Predictive value of the results of a first in-vitro fertilization cycle on the outcome of subsequent cycles

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This study examines the relationship between the first cycle of in-vitro fertilization (IVF) and subsequent cycles. The results of all IVF cycles conducted at The Hammersmith Hospital or The Royal Masonic Hospital between 1988 and 1995 were studied including those cycles where egg recovery was abandoned due to poor ovarian response. All patients underwent a standardized treatment protocol. Of those women who achieved a clinical pregnancy during their first IVF attempt, 33% achieved a pregnancy during their second cycle, statistically significantly different from the 24% of patients conceiving during a second cycle who had failed to conceive during their first. 36% of those who achieved a biochemical pregnancy in their first cycle became pregnant in their second. Age was an important factor in the success of IVF treatment, with pregnancy rates of 48% in the 20–25 year age group falling to 8% in those aged ≥41 years. Cumulative pregnancy rates were 26% after one cycle, increasing to 43% after two cycles and reached 80% after seven cycles. A previous pregnancy significantly improved a couple’s probability of conception in a later IVF cycle. Overall pregnancy rates per cycle were constant for the first three attempts. Cumulative pregnancy rates continued to rise to 72% after six cycles. Thus the more cycles a couple undergo (up to six) the greater their chance of a pregnancy.

Key words: cumulative pregnancy rates/cycle number/IVF

Introduction

Couples undergoing in-vitro fertilization (IVF) are faced with considerable uncertainty. Because the chance of conception with a single treatment is still low, treatment cycles cannot be realistically considered in isolation. Calculation of cumulative pregnancy rates are needed as are trends in success rates with repeated cycles. Those women returning for a repeated IVF attempt, having delivered a live infant after a previous IVF cycle, are reported to have a better prognosis (Molloy et al., 1995). The aim of this study was to assess those cycles which had been successful, where a large database of patients had been accumulated, and hence to identify those patients more likely to conceive. Simon et al. (1993) compared women who conceived naturally with those who conceived in a previous IVF cycle. The numbers were small and male factor infertility was excluded, making comparisons less valid. However, a previously successful IVF cycle did offer an improved prognosis in comparison to those who had previously conceived naturally.

Certain factors have been shown to affect conception rate, e.g. age (Tan et al., 1992). The aetiology of infertility ought to affect the success of IVF especially if sperm dysfunction decreases the fertilization rate. Intracytoplasmic sperm injection (ICSI) has now altered the odds for these couples but in this study none of the patients underwent this treatment which had only recently become available within the unit.

Many women are now having repeated IVF treatment cycles and want to know whether their chances of conceiving increase with an increasing number of attempts. This can be best assessed by evaluating the cumulative pregnancy rate, helping a couple to plan how many cycles to undergo. Cumulative pregnancy rates also enable the comparison of IVF results between units. Few centres have produced such information; those that have done so have analysed relatively few cycles. Other problems with published data are that reports frequently include heterogeneous techniques, with gamete intra-Fallopian transfer (GIFT), IVF and frozen replacement cycles all considered in the same series. Moreover, many reports have analysed pregnancy rates only after embryo transfer or oocyte retrieval, thus excluding cycles where fertilization has failed or the cycle was abandoned before attempts at oocyte retrieval.

Matrals and methods

A total of 9316 cycles were commenced at the Hammersmith and Royal Masonic Hospitals between 1988 and 1995. All these couples were treated using one standard treatment protocol, with the same clinical and embryological team involved in all treatments. The only difference between the two hospitals was that the majority of patients at The Hammersmith were in the public sector whereas those at The Royal Masonic were largely treated on a fee-paying private basis. Recent data from the Human Fertilisation and Embryo Authority (1996) show that the success rates, measured as live births per treatment cycle, at both these centres are identical.

