Treatment of anovulatory infertility: the problem of multiple pregnancy

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The aim of the study was to assess patient, treatment and cycle characteristics in relation to the risk of multiple conception following ovulation induction in order to reduce the prevalence of this complication of treatment. We performed a retrospective analysis of 208 pregnancy cycles achieved in the Middlesex Hospital outpatient fertility unit. These pregnancies were achieved in 175 anovulatory women who conceived after gonadotrophin or pulsatile GnRH therapy. The multiple conception rate was 13.4%. After spontaneous reductions and abortions the multiple delivery rate was 9.6%. Clinical features associated with an increased risk of multiple pregnancies were the presence of polycystic ovary syndrome and secondary infertility. Comparison between different protocols of ovulation induction revealed no relationship with the risk of multiple conceptions. Although total number of follicles was increased in the multiple conception cycles, the distribution of follicles according to their diameter on the day of human chorionic gonadotrophin (HCG) administration was similar in multiple and singleton conception cycles. Thus, the risk of multiple conception could not be attributed to an increased number of follicles of any particular size but directly related to the total number of the cohort follicles (≥14 mm) and leading follicles (≥17 mm), rising from 7% with one follicle to 33% with six or more follicles. As we could not find a specific pattern of follicular development that could be associated with multiple conception, we conclude that the difference in the ovarian response leading to multiple conception is quantitative rather than qualitative. The data presented enable the assessment of the risk of multiple conception in any given cycle. Key words: cycle characteristic/multiple pregnancies/ovulation induction

Introduction

Over the last 2 decades there has been a marked increase in the number of multiple pregnancies because of the burgeoning use of infertility treatments (Levene et al., 1992). A 15–53% prevalence of multiple pregnancy after induction of ovulation with gonadotrophin injections was reported in 1981 (Schenker et al., 1981) and, despite attempts to reduce the risk of this complication by using careful and sophisticated monitoring, recent reports describe a similarly high rate (Navot et al., 1991; Kiely et al., 1992; Derom et al., 1993; Petterson et al., 1993). The current approach to the problem of multiple pregnancies in women undergoing in-vitro fertilization (IVF) and embryo transfer treatment is to restrict the number of embryos transferred (Nijs et al., 1993). Thus in the United Kingdom, the Human Fertilisation and Embryology Authority does not permit transfer of more than three embryos (HFEA, 1993) and for younger women many centres now advise transfer of only two embryos per cycle of treatment. With the use of gonadotrophins for induction of ovulation for the treatment of anovulatory infertility, there is, however, limited control over the number of oocytes released and there is, therefore, an obligatory increase in the risk of a multiple pregnancy.

Having recently described our experience over the last 12 years on the outcome of induction of ovulation for anovulatory infertility in terms of efficacy (Balen et al., 1994), we now report our experience of one of the serious adverse effects of this treatment, namely the risk of multiple pregnancy. We aimed to determine whether there were specific characteristics of the patient, the treatment modality, or the cycle in which conception occurred that might be associated with the occurrence of multiple conception. We hope this analysis will help in the assessment of the risk of multiple pregnancy in a given treatment cycle.

Material and methods

Patients

This is a retrospective analysis of all conception cycles that followed induction of ovulation in the Reproductive Endocrine Unit at the Middlesex Hospital between January 1982 and June 1994. During this time, 262 women underwent 1435 cycles of treatment resulting in a total of 208 pregnancies in 175 women. For the present analysis, the patients have been divided into groups according to the female diagnosis of infertility: polycystic ovary syndrome (PCOS), hypogonadotropic hypogonadism (HH), weight related amenorrhoea (WRA), and anovulation caused by hyperprolactinaemia or associated with normogonadotropic normogonadism with normal ovarian appearances on ultrasound.

PCOS was defined by the presence of polycystic ovaries on ultrasound, according to the criteria of Adams et al. (1985), together with anovulatory infertility. Because of the clinical and biochemical heterogeneity of this syndrome (Conway et al., 1989), biochemical and clinical markers have not been used to subdivide this group of
patients. After they had failed to respond or to conceive with treatment with anti-oestrogens (e.g. clomiphene citrate or tamoxifen) patients with PCOS were treated with gonadotrophins or pulsatile gonadotrophin releasing hormone. Hypogonadotrophic hypogonadism was diagnosed in patients with low serum gonadotrophin concentrations caused by gonadotrophin releasing hormone (GnRH) deficiency (idiopathic or Kallman’s syndrome), following pituitary surgery or caused by structural disease of the pituitary. Patients classified as WRA were those in whom anovulation followed a period of 6 months or more in which their body mass index (BMI) was less than 19 kg/m². Detailed clinical descriptions of these patients and their groupings have been given in the report of Balen et al. (1994).

