Ovulation induction combined with intrauterine insemination in women 40 years of age and older: is it worthwhile?

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The use of ovulation induction combined with intrauterine insemination (IUI) as a treatment for subfertility in women with patent Fallopian tubes has increased in recent years. Little is known regarding the efficacy of this treatment in women aged ≥40 years. We reviewed our data in our ovulation induction with IUI programme for 168 consecutive patients aged ≥40 years undergoing a total of 469 cycles of treatment. Either sequential clomiphene citrate and human menopausal gonadotrophins or daily gonadotrophins were utilized along with timed IUI insemination. In 402 completed cycles, 28 clinical pregnancies occurred. The pregnancy loss rate was 34.4%. The overall ongoing/viable pregnancy rates per initiated and completed cycles were 4.47 and 5.22% respectively. No viable pregnancies occurred in 136 cycles in women aged ≥43 years. The ongoing/viable cycle fecundity rates for women aged 40, 41, and 42 years were 9.6, 5.2, and 2.4% per cycle respectively. When utilized in women aged ≥40 years, ovulation induction with IUI is most likely to result in successful pregnancy in women 40–42 years of age. Women ≥43 years should consider other alternatives such as adoption or egg donation.

Key words: age/fertility/intrauterine insemination/ovulation induction

Introduction

It is widely recognized that fertility in women declines with advancing age (Schwartz and Mayaux, 1982; Gindoff and Jewelewicz, 1986; Navot et al., 1991; van Noord-Zaadstra et al., 1991). Socio-economic trends occurring over the last 20 years have led to alterations in the pattern of childbearing in Western countries, with more women now delaying reproduction into the fourth or even fifth decade of life. This has lead to an increased interest in the reproductive capacity of women in their late 30s and 40s and a search for treatment options that may improve the fertility of these women (Penzias et al., 1991; Stovall et al., 1991; Cnattingius et al., 1992; Wood et al., 1992; Bopp et al., 1995).

Because of the greater pressures placed on older infertile couples and their physicians as a result of their narrower window of opportunity to achieve a pregnancy, techniques of assisted reproduction which may increase the fertility of these couples have been actively sought (Craft et al., 1988; Penzias et al., 1991; Pearlstone et al., 1992; Frederick et al., 1994; Bopp et al., 1995). While in-vitro fertilization (IVF)/embryo transfer and gamete intra-Fallopian transfer (GIFT) may represent those procedures that offer these older patients the best hope of achieving a live birth (Qasim et al., 1995), many couples may not have access to these technologies for financial or other reasons, or may not wish to pursue them. Accordingly, ovulation induction with intrauterine insemination (IUI) either as an alternative treatment or preliminary to an IVF-embryo transfer or GIFT cycle may be offered (Corsan and Kemmann, 1991; Dickey et al., 1991; Dodson and Haney, 1991).

Ovulation induction with gonadotrophins combined with IUI has become more commonly utilized as a means to increase the fertility of subfertile couples with patent Fallopian tubes. However, there is a paucity of studies describing the applicability of ovulation induction with IUI in women ≥40 years of age (Dickey et al., 1991; Pearlstone et al., 1992; Frederick et al., 1994). The purpose of this report is to analyse our experience in using ovarian stimulation with exogenous gonadotrophins with IUI in subfertile women ≥40 years of age with the goal of identifying those patients most likely to benefit from this form of assisted reproduction.

Materials and methods

We retrospectively reviewed our patient database to identify patients who were ≥40 years of age while undergoing ovulation induction with IUI programme at UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA between January 1992 and October 1995 (group A). All couples were infertile for at least 1 year and had documented tubal patency with a normal-appearing uterine cavity detected on hysterosalpingography or hysteroscopy performed within the previous 18 months. Diagnoses included unexplained infertility (n = 35), American Fertility Society stage 1-II endometriosis (n = 59), male factor infertility (n = 63), cervical factor infertility (n = 8), and ovulatory dysfunction (luteal phase defect, oligo- or amenorrhoea) (n = 33). In many cases (18%), a combination of factors were identified in the couple. Male factor infertility was defined as two or more abnormal semen analyses at least 3 months apart, demonstrating one or more of the following abnormalities: sperm concentration < 20 × 10⁶/ml, motility < 40%, and normal forms < 14% by strict criteria. There was no difference in the distribution of diagnoses between women <42 years of age and those ≥43 years. Laparoscopy was generally not performed until after three cycles of sequential clomiphene citrate, human menopausal gonadotrophins (HMG) and human chorionic gonadotrophins (HCG) with IUI had
failed to achieve pregnancy unless the history, physical examination, or other diagnostic tests suggested a high risk for tubo-peritoneal disease.