During ovulation induction all patients were treated using a standard protocol (Rutherford et al., 1988) for pituitary desensitization with 150 mg/daily of a gonadotrophin agonist (buserelin; Hoechst, Hounslow, Middlesex, UK; administered from the second day after menstruation commenced. When complete ovarian suppression was observed (serum oestradiol concentration <80 pmol/l and no follicles seen on ultrasound), the ovaries were stimulated with human menopausal gonadotrophin (HMG; Pergonal, Metrodin; Serono Labora-
Table I. Correlation between patient age and pregnancy rate in a first in-vitro fertilization attempt

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of cycles</th>
<th>Cancelled cycles (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of pregnancies</th>
<th>Pregnancy rate per cycle&lt;sup&gt;b&lt;/sup&gt;</th>
<th>No. of miscarriages (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25</td>
<td>89</td>
<td>8 (12.0)</td>
<td>43</td>
<td>48.3</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>26–30</td>
<td>939</td>
<td>129 (13.7)</td>
<td>311</td>
<td>33.1</td>
<td>37 (11.9)</td>
</tr>
<tr>
<td>31–35</td>
<td>2089</td>
<td>331 (15.8)</td>
<td>597</td>
<td>28.6</td>
<td>73 (12.2)</td>
</tr>
<tr>
<td>36–40</td>
<td>1632</td>
<td>350 (21.4)</td>
<td>348</td>
<td>21.3</td>
<td>52 (14.9)</td>
</tr>
<tr>
<td>≥41</td>
<td>324</td>
<td>128 (39.5)</td>
<td>25</td>
<td>7.7</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Total</td>
<td>5073</td>
<td>946 (18.6)</td>
<td>1324</td>
<td>26.1</td>
<td>170 (12.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cancellation rate is higher in women >35 years old (P < 0.001).
<sup>b</sup>Pregnancy rate drops with increasing age (P < 0.01 between each age group).
<sup>c</sup>There is no significant difference in miscarriage rates between the age groups.

Table II. Relationship between patient age and ovulation induction response

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. of ampoules of HMG</th>
<th>Serum oestradiol concentration (pmol/l)</th>
<th>Days of HMG</th>
<th>No. of oocytes retrieved</th>
<th>No. of oocytes fertilized</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–25</td>
<td>29.5</td>
<td>7376</td>
<td>12.9</td>
<td>12.3</td>
<td>6.6</td>
</tr>
<tr>
<td>26–30</td>
<td>31.6</td>
<td>6961</td>
<td>13.2</td>
<td>10.9</td>
<td>6.0</td>
</tr>
<tr>
<td>31–35</td>
<td>35.6</td>
<td>6625</td>
<td>13.1</td>
<td>9.6</td>
<td>5.2</td>
</tr>
<tr>
<td>36–40</td>
<td>46.3</td>
<td>6418</td>
<td>13</td>
<td>9.4</td>
<td>4.5</td>
</tr>
<tr>
<td>≥41</td>
<td>61.1</td>
<td>5736</td>
<td>13.5</td>
<td>6.9</td>
<td>3.5</td>
</tr>
</tbody>
</table>

HMG = human menopausal gonadotrophin.
Differences were statistically significant (P < 0.01) between all age groups and parameters except for HMG dosage and peak oestradiol between the 20–25 and 26–30 year age groups.

Statistics

χ²-Test and the Student’s t-test for unpaired data were used to test for the significance of any differences (P < 0.05) on the Stat View statistical package (Abacus Concepts Inc., Berkeley, CA, USA). In addition, using life table analysis (Petö et al., 1977), a cumulative pregnancy rate as a percentage for repeat attenders was calculated (Kovacs et al., 1986) using the formula:

cumulative pregnancy rate = P% = (100 – S) + (S×P)/100

where S is the percentage of women who were not pregnant at the start of the cycle.

Results

A total of 5073 first cycles were started, of which 4121 went to oocyte retrieval (OR). Of these cycles, 1325 (26% per cycle commenced; 32% per OR) resulted in a clinical pregnancy. Subsequently 2396 patients underwent a further IVF attempt.

The cause of infertility had no bearing on outcome. However, the age of the female partner was highly significant. A difference of only 5 years had an influence on outcome in each of the age ranges studied. The miscarriage rate also increased with age but no statistical difference was recorded (Table I).

With increasing age, significantly more HMG was required to produce an adequate response. Moreover, older women produced fewer eggs (Table II). This was irrespective of whether this was a first cycle.

Women who had more than one cycle of IVF needed more HMG and in spite of this yielded fewer eggs. The mean number of eggs collected in a first cycle was 9.4 requiring 39...
ampoules of HMG. In a second cycle 47 ampoules produced
8.7 eggs and in a third cycle 52 ampoules were needed to
produce 8.7 eggs. The difference in the amount of HMG
required was significant (P < 0.001), as was the difference
between the number of eggs collected in the first and second
cycles (P < 0.001). There was no difference in the length of
time that HMG was given (mean 12.9 ± 3.0 days) or in
fertilization rates.