**Stimulation protocols**

Patients underwent hormonal stimulation with human menopausal gonadotrophin (HMG), follicle stimulating hormone (FSH), pulsatile gonadotrophin releasing hormone (GnRH) or a combination of pulsatile GnRH and HMG, using protocols that have been reported in detail elsewhere (Eshel et al., 1988; Homberg et al., 1989, 1990).

Ovarian stimulation with HMG [75 IU luteinizing hormone (LH) and 75 IU FSH; Pergonal; Serono Laboratories, Welwyn Garden UK or Humegon: Organon Laboratories, Cambridge, UK] or FSH (75 IU; Metrodin or Metrodin HP; Serono) was started within 5 days of spontaneous or induced menstruation. The initial dose in the first cycle was one ampoule per day of either HMG or FSH for 7 days. The subsequent dose was titrated according to the ultrasound assessment of ovarian response and endometrial thickness (Shoham et al., 1991). Blood samples were taken for oestradiol, FSH and LH concentrations in accordance with the ultrasound surveillance until an adequate ovarian response was achieved. In subsequent cycles the starting dose of HMG/FSH was determined by the patient’s previous dose gonadotrophin stimulation (Hamilton-Fairly et al., 1991; Shoham et al., 1991) was introduced for patients with PCOS. Finally, patients with PCOS with repeated multifollicular response to ovarian stimulation despite using the low dose protocol of gonadotrophin stimulation were treated by laparoscopic ovarian diathermy (Armar et al., 1990; Farhi et al., 1994).

Pulsatile GnRH (Fertiral; Hoechst UK Ltd, Hounslow, Middlesex, UK or HRF: Ayerst-Wyeth Laboratories, Maidenhead, UK) was usually administered s.c. (15 mcg/pulse) or occasionally i.v. (5–10 mcg/pulse) by a purpose-built miniaturized infusion pump set to inject at intervals of 90 min (Homberg et al., 1989). Patients in whom GnRH failed to elicit follicular development were treated with a combination of pulsatile GnRH and HMG or FSH, starting with one ampoule per day for 7 days and then individually adjusted with 0.5 ampoule increments according to the ovarian response.

In all treatment modalities ovulation was triggered by human chorionic gonadotrophin (HCG, 10 000 IU, i.m.; Profasi: Serono or Pregnyl: Organon), given when the diameter of the leading follicle was at least 17 mm. Occasionally, ovulation was not triggered by HCG in patients with HH treated with pulsatile GnRH alone and they were followed by ultrasound until spontaneous ovulation occurred. Ovulation was confirmed 7 days after administration of HCG by ultrasound imaging of a corpus luteum and a serum progesterone concentration >30 nmol/l. Pregnancy was diagnosed after a positive urine pregnancy test and ultrasound confirmation of a gestational sac.

Ultrasound assessments of follicular development and pregnancies were performed transabdominally using a B-scanner for the first 2 years of the clinic (1982–1984), then with transabdominal real time scanning between 1984 and 1989 and transvaginally since 1989. Ultrasound follow-up of most of the pregnancies was carried out after 6, 8, 10 and 12 weeks of gestation. The order of the multiple pregnancy was classified according to the highest number of pregnancy sacs observed by ultrasound imaging, including empty pregnancy sacs which did not contain an embryonic pole (blighted ovum), and is referred to in the text as a multiple conception. We have used the term multiple delivery rate to describe the final number of multiple pregnancies that were delivered after spontaneous reduction and miscarriage (includes one ongoing second trimester (≥25 weeks) twin pregnancy).

**Statistics**

Two sample t-tests were used to compare the means of study groups. The frequencies of observations between the study groups were compared by χ² and calculation of Fisher’s exact probability. A value of P < 0.05 was considered statistically significant.

**Results**

Between 1982 and 1994, 175 women conceived 208 pregnancies. Twenty-eight (13.4%) conceptions were multiple: 21

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**Table I. Outcome of multiple conceptions**

<table>
<thead>
<tr>
<th>Number of gestational sacs</th>
<th>Number of pregnancies</th>
<th>Spontaneous reductions</th>
<th>Spontaneous abortions</th>
<th>Deliveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1</td>
<td>1 (to 4)</td>
<td>1 quadruplet</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1 (to 3)</td>
<td>1 triplet</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1 (to 2)</td>
<td>4 triplet</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>5 (to 1)</td>
<td>1 twin</td>
<td>13 twins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 ongoing</td>
</tr>
</tbody>
</table>

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**Table II. Patients clinical characteristics**

<table>
<thead>
<tr>
<th>Multiples</th>
<th>Singletons</th>
<th>Proportion of multiple</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>147</td>
<td>175</td>
</tr>
<tr>
<td>Number of pregnancy cycles</td>
<td>28</td>
<td>180</td>
<td>208</td>
</tr>
<tr>
<td>Age</td>
<td>29.9 ± 6.4</td>
<td>31.4 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Primary infertility</td>
<td>10</td>
<td>107</td>
<td>8.5% *</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>18</td>
<td>73</td>
<td>19.7%</td>
</tr>
<tr>
<td>Duration of infertility</td>
<td>3.7 ± 0.5</td>
<td>3.82 ± 2.41</td>
<td></td>
</tr>
</tbody>
</table>

