Different perspectives of patients and health care professionals on the potential benefits and risks of blastocyst culture and multiple embryo transfer

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BACKGROUND: A trade-off exists between the risk of multiple pregnancy and prospects of pregnancy itself in assisted reproduction. Blastocyst culture and embryo transfer after ~5 days may be one method of reconciling this dilemma, although a controversial one. METHODS AND RESULTS: We presented a questionnaire to groups of patients, embryologists and clinicians to solicit views on the potential benefits and risks of blastocyst culture and multiple pregnancy. The results indicate that patients are more accepting of multiple pregnancy as a prospective outcome of treatment than those involved in their treatment, despite awareness of the risks. Our data tend to support a genuine difference in values on this point. We also sought views on the patient selection criteria and treatment protocols which should apply in a planned randomized controlled trial comparing blastocyst culture with cleaving embryo transfer (e.g. numbers of embryos to transfer, acceptable levels of risk of twin and triplet pregnancy, the proportion of patients who would be put off from entering the trial by the risk of no embryo transfer). These are presented and discussed with reference to their likely impact on trial recruitment, highlighting differences in perspective between patients and professionals. CONCLUSIONS: We conclude that there are differences among patients, embryologists and clinicians in their perceptions of the desirability of multiple pregnancy, their preferences in certain practical aspects of treatment such as embryo transfer numbers, and their ideas on blastocyst culture and its prospective outcomes and risks.

Key words: blastocyst/embryo transfer/human/multiple pregnancy/questionnaire

Introduction

The proportion of twins and triplets occurring naturally has dwindled owing to the widespread application of modern fertility treatments (Keith et al., 2000). Multiple pregnancies, including twins, have significantly elevated risks for both mothers and babies in comparison with singletons. Their collective needs in antenatal care, delivery and intensive care cots are considerable, and, in addition, serious long-term consequences for health may arise from prematurity and low birthweight, which are commonly associated with multiple gestations (Elster, 2000). Psychological and social problems for families also give cause for concern (Garel et al., 1997).

After IVF, multiple pregnancies arise mainly when more than one embryo is transferred to the uterus. This is done to increase the chances of at least one embryo implanting and resulting in pregnancy, however, the outcome is unpredictable and multiple pregnancies often result. In the UK, up to three embryos may be transferred concurrently, but concerns about high order multiple pregnancies prompted the Royal College of Obstetricians and Gynaecologists (RCOG) to recommend a maximum of two, in women aged <40 years (Royal College of Obstetricians and Gynaecologists, 2000). The Human Fertilisation and Embryology Authority (HF EA) now requires exceptional circumstances to be documented before three embryos are transferred, and recommends not more than two as routine (Human Fertilisation and Embryology Authority, 2001).

A trade-off exists between the risk of multiple pregnancy and prospects for pregnancy itself. This trade-off could be moved further against multiple pregnancy by selecting the most viable embryos (Shoukir et al., 1997; Scott and Smith, 1998). One suggestion, ‘blastocyst culture’, is the prolonged culture of embryos in vitro for ~5 days, by which time the least viable may have succumbed, leaving the most competent available for transfer (Steptoe et al., 1971). This is reputed to mimic the physiological process (Buster et al., 1985), and in many species is the most successful approach to IVF. In humans, blastocyst culture has been reported to increase substantially the implantation rate per embryo transferred, provided that newer purpose designed culture media are used [new: (Gardner et al., 1998; Huisman et al., 2000; Milki et al., 2000) old: (Bolton et al., 1991; Scholtes and Zeilmaker, 1996)]
yet it remains highly controversial for several reasons. Extended culture is an artificial means of selection and may not reflect in-vivo competence. The safety of prolonged culture has not yet been established (Ménézo et al., 1999; Sinclair et al., 2000). The outstanding results obtained by the most successful proponents have generally not been reproduced elsewhere (Coskun et al., 2000). Crucially, even using the latest developments in culture medium, only ~50% of fertilized oocytes survive to become blastocysts. This could result in a proportion of patients having no blastocysts to transfer, despite having embryos available at an earlier stage. Nevertheless, if the potential to select more competent embryos for transfer could be realised, a reduction in the number of embryos transferred, whilst maintaining an acceptable pregnancy rate, would offer a valuable prize of reduced risk of multiple pregnancies. As a bonus, there would be major savings for health services. It is our belief that a properly conducted trial is essential to provide an evidence base on whether the potential benefits of blastocyst culture can be realised in assisted conception centres across the country.

In preparation for a multicentre clinical trial comparing blastocyst culture with the current common practice of embryo transfer on day 2 or 3, we wished to explore the perceptions of patients and health care personnel on the potential benefits and risks of blastocyst transfer, in particular with reference to the above-mentioned trade-off between multiple pregnancy and any pregnancy. This would provide useful information on the likelihood of patients wishing to participate in the trial, and the likelihood of participating clinics engaging actively in recruitment. The findings have provided insights and highlighted differences in the priorities of patients and those involved in their treatment.