Ovulation induction protocols involved sequential clomiphene citrate, HMG, HCG or daily HMG followed by HCG, or follicle stimulating hormone (FSH) (Metrodin: Serono Laboratories, Randolph, MA, USA) at an individualized dose beginning on cycle day 3 as described previously (Kemmann and Jones, 1983; Ransom et al., 1994). Cycle monitoring involved serum oestradiol-17β assays and vaginal sonography, begun when oestradiol was estimated to be at least 1285 pmol/l (350 pg/ml). HCG (10 000 IU i.m.), was administered when at least one follicle with a mean diameter of ≥18 mm was noted together with an appropriately elevated serum oestradiol concentration. No serum luteinizing hormone (LH) monitoring was done. Luteal phase support consisted of a single injection of 2500 IU of HCG 1 week after the ovulatory HCG dose. IUI was cancelled when premature luteinization (defined as serum progesterone >2.0 ng/ml) was identified or oestradiol and/or follicular response was considered inadequate. There was no maximum number of mature follicles visible on ultrasound for HCG to be administered. Sperm preparations were washed and IUI (36 h after HCG) was performed using techniques previously described (Ransom et al., 1994). A clinical pregnancy was defined as a rising serum β-hCG concentration associated with the appearance of an intrauterine gestational sac ~3–4 weeks after conception detected by vaginal sonography. Biochemical pregnancies were not included in the data analysis. To serve as a control group, we randomly selected 210 cycles of ovulation induction with IUI in 180 women aged ≤40 years treated during the same period of time with identical protocols (group B).

The χ² and Fisher’s exact tests were used to compare rates in groups A and B. Student’s t-test was used to compare the demographic parameters and day of HCG. Statistical significance was defined as P < 0.05. Values are given as means ± SD.

Results

A total of 469 cycles of ovulation induction with IUI occurring in 168 patients (group A) aged ≥40 years was reviewed. The mean patient age was 41.8 ± 1.68 years (range 40–47 years). Sequential clomiphene citrate–HMG–HCG was administered in 215 (45.8%) cycles, with daily HMG or FSH in the remaining cycles. Of 469 cycles initiated in women ≥40 years, 14.3% (67) were cancelled because of premature luteinization, poor oestradiol and/or follicular response. This compared to a cancellation rate of 7.14% for the 210 ovulation induction with IUI cycles initiated in 180 women aged <40 years (P < 0.05). The mean oestradiol concentration on day of HCG for group A was 1875 ± 1156 pmol/l (511.0 ± 315.0 pg/ml) and the mean number of follicles ≥18 mm was found to be 2.49 ± 1.87.

A total of 34 pregnancies occurred in the 469 cycles initiated in group A (7.25% per initiated cycle). Four pregnancies resulted from the 67 cancelled cycles where HCG and IUI were withheld (5.97% per cycle); however, three of these four patients experienced a first-trimester pregnancy loss. When pregnancies in cancelled cycles and ectopic gestations (n = 2) were excluded, a total of 28 clinical pregnancies occurred in 402 completed cycles (6.96%/cycle). The clinical pregnancy rate per completed cycle for group A was 5.45% for male factor infertility, 12.12% for unexplained infertility, 6.09% for endometriosis-related infertility, 5.0% for ovulation dysfunction, 8.33% for cervical factor, and 7.69% for combined problems. A total of 11 first-trimester spontaneous abortions occurred in the 32 intrauterine pregnancies, resulting in a pregnancy loss rate of 34.4%. The ongoing/delivered pregnancy rates per initiated and completed cycle in group A were 4.47 and 5.22% respectively. Three multiple gestations occurred in group A, all of which were twin gestations, giving a multiple gestation rate of 9.38% (3/32) of all pregnancies. No woman conceiving above age 41 (n = 6) delivered a multiple gestation.