*P = 0.01.
Patient and cycle characteristics in multiple pregnancies

Table III. Distribution of patients according to diagnosis of the cause of infertility

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Singletons (180)</th>
<th>Multiples (28)</th>
<th>Proportion of multiple pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH</td>
<td>88</td>
<td>7</td>
<td>9.4*</td>
</tr>
<tr>
<td>PCOS</td>
<td>73</td>
<td>18</td>
<td>19.8</td>
</tr>
<tr>
<td>WRA</td>
<td>11</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>Anovulation</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAH</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*(n) = number of patients.
HH = hypogonadotropic hypogonadism.
PCOS = polycystic ovary syndrome.
WRA = weight related amenorrhoea.
CAH = congenital adrenal hyperplasia.

$P = 0.01$ compared with PCOS.

Table IV. Distribution of multiple conceptions according to patient characteristics

<table>
<thead>
<tr>
<th>Patient clinical characteristics</th>
<th>Order of multiple conception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Twins</td>
</tr>
<tr>
<td>Primary infertility</td>
<td>6</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>15</td>
</tr>
<tr>
<td>PCOS</td>
<td>12</td>
</tr>
<tr>
<td>HH</td>
<td>6</td>
</tr>
<tr>
<td>WRA</td>
<td>2</td>
</tr>
<tr>
<td>CAH</td>
<td>1</td>
</tr>
</tbody>
</table>

twins, five triplets, one quadruplet and one quintuplet. Their outcome is shown in Table I. Eight pregnancies underwent spontaneous reduction between 7 and 10 weeks of gestation and two twin gestations spontaneously aborted. The deliveries of one quadruplet, five triplets, 15 twins (together with one ongoing second trimester twin pregnancy) gave an overall multiple delivery rate of 9.6%.

Comparisons between patient characteristics in multiple and singleton conception cycles are presented in Tables II, III and IV. Secondary infertility was more frequently found in the multiple conception group (64%, 18/28) compared with the singleton group (40%, 73/180) and the frequency of multiple conception within all the secondary infertility patients was significantly higher (19.7%) than that in all the primary infertility patients (8.5%). The quadruplet and quintuplet conceptions, however, occurred in patients with primary infertility (Table IV). The mean age and duration of infertility were similar in the multiple and singleton conception groups (Table II).

Analysis of the multiple conceptions year by year revealed a sustained increase (20-26%) between 1986 and 1988 compared with an incidence of 8-12% before and after that period (Figure 1). The increase between 1986 and 1988 was coincident with the introduction to this clinic of treatment with gonadotrophin injections (Table Va,b). The fall in the multiple conception rate after 1988 was coincident with the changes in the clinic policy described in the Methods section.

Figure 1. Multiple conception rate according to the year of treatment.

Table Va. Distribution of conceptions of treatment protocol in different years

<table>
<thead>
<tr>
<th>Year</th>
<th>LHRH</th>
<th>LHRH + HMG</th>
<th>HMG</th>
<th>FSH</th>
<th>An + HMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>83</td>
<td>12</td>
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<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>84</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<td>85</td>
<td>6</td>
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<td></td>
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<tr>
<td>86</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>5</td>
<td>1</td>
<td>1</td>
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<td>88</td>
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<tr>
<td>90</td>
<td>2</td>
<td>5</td>
<td>1</td>
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</tr>
</tbody>
</table>

Table Vb. Distribution of multiple conceptions according to treatment protocol in different years

<table>
<thead>
<tr>
<th>Year</th>
<th>LHRH</th>
<th>LHRH + HMG</th>
<th>HMG</th>
<th>FSH</th>
<th>An + HMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
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<td>83</td>
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<td>2</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Comparison of the prevalence of multiple conceptions between treatment protocols (Table VI) revealed similar rates with each of the modes of treatment. Combining all cycles involving gonadotrophin stimulation did not reveal a significant increase of multiple conceptions when treatment with gonado-

Table VI. Distribution of pregnancies according to mode of treatment

<table>
<thead>
<tr>
<th></th>
<th>Singleton</th>
<th>Multiple</th>
<th>Total</th>
<th>%Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHRH</td>
<td>81</td>
<td>11</td>
<td>92</td>
<td>11.9</td>
</tr>
<tr>
<td>LHRH + HMG</td>
<td>14</td>
<td>3</td>
<td>17</td>
<td>17.6</td>
</tr>
<tr>
<td>HMG</td>
<td>63</td>
<td>9</td>
<td>72</td>
<td>13.0</td>
</tr>
<tr>
<td>FSH</td>
<td>33</td>
<td>25</td>
<td>58</td>
<td>16.0</td>
</tr>
<tr>
<td>An + HMG</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

LHRH = luteinizing hormone releasing hormone.
HMG = human menopausal gonadotrophin.
FSH = follicle stimulating hormone.
An = GnRH analogue.