Only 2396 women (47.2%) returned for a subsequent cycle.
Of these, 1125 had not conceived at their first attempt. We
found no clinical difference in those women returning for a
subsequent treatment cycle, nor was there any evidence of
specific factors influencing return for a third or fourth treatment
attempt (Table III).

The results after a second IVF cycle, shown in Table IV,
demonstrate a significant increase in pregnancy rate in women
experiencing a clinical (32.5%) or biochemical (36.4%)
pregnancy in a first cycle compared to those whose first cycle
was cancelled (19.5%) or yielded a negative result despite
reaching oocyte retrieval (23.6%). Table V shows that the
pregnancy rates among those whose first cycle produced a live
infant (32.5%) or ended in miscarriage (31.5%) were similar.

In our study, of the 26 women who had an ectopic pregnancy
in their first cycle and ventured further treatment, six (23%)
subsequently conceived a normal pregnancy in their second
cycle. Despite the small numbers this finding supports the
view of Karande et al. (1991) whose patients had a good
chance of a normal pregnancy with subsequent IVF. In their
study, 3.3% of pregnancies were ectopic. We found that only
one of 26 (3.8%) women previously experiencing an ectopic
IVF pregnancy had a second ectopic. The incidence of ectopic
pregnancy is higher among those with tubal disease as the
cause of their infertility, possibly because embryos are regurgi-
tated into a damaged tube after transfer. Of those women who
had an ectopic pregnancy in their first cycle, 25 (96.2%) had
tubal disease as their cause of infertility. In all IVF patients
with tubal disease, there should be an awareness of the
possibility of ectopic pregnancy.

Table VI shows the cumulative pregnancy rate after all
cycles. Figure 1 shows the cumulative pregnancy rate per cycle
and per retrieval up to six cycles. The seventh and subsequent
attempts were not included due to the small number of patients
involved.

### Table III. Comparison between patients who did not conceive in their first
cycle and returned for a second attempt and those who chose not to return

<table>
<thead>
<tr>
<th>Returned for 2nd cycle</th>
<th>Did not return</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1125</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.5 ± 4.3</td>
</tr>
<tr>
<td>No. of HMG ampoules</td>
<td>42.4 ± 20.9</td>
</tr>
<tr>
<td>Days of HMG</td>
<td>13.1 ± 2.9</td>
</tr>
<tr>
<td>Peak oestradiol (pmol/l)</td>
<td>6589 ± 3335</td>
</tr>
<tr>
<td>No. of oocytes recovered</td>
<td>9.1 ± 4.7</td>
</tr>
<tr>
<td>No. of oocytes fertilized</td>
<td>4.4 ± 3.5</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>1923</td>
</tr>
<tr>
<td></td>
<td>33.9 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>39.7 ± 20.1</td>
</tr>
<tr>
<td></td>
<td>13.3 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>6319 ± 2368</td>
</tr>
<tr>
<td></td>
<td>9.2 ± 4.6</td>
</tr>
<tr>
<td></td>
<td>4.9 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>1.9 ± 0.9</td>
</tr>
</tbody>
</table>

Values are mean ± SD. No significant difference between the groups.

HMG = human menopausal gonadotrophin.

Discussion

To our knowledge this is the first study of cumulative pregnancy
rate after IVF in a large series, with one team of embryological
and clinical staff and the most effective ovulation induction
protocol available. This protocol involves administration of the
luteinizing hormone (LH)-releasing hormone agonist for a
longer period, leading to fewer cycles being abandoned either
because of poor ovarian response or inappropriate release of
LH. Abolition of spontaneous LH surges also has the advantage
of permitting convenient, planned oocyte collection. Tan et al.
(1994a) showed an improved conception and live birth rate
with this approach.

Age is the most important factor in the outcome of IVF
(Bopp et al., 1995). In our study, women in the 20–25 year
age group with a 48% pregnancy rate are at an advantage over
those aged ≥41 years who had an 8% chance of pregnancy.
This seems in part to be due to a decreasing response to
ovulation induction. In spite of increased dosage of HMG
older women yielded fewer oocytes and had a higher cancella-
tion rate. However, the fertilization rate of their eggs remained
constant, suggesting that oocyte quality may not decrease very
much with age.