The mean number of follicles ≥18 mm in group B was 2.84 ± 1.21. The distribution of infertility diagnoses was not significantly different between groups B and A (data not shown). There were 15 cancelled cycles in the 210 cycles initiated in group B (7.14%) (Table I). A total of 35 clinical pregnancies and one ectopic gestation occurred in these younger patients (16.7% per initiated cycle and 17.95% per completed cycle). Six first trimester abortions occurred (17.14% pregnancy loss rate) along with six multiple pregnancies (17.14%). The ongoing/delivered pregnancy rate for group B was 13.8% per initiated cycle, 14.9% per completed ovulation induction with IUI cycle.

Table II displays the pregnancy rate as a function of female age. No deliveries resulted from the 136 cycles performed in women >42 years old. A single clinical pregnancy resulting in a spontaneous abortion was found in 56 cycles of ovulation induction with IUI done in women aged 43 years. In 135 cycles of ovulation induction with IUI done in women aged 40 years, there were 18 clinical pregnancies and one ectopic gestation, resulting in five spontaneous abortions and a viable delivery rate of 9.63% per cycle.

We analysed mean patient age, number of 75 IU ampoules of gonadotrophins utilized, number of follicles ≥18 mm, and serum oestradiol concentration at time of HCG, between those who conceived and those who did not in group A. The mean age of those women who conceived (40.67 ± 0.78 years) was significantly lower than those who did not (41.77 ± 2.77) (P < 0.05). However, the respective number of ampoules of gonadotrophins utilized (15.23 versus 18.73 ampoules), number of follicles ≥18 mm (3.03 versus 2.40) and serum oestradiol levels (1791 versus 2030 pmol/l (488 versus 553 pg/ml)) did not differ significantly between those conceiving and not conceiving. The probability of pregnancy did not differ whether sequential clomiphene citrate–HMG or a gonadotrophin-only protocol was used.

Discussion

Socio-economic trends resulting in an increasing number of women delaying childbearing until the late fourth or fifth
decades of life are unlikely soon to reverse. The probability of successful pregnancy following unprotected coitus begins to decline sharply as a woman enters her late 30s and early 40s. Declines in fecundity have been reported to be detectable as early as 30 years of age (Schwartz and Mayaux, 1982; van Noord-Zaadstra et al., 1991). Possible explanations for the reduced fecundity of older women include a decline in oocyte quality (Navot et al., 1991), reduced uterine receptivity (Abdalla et al., 1990; Levran et al., 1991; Borini et al., 1995), a higher rate of chromosomal abnormalities (Richardson and Nelson, 1990), reduced coital frequency, an increased incidence of spontaneous abortion, and the presence of associated pelvic disease.

With increasing numbers of reproductively older women now seeking out evaluation and treatment for subfertility, many patients will be offered some type of assisted reproductive technique in an attempt to improve fertility. Although assisted conception techniques may increase the cycle fecundity of reproductively older women, they can only be expected to partially reverse the age-related decline in fertility that these women experience (Penzias et al., 1991). It appears that GIFT may be the most effective treatment option in women aged ≥40 years with patent tubes. GIFT has been reported to result in a delivery rate per transfer of 6.85% in one study (Penzias et al., 1991), while a more recent report found that a more aggressive high-order oocyte transfer results in a viable pregnancy rate of 14.3% per procedure (Qasim et al., 1995). Few studies describe pregnancy and livebirth rates for women aged ≥40 undergoing ovulation induction (Dickey et al., 1991; Pearlstone et al., 1992; Frederick et al., 1994). Pearlstone et al. (1992) reported a clinical pregnancy rate of 3.5% per cycle, but nearly two-thirds of these pregnancies ended in spontaneous abortion resulting in a livebirth rate of 1.2% per cycle. Similarly, Frederick et al. (1994) described 210 treatment cycles in 77 patients undergoing ovarian stimulation and IUI resulting in a livebirth rate of 1.4% per cycle. The high abortion rate observed in this study (72.7%) and by Pearlstone et al. (1992) (64.3%) was primarily responsible for the low livebirth rate.