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The risks appear to be directly related to the number of leading and cohort follicles (Hobbins 1988; Collins and Bleyl, 1990; Petterson et al., 1992; Derom et al., 1993; Powers and Kiely, 1995). There is a significant increase in the number of leading and cohort (diameter ≥14 mm) follicles. Figure 2 indicates that the main factor related to multiple conception was the ability to develop a multifollicular response.

The magnitude of ovarian response, as assessed by the number of developing follicles, is determined primarily by the size of the cohort of follicles able to respond to gonadotrophin stimulation. The ability of ovaries to produce a large number of growing follicles in response to exogenous stimulation is therefore the key feature of an increased risk of multiple pregnancies. Hanning et al. (1984) concluded that the best predictor for multiple pregnancies was the number of follicles of >10 mm diameter. In our study, significantly more follicles developed in the cycles that resulted in multiple conceptions. Higher oestradiol levels, together with a thicker endometrium (Figure 3), reflected an overall increased steroidogenesis by the ovaries in multiple conception cycles. The significant difference in clinical features of the patients who had multiple and those who had singleton conceptions also indicated that the main factor that was related to multiple conception was the ability to develop a multifollicular response. Thus, significantly more patients with polycystic ovaries were identified with multiple conception.
found in the multiple conception group (Table III). Previous
reports on the association of multiple pregnancies with the
aetiology of anovulation have been conflicting. Caspi et al.
(1976) and Oelsner et al. (1978) found a higher prevalence in
WHO group I patients (1973), whereas Navot et al. (1991)
did not find any association of the cause of the infertility with
multiple pregnancies. In our study, multiple conceptions were
significantly more common in women with PCOS, the group
that corresponds with WHO group II.

We then studied the nature of the ovarian response in all
pregnancy cycles to determine whether there was a particular
pattern of follicular development that was associated with
multiple conception. We analysed two main features: first, the
distribution of the follicles according to their diameter on the
day of HCG administration and second, the relationship
between the number of leading and cohort follicles and the
risk of multiple conception.

On the day HCG was administered, there was no difference
in the distribution of follicles between women who conceived
singleton and those who conceived multiple pregnancies (Figure 2). Similar results have been reported by Kurachi et al.
(1985). On the other hand, Navot et al. (1991) found, in
addition to the dominant follicle, an increased number of
intermediate follicles, of diameter 15–17 mm, in cycles that
resulted in multiple pregnancies. As we could not detect an
increase in any specific size of follicles that indicated an
increased risk of multiple conception, we conclude that the
difference in the ovarian response leading to multiple rather
than singleton conceptions is quantitative rather than
qualitative.

In studies of induction of ovulation for anovulatory infertility,
Silverberg et al. (1991) reported that the percentage of ovulating
follicles was 0.5% for those smaller than 14 mm, 37–81% for
follicles ranging from 15 to 20 mm and 95% for those
>20 mm. These results are in agreement with those of Siebel
et al. (1981) and Su Ling Yu et al. (1991), and for our analysis
we therefore set our cut-off point for cohort follicles at 14 mm.
In our series there was a direct relationship between the total
number of leading and cohort follicles of diameter ≥14 mm
(i.e. all the follicles able to release the oocyte in response to
HCG) and the occurrence of multiple conception. The risk of
multiple conception rose from 7% with one follicle to 18–
24% with two to five follicles and up to 33% with six or more
follicles. In part, a similar relationship was reported by Tal
et al. (1985), who observed 18.2% multiple pregnancy rate
with three or four follicles (≥18 mm).

In conclusion, the main parameter that we have found to be
associated with multiple conception is the ultrasonic ovarian
picture on the day of administration of HCG. In this series,
treatment cycles that resulted in multiple conception had
an overall enhanced ovarian response. The risk of multiple
pregnancies were related to the number of leading and large
cohort follicles that developed. An ultrasound diagnosis of
polycystic ovaries implies that the patient is prone to develop
a multifollicular response and therefore faces an increased risk
of multiple conception. In the management of anovulatory
infertility in our clinic, ovulation is now triggered with HCG
when at least one leading follicle is ≥17 mm but HCG is
 withheld when any combination of three follicles with a
diameter ≥14 mm is present. If these criteria are adhered to,
we anticipate a fall in the multiple conception rate because
our own figure of 13.4%, with a multiple delivery rate of
9.6%, is based on data largely acquired before the advent of
today’s sensitive methods of ultrasound surveillance.

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