It is widely believed that couples who discontinue IVF after
a failed attempt do so because they have a poor prognosis.
We found little evidence for this view. When we compared
the aetiology, age, ovarian response and fertilization rate of
those who returned against those who did not, we found no
difference in outcome. This suggests that poorer responders
were not dissuaded from returning. It is inevitable that some
immeasurable, inherent bias exists between those patients
who stop assisted reproductive techniques versus those who
continue. If motivation were to influence outcome with
“quitters” having a poorer prognosis, then results would
obviously be biased towards those persevering.

Why do couples not persevere with treatment? Of those not
returning, 39.2% became pregnant in their first cycle. After a
successful pregnancy many women decided not to proceed
with further treatment; however, couples were more likely to
return if a pregnancy test had been positive but no live infant
had been born. The number of women undergoing many cycles
is low. Undoubtedly some patients transfer to other centres
because of dissatisfaction. Others discontinue treatment
because it is much more demanding than they expected.
Many couples have limited finances, which is an important
consideration with such expensive treatment.

The cause of infertility, even when two or more factors
were involved, did not affect IVF outcome. Unlike the findings
of Tournaye et al. (1992), we did not find that male factor
infertility was associated with lower pregnancy rates per cycle.
One of the major advantages of IVF is its ability to detect
fertilization disorders. When there was fertilization failure in
normozoospermic men at a first IVF attempt (Molloy et al., 1991),
the prognosis was still surprisingly good with IVF. Such
couples had mostly consistent fertilization rates (51–66%) in any
subsequent cycle with an equally favourable outcome. However,
Gabrielsen et al. (1996) showed a previous failure of fertilization
with normal sperm parameters may not be alleviated by ICSI in a future attempt.
transiently, indicates that the embryo was sufficiently well because of low numbers.

Séventh and subsequent attempts were excluded SEM.

mean ±

loss happens frequently. The fact that HCG rises, however up to six cycles. Results are expressed as

et al., 1988) that early pregnancy Cycle number 3 4

Figure 1. The cumulative pregnancy rate per started cycle and per oocyte retrieval (OR) up to six cycles. Results are expressed as mean ± SEM. Seventh and subsequent attempts were excluded because of low numbers.

Couples who have previously achieved an IVF pregnancy have a significantly better prognosis in a subsequent IVF cycle (33%) compared to those not conceiving (24%; P = 0.001). A 24% pregnancy rate in those with a prior failure is still clinically acceptable. Although a previous miscarriage in an IVF-pregnancy appeared to be associated with a possibly increased risk of miscarriage in a subsequent pregnancy, the difference was not statistically significant. The overall miscarriage rate was 3% in the 20–25 year age group and 20% in those >40 years old, but again, this increase was not statistically significant. The rate in the >40 year age group was much lower than the 50% reported by Padilla and Garcia (1989). Tan et al. (1994b) also concluded that women with a previous IVF pregnancy had a higher cumulative conception rate than couples in their first IVF cycle. However, they used six different stimulatory regimes, which makes valid comparison difficult.

A prior biochemical pregnancy was a significant, favourable indicator. Our patients had a clinical pregnancy rate of 36.4% in second cycles following a biochemical pregnancy in the first cycle. This is similar to the chance of pregnancy (32.5%) after a clinical pregnancy. Molloy et al. (1995) also concluded that previous biochemical pregnancy was a good prognostic feature. However, they studied a heterogeneous group of treatments using either frozen embryo replacement, GIFT or routine IVF alone to gather sufficient data. They also found that second and third IVF attempts had a better outcome among their 784 women who returned after having had a child. They studied the outcome in fewer patients, and accurate comparison between successful and unsuccessful treatment was not possible. We do not know the reason for the favourable influence of a pregnancy upon a subsequent attempt. This may be due to embryological or endometrial response, or perhaps a combination of the two, and requires further investigation.

Biochemical pregnancy may provide useful information. In normal fertile, ovulatory women there is considerable evidence (Miller et al., 1980; Wilcox et al., 1988) that early pregnancy loss happens frequently. The fact that HCG rises, however transiently, indicates that the embryo was sufficiently well
developed to implant. Embryo quality as measured by morphological appearance was shown to be no different after IVF given an ongoing pregnancy or a biochemical pregnancy (Levy et al., 1991). However, it was less good in cycles which gave rise to an abortion.