Materials and methods
A questionnaire was compiled to elicit views on the benefits and risks of blastocyst culture, and on factors likely to affect recruitment to our planned clinical trial. The first section of seven open questions was answered in free form. Some topics were revisited in the second section, which consisted of seven questions requiring quantitative answers. The questions are summarized in the Appendix.

The respondents were given information based upon recently published literature, before answering the questions. The base-line information was as follows: Once fertilization is assured, a normal IVF or ICSI cycle has a 99% chance of embryos being transferred on day 2 or 3 (local audit) and blastocyst culture has about a 90% chance of embryos being transferred on day 5 or 6 (Jones et al., 1998; Marek et al., 1999). The average risk of a pregnancy being twins with current practice was taken to be 28% and triplets 3% (Human Fertilisation and Embryology Authority, 1999). We assumed that about 50% of embryos would become blastocysts in vitro (Gardner et al., 1998; Jones et al., 1998; Cruz et al., 1999). The assumption in Questions 2 and 3 that blastocyst transfer might result in a 7% increase in pregnancy rate was based upon a straw poll by telephone of clinicians and scientists in 20 UK assisted conception centres (G.Hartshorne, unpublished data). A copy of the full questionnaire is available from the corresponding author.

The questionnaire was presented to three groups. The provision of identifying or non-identifying information by the respondents about themselves was optional.

Group 1. Prospective, current and past patients attending an open meeting of the Centre for Reproductive Medicine Patient Support Group. An invitation was extended to G.H. to address the meeting, at the recommendation of the Quality Focus Group. Those present were invited to complete the questionnaire, after a brief informal talk on our proposal for a trial of blastocyst culture, including information on the chances of multiple pregnancy and its consequences. The session was relaxed and patients asked questions freely. The responses were discussed anonymously with the Quality Focus Group to facilitate interpretation and to provide feedback to the Patient Support Group.

Groups 2 and 3. Delegates attending relevant conferences were offered the questionnaire for completion during a slot in the programme. The conferences were a symposium on blastocyst culture, hosted by Birmingham Women’s Hospital, and the winter workshop of the British Fertility Society (BFS, St Thomas’s Hospital, London). The responses were allocated into the following groups for analysis: patients, scientists, clinicians (medical doctors) and nurses. Answers to the quantitative questions were analysed statistically using the non-parametric Kruskal Wallis test and p x q contingency tables (Campbell, 1989). Qualitative issues arising from the open questions were assessed by counts of like answers.

Results
A total of 22, 39 and 15 analysable questionnaires were received from the three meetings of patients, symposium delegates and BFS delegates respectively, representing 67, 53 and 21% of those offered the questionnaires. Four respondents (two patients, two embryologists) answered only the open questions. One additional form from a clinician in the BFS group was annotated without answering the questions, and could not be analysed. The low response rate in the BFS group brings into question the representativeness of this sample, consequently, statistical analyses of this group may be less reliable. The low response rate was most probably the result of the short time available within the BFS programme. However, despite this caveat, the answers from both groups of professionals were similar in most respects.

The information presented voluntarily showed that the patient group included three who had had successful treatment previously, one resulting in twins. Three of the other 17 were embarking upon their first IVF or ICSI cycle, the remainder had had 1–9 previous IVF or ICSI attempts.

The respondents attending conferences comprised three fertility nurses, 33 embryologists, 16 medical doctors (clinicians) and two who did not specify their job titles. These two were included in the clinician group since they were attending the BFS meeting, from which all the other respondents were clinicians. The small number of nurses (three) precluded statistical evaluation. All the clinicians practised assisted conception, while eight did and five did not practice obstetrics. Thirteen clinicians and 22 embryologists were from units that had attempted blastocyst culture.

Open questions
The positive and negative points volunteered in response to Question 1 (general feelings about blastocyst culture) are summarized in Table I. Patients produced a significantly (P < 0.05) greater proportion of positive replies than specialists, with embryologists producing nearly equal numbers of
positive and negative comments. A total of 41% of the patients’ positive remarks related to the higher chance of pregnancy, compared with 23 and 14% of embryologists and clinicians respectively. None of the patients remarked upon a reduction in multiple pregnancy rate as an advantage of blastocyst culture, whereas this accounted for a quarter of the comments from health care professionals. The increased availability of information about embryo development resulting from blastocyst culture was recognized by all groups. The main disadvantages noted were the increased chance of having no embryo transfer and the need for further information and follow-up of children. Workload, resource and technical concerns featured strongly among the embryologists’ replies.

Question 2 (indications for blastocyst culture) produced usable data on age and number of previous attempts, but not on the number of embryos available, which was interpreted differently by the different groups. The results (Table II) show that about half the respondents did not think discrimination on prognostic criteria was appropriate. However, of the other responses, patients thought that older/poor prognosis patients were particularly suitable for blastocyst culture, whereas embryologists favoured young/good prognosis patients. Consistent with this difference in viewpoint, no patient felt that blastocyst culture was suitable for first time couples, whereas both embryologists and clinicians considered them neither more nor less suitable than veterans of assisted conception.

Question 3, concerning the increase in pregnancy rate which would make blastocyst culture worthwhile, