocol. All patients included in this study previously received ≥three unsuccessful ovulatory treatment cycles with CC/IUI therapy. A midluteal serum progesterone concentration of >10 ng/ml was considered to be indicative of an ovulatory treatment cycle. All couples were diagnosed as infertile based on at least 1 year of unprotected intercourse with the exception of a few couples where the female age was >40 years, where therapy was initiated following 6 months of the inability to conceive. The infertility evaluation consisted of an assessment of ovulation, semen analysis, evaluation of the luteal phase and confirmation of tubal patency (hysterosalpingogram and/or laparoscopy). Laparoscopy was performed in a selective manner consistent with published protocols (Navot et al., 1987; Collins and Rowe, 1989). Patients were classified into one of five diagnostic categories based on their principle diagnosis including ovulatory dysfunction, endometriosis, tubal, uterine and cervical factor, and unexplained infertility. Ovulatory dysfunction included patients with oligo-ovulation or anovulation secondary to either hyperprolactinaemia, hypothyroidism or subclinical ovulatory disorder as diagnosed by standard criteria. Endometriosis was diagnosed at laparoscopy and classified according to the revised American Society of Reproductive Medicine (1985) classification.

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system. All females, including those with tubal factor, had at least one patent Fallopian tube. Couples were classified as having unexplained infertility if there was no evidence of abnormality during their evaluation. Patients were diagnosed as having male factor subfertility by the results of at least two semen analyses separated by at least 3 months that confirmed any of the following abnormalities: sperm density <20×10⁶/ml, motility <50% or normal morphology <50%.

To avoid the confounding effect of poor semen quality, all couples diagnosed with male factor were excluded from this analysis.

**Ovulation induction protocols**

Controlled ovarian stimulation protocols utilized in this study employed HMG in combination with IUI. In order to exclude residual cysts, a baseline transvaginal ultrasound was performed on cycle day 2 prior to initiating each treatment cycle. Human menopausal gonadotrophins [Pergonal (354 cycles) which contains 75 IU of follicle stimulating hormone (FSH) and 75 IU of luteinizing hormone (LH) and/or Metrondin (nine cycles) containing 75 IU of FSH; Serono Laboratories, Norwell, MA, USA] were subsequently started on cycle day 2 of either a spontaneous cycle or following progestin-induced withdrawal bleeding at an individualized dose ranging from 1–4 ampoules per day for 5 consecutive days. A repeat transvaginal ultrasound and serum oestradiol concentration were obtained after 5 days of HMG therapy to confirm follicular development. Adjustments in dosage and duration of HMG administration were made on the basis of ultrasound examination findings and oestradiol concentrations.

Inseminations were timed by the administration of human chorionic gonadotrophin (HCG) (5000–10 000 IU) (Profasi; Serono Laboratories, Randolph, MA, USA) when the lead follicle(s) attained a mean diameter of 16 mm. Single inseminations were performed ~36 h following HCG administration. A total volume of 0.3–0.5 ml was inseminated in all cases following standard swim-up procedure as described by Dodson et al. (1987). Initial serum HCG quantifications were performed 16 days following IUI in those women without menses to confirm pregnancy.

**Outcome**

Clinical pregnancy was defined as the detection of fetal cardiac activity by transvaginal ultrasound scan performed 5 weeks following insemination in the presence of a rising HCG titre. Live births referred to pregnancies ending in the delivery of a viable infant. The clinical pregnancy rate was defined as the number of clinical pregnancies divided by the number of treatment cycles performed. The live birth rate was defined as the number of live births divided by the number of treatment cycles performed.

**Statistical analysis**

Proportions were compared using χ² analysis and exact permutational P values were computed. A Kaplan–Meier Life Table analysis was used to estimate the cumulative pregnancy rates. Log-Rank analysis was used to compare the cumulative pregnancy rates between groups. Analysis of variance (ANOVA) was used for comparison of means. Mean values are expressed as mean ± SEM. Statistical significance was considered as P <0.05.

**Results**

In this series, 363 treatment cycles in 184 patients resulted in 44 clinical pregnancies for an overall clinical pregnancy rate of 12.1% per treatment cycle. There was no difference in the mean female patient age or the clinical pregnancy rates between different infertility diagnoses, P >0.15.

**Influence of female patient age**

There was a significant decline in both clinical pregnancy rates (19.4 versus 9.4%, P = 0.001), and live birth rates (17.3 versus 7.2%, P = 0.004) in female patients aged <35 years compared with those aged ≥35 years (Table I). Furthermore, in female patients aged <35 years, and 35–40 years, both the clinical pregnancy rates (19.4 and 13.6%) and live birth rates (17.3 and 10.4%) were significantly higher compared with the clinical pregnancy rate (3.6%) and live birth rate (2.7%) in female patients ≥40 years, P ≤0.02 (Table I). The cumulative pregnancy rate by cycle attempt is shown in Table II. The majority of pregnancies (92%) occurred in the first three treatment cycles irrespective of female partner age group. After three treatment cycles, the cumulative clinical pregnancy rate (49.9 versus 26.9%, P = 0.04) and cumulative live birth rate (48.8 versus 24.5%, P = 0.01) were both significantly greater in women aged <35 years compared with women aged ≥35 years.

**Influence of male patient age**

The clinical pregnancy rates per treatment cycle as a function of male partner age after controlling for female partner age are shown in Table III. The clinical pregnancy rate was significantly lower in males aged ≥40 years compared with males aged <40 years whose female partners were ≥35 years (16.3 versus 6.5%, P = 0.02). No differences were observed in the clinical pregnancy rates in treatment cycles in which males aged ≥40 years were compared with males aged <40 years whose female partners were aged <35 years, P = 0.81. Furthermore, the mean inseminating sperm concentrations did not differ between males of <40 years compared with males aged ≥40 years (35.0 ± 3.0×10⁶/ml versus 35.3 ± 3.3×10⁶/ml, P = 0.94). In addition, the mean inseminating sperm concentrations did not differ between conception and non-conception cycles (39.1 ± 5.9×10⁶/ml versus 34.3 ± 2.4×10⁶/ml, P = 0.45).

**Menotrophin requirements and cycle parameters**

No pregnancies occurred in treatment cycles requiring >25 ampoules (1875 IU) of menotrophins, independent of female partner age. Furthermore, in treatment cycles in which the female partner was aged ≥40 years no pregnancies occurred when ≥20 ampoules (1500 IU) were necessary to achieve follicular maturity. In women aged <35 years, 5.1% of treatment cycles (5/98) required ≥25 ampoules of menotrophins, while 20.0% of cycles (53/265) in women aged ≥35 years utilized ≥25 ampoules to achieve follicular maturity. In treatment cycles in which the female partner was <35 years of age, there was no difference in the mean number of ampoules (75 IU) of menotrophins (16.8 ± 5.0 versus 15.5 ± 5.7, P = 0.34), between conception and non-conception cycles. Fewer ampoules (75 IU) of menotrophins were required for follicular maturation in treatment cycles resulting in conception, compared with non-conception cycles in women ≥35 years, (16.2 ± 4.5 versus 20.2 ± 10.3, P = 0.05).

As shown in Figure 1, treatment cycles requiring 16–25 ampoules (1200–1875 IU) of menotrophins had significantly
TABLE I. Pregnancy rates by age of female partner

<table>
<thead>
<tr>
<th>Cycle no.</th>
<th>Clinical pregnancy rate (%)</th>
<th>Live birth rate (%)</th>
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<tbody>
<tr>
<td>&lt;35</td>
<td>20.0 b (14/70)</td>
<td>17.9 (5/28)</td>
</tr>
<tr>
<td>35–40</td>
<td>16.3 b (13/80)</td>
<td>6.5 (12/185)</td>
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*Values represent clinical pregnancy rate (%).

**Discussion**

The influence of reproductive ageing on fecundity rates is particularly relevant in the present era with the increasing trend of couples to delay childbearing (Mosher et al., 1991). A decline in reproductive capacity with increasing chronological age in the female is well established (Gindoff and Jawelewicz, 1986; Menken et al., 1986; Pearlstone et al., 1992; Magarelli et al., 1996). Recently, a large case-control study in women undergoing in-vitro fertilization (IVF) with intracytoplasmic sperm injection demonstrated a significantly lower implantation and delivery rate in women aged ≥40 years of age compared with women aged <40 (Devroye et al., 1996). However, a decline in male fertility potential with advancing chronological age remains controversial. The goals of this study were firstly, to determine the significance of female and male partner age on clinical pregnancy rates and live birth rates with HMG/IUI therapy and secondly, to ascertain whether a critical threshold exists between menotrophin requirements and clinical pregnancy rates in patients receiving this therapy. This study revealed a profound decline in clinical pregnancy rates and live birth rates with increasing age of the female partner. A significant decline in clinical pregnancy rates was also observed with increasing male partner age when the female partner was ≥35 years. Finally, this study demonstrated a relationship between menotrophin requirements and clinical pregnancy rates in patients receiving HMG/IUI therapy.

Controlled ovarian stimulation with HMG in combination with IUI is an established treatment protocol for patients undergoing ovulation induction therapy (Dodson et al., 1991). This regimen is frequently utilized in patients who fail to conceive with CC/IUI and/or sequential CC/HMG/IUI therapy prior to initiating assisted reproductive technologies (Corsan and Kemmann, 1991). The decline in pregnancy rates with HMG/IUI therapy in females ≥35 years is consistent with our earlier reports which revealed a substantial decline in pregnancy rates using CC/IUI and/or sequential CC/HMG/IUI therapy.
(Agarwal and Bugalos, 1996; Brzechffa et al., 1996). There are limited data evaluating the impact of female partner age on pregnancy rates using HMG/IUI therapy (Dodson and Haney, 1991; Dickey et al., 1993). Furthermore, the vast majority of patients in these reports were ≤39 years of age. A recent study in women ≥40 years of age undergoing controlled ovarian stimulation with IUI reported no viable pregnancies in women aged ≥43 years (Corsan et al., 1996).

In contrast, this study evaluates a broader spectrum of reproductive aged females, in which approximately one-third of female partners were ≥40 years of age. Thus, these data are valuable for counselling the increasing percentage of couples who electively delay childbearing.

Studies which have addressed the influence of male partner age on pregnancy rates in couples undergoing infertility therapy have been inconclusive (Galle et al., 1990; Piette et al., 1990). Furthermore, there are no data examining the significance of male partner age on treatment cycle outcome in patients receiving HMG/IUI therapy which control for the age of the female partner. This study demonstrates a marked decline in clinical pregnancy rates with increasing male partner age after controlling for female partner age. When the female partner was ≥35 years of age, a significant decline in clinical pregnancy rates was observed when the male partner was ≥40 years. Furthermore, the inseminating sperm concentrations were similar between younger (<40 years) and older (≥40 years) males as well as between conception and non-conception cycles. Thus, the decline in pregnancy rates as a function of increasing paternal age cannot be attributed to differences in in-semination sperm concentrations. Our observation that male partner age ≥40 years may negatively impact pregnancy rates with HMG/IUI therapy is supported by several reports. An epidemiological study which examined fecundity rates in fertile couples prior to 1911 in Ireland, reported decreased fecundity rates when the male partner was >42 years of age after controlling for female partner age (Anderson, 1975). Previously, we reported a trend toward declining pregnancy rates with increasing male partner age when the female partner was ≥35 years of age in couples receiving sequential CC/HMG therapy (Brzechffa et al., 1996). Mathieu et al. (1995) reported that the age of the male partner was the most significant prognostic factor for pregnancy in infertile couples undergoing controlled ovarian stimulation with IUI therapy where the female partner was ≤43 years of age. Two additional studies have reported a decline in pregnancy rates with increasing paternal age in infertile couples, however, these reports did not control for the age of the female partner (Ducot et al., 1988; Galle et al., 1990). The mechanism(s) whereby advancing paternal age is associated with decreasing pregnancy rates is unknown. Sperm counts and the fertilizing capacity of spermatozoa are not negatively affected by increasing male age, although the pituitary and testes demonstrate decreased endocrine reserve with advancing age (Nieschlag et al., 1982; Haidl et al., 1996). However, increasing paternal age has been linked to an increase in structural chromosome anomalies (Martin and Rademaker, 1987), as well as autosomal dominant and X-linked recessive disorders, which have been attributed to fresh gene mutations (Jones et al., 1975). In contrast, a review of couples undergoing IVF and embryo transfer observed no adverse effect of male partner age on pregnancy rates after controlling for female partner age (Piette et al., 1990).

This study is the first to document the existence of a critical threshold between menotrophin requirements and pregnancy rates in patients receiving HMG/IUI therapy. Patients who required >25 ampoules (1875 IU) of menotrophins to achieve follicular maturity failed to conceive with this therapy, independent of female patient age. The decline in reproductive capacity in the human female has been attributed to a depletion in the follicular pool (Aschheim, 1979), a deterioration in oocyte quality (Peluso et al., 1982; Schwartz and Mayaux, 1982; Gindoff and Jewelewicz, 1986; Stovall et al., 1991), and reduced sensitivity of the follicular apparatus to menotrophin stimulation (Menken et al., 1986; Pearlstone et al., 1992). Based on these observations we conclude that HMG/IUI cycles which require >25 ampoules of menotrophins portend a poor prognosis for conception and reflect a reduction in reproductive capacity.

In summary, this study demonstrates that both increased female and male partner age contribute to the decline in clinical pregnancy rates and live birth rates with HMG/IUI therapy. In addition, menotrophin requirements increase with advancing age of the female partner and significantly influence clinical pregnancy rates with this treatment regimen. Importantly, a critical threshold exists between menotrophin requirements and the ability to achieve a clinical pregnancy, and this threshold declines with increasing female partner age. This information should be useful for counselling infertile couples of all ages, and provides valuable information for the increasing number of couples who delay childbearing.

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References


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Patient age, HMG requirements and pregnancy rates


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