The chance of pregnancy after a single IVF cycle (26%) is similar or better than the chance of conception in 1 month of normal intercourse in a normal fertile population (Sharp et al., 1986) and remains constant for the first three attempts at our unit. This point has major implications for the National Health Service when health authorities make purchasing decisions concerning IVF. Templet’s data (1996) differed from these findings and showed a decreased success rate with each IVF cycle. However, multiple treatment regimes from different centres can distort real trends within individual units, especially during a short study period. In the UK, the cumulative probability of pregnancy is 32% after 3 months of intercourse. After three IVF cycles the pregnancy rate per cycle does decline, as does the number of patients, but the chance of pregnancy remains 17–23%. A cumulative pregnancy rate of 80% after seven cycles is encouraging despite the small numbers undergoing repeated cycles. We found the cumulative pregnancy rate to be 54% after three cycles and 72% after six, compared with nearly 55% after 6 months in a normally cohabiting, fertile population.

Of the 5073 patients who underwent their first cycle at our unit, some had undergone a prior IVF attempt elsewhere. These cycles would have consisted of different protocols and were therefore not taken into account. However, this could adversely affect our pregnancy rates if poorer responders from elsewhere were inclined to try a different unit. Alternatively, a favourable bias would result from couples who had previously conceived with another team.

Unlike Guzick et al. (1986) who reported the probability of pregnancy remaining constant throughout successive cycles, we found an equal probability in the first three cycles followed by a significantly reduced chance. An early study by Kovacs et al. (1986) reported constant pregnancy rates in up to eight cycles. These authors concluded that, provided patients were prepared to undergo several IVF cycles, their clinical success rates rose to 49% after five egg collections. Dor and colleagues (1996) showed a constant increase in cumulative pregnancy rate which reached a plateau of 56% after six cycles. This was a small series and used three different protocols, so that unbiased comparisons are impossible. Two groups of patients undergoing IVF were considered by Simon et al. (1993). The first group had previously conceived with IVF and the second had previously conceived naturally. Those who conceived naturally, but were subsequently infertile, were less likely to achieve a pregnancy than those who had initially conceived with IVF. Possibly these successful women had a better endometrial response or were less susceptible to any deleterious effects on their eggs or uterus occurring during gonadotrophin stimulation.

To conclude, IVF treatment should not be seen as an isolated event, and biochemical and failed clinical pregnancy should be viewed with a degree of cautious optimism. All couples undergoing IVF treatment should consider that this implies a course of three or more treatment cycles with equal chances of pregnancy in each cycle. The probabilities of success are somewhat higher than those after natural intercourse. Beyond three cycles, success rates per cycle fall, though cumulative pregnancy rates continue to rise, albeit at a slower rate and the chances are still sufficiently high to encourage those with sufficient resources and commitment to try three more. Although it is impossible to predict accurately those who are likely to have a child, analysis of the cumulative pregnancy rate from a treatment centre provides useful information in making decisions about IVF treatment.

Table VI. Pregnancy rate and cumulative pregnancy rate (per cycle)

<table>
<thead>
<tr>
<th>Cycle number</th>
<th>No. of patients in cumulative data</th>
<th>No. of pregnancies in cumulative data</th>
<th>Pregnancy rate (%)</th>
<th>Cumulative pregnancy rate (%)</th>
<th>SE of cumulative pregnancy rate</th>
<th>Total no. of patients per cycle</th>
<th>Total no. of pregnancies</th>
<th>Pregnancy rate per cycle (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5073</td>
<td>1325</td>
<td>26.1</td>
<td>26.1</td>
<td>0.5</td>
<td>5073</td>
<td>1325</td>
<td>26.1</td>
</tr>
<tr>
<td>2</td>
<td>2078</td>
<td>477</td>
<td>23.0</td>
<td>43.1</td>
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<td>2396</td>
<td>588</td>
<td>24.5</td>
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<tr>
<td>3</td>
<td>784</td>
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<td>480</td>
<td>83</td>
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<td>5</td>
<td>117</td>
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<td>19.7</td>
<td>68.0</td>
<td>2.4</td>
<td>193</td>
<td>36</td>
<td>18.7</td>
</tr>
<tr>
<td>6</td>
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<td>12.8</td>
<td>72.1</td>
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<td>7</td>
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<td>27.3</td>
<td>79.7</td>
<td>5.5</td>
<td>22</td>
<td>5</td>
<td>22.7</td>
</tr>
</tbody>
</table>

The pregnancy rate in each of the first three cycles was the same. In the forth and subsequent attempts the pregnancy rate was significantly decreased (P < 0.0001).

References


Kovacs, G.T., Rogers, P., Leeton, J.F. et al. (1986) In-vitro fertilization and...

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