Our study confirms the generally low probability of a livebirth resulting from ovulation induction with IUI in women ≥40 years of age. We found that the great majority of ongoing viable pregnancies (19 of 21) resulting from ovulation induction with IUI therapy occurred in women age 40 and 41 years (Table II), with none being seen in women ≥42 years old. The livebirth rate in the 40 year old subgroup was 9.63% per initiated cycle and dropped to 5.2% per cycle in the 41 year old, and 2.38% per cycle in the 42 year old subgroups, probably a reflection of the rapid decline in fertility rates occurring after age 40. Therefore, the use of ovulation induction with IUI therapy in women ≥43 years of age appears very unlikely to lead to a viable birth and should probably be abandoned as a treatment option. A short trial of ovulation induction with IUI in 40–42 year old women may be a reasonable treatment option in some couples and can be attempted prior to GIFT and IVF/embryo transfer.

The relative contribution of oocyte and uterine factors in causing the reduced fecundity of older women remains controversial (Meldrum, 1993). Some authors have speculated that endometrial receptivity and pregnancy rates can be improved in patients with severe endometriosis undergoing IVF–embryo transfer or in oocyte donation cycles by using long-term gonadotrophin-releasing hormone agonist (GnRHa) down-regulation (Marcus and Edward, 1994). Whether this approach may improve the pregnancy rates in women ≥40 undergoing ovulation induction with IUI remains to be seen.

It is interesting to note that the clinical pregnancy rate in the 67 cancelled cycles (5.97%) where IUI was withheld was similar to the pregnancy rate in completed ovulation induction with IUI cycles in women aged ≥40 years (6.96%). This suggests that some patients undergoing ovulation induction with IUI may not gain benefit from the performance of the IUI itself. The relative contribution that each of the components of ovulation induction with IUI treatment offers (e.g. ovulation induction, HCG administration, ultrasound, oestradiol monitoring, IUI) to the improved pregnancy rates remains an unresolved issue.

In our present cost-conscious medical environment, it is increasingly critical to consider the cost-effectiveness of any treatment designed to improve fertility (SART, 1993; Neumann et al., 1994; Collins et al., 1995). Ovulation induction with IUI is an expensive treatment modality with total cycle costs (physician fees, medications, sonographic monitoring, laboratory fees, and IUI costs) commonly between $1500 and $2500 (US). If this therapy is applied to women aged 40–42 years, the cost per successful pregnancy can be estimated to be between $23 800 and $39 600 assuming an overall 6.3% ongoing/viable pregnancy rate per cycle in this age group. Examining American data for IVF/embryo transfer results in women ≥40 years with no male factor reveals a live delivery

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of initiated cycles</th>
<th>No. of clinical pregnancies (%)</th>
<th>No. of spontaneous abortions (%)</th>
<th>No. of multiple gestations</th>
<th>No. of ectopic pregnancies</th>
<th>No. of deliveries (%)</th>
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<td>32</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>21</td>
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</table>

Table II. Pregnancy rate after ovulation induction with intrauterine insemination treatment as a function of female age.
rate per completed IVF–embryo transfer cycle of ~8% per cycle (Society for Assisted Reproductive Technology, 1993). A recent study estimated the average cost of an IVF cycle to be $6223 (Collins et al., 1995). One can then determine the cost per successful pregnancy from IVF–embryo transfer for women ≥40 years to be approximately $77,912. Another report by Neumann et al. (1994) estimated that using IVF/embryo transfer for women ≥40 years with a male factor resulted in a marginal cost per successful pregnancy ranging from $160,000 to $380,000 depending on the number of cycles attempted.

Decisions regarding age cut-offs for infertility treatment and precisely which services our society is willing to pay for in older infertile women attempting pregnancy are issues that cannot be decided here. However, it does appear that ovulation induction with IUI is an economically reasonable alternative to IVF–embryo transfer and GIFT for some women in this older age group. The availability of information describing the effectiveness of assisted conception techniques in women aged ≥40 years is critical for clinicians and patients alike in order to make rational decisions regarding treatment options. When applied to women ≥40 years of age, ovulation induction with IUI is most likely to result in successful pregnancy in women aged 40–42 years. Women ≥43 years of age should consider alternative options, including adoption and egg donation.

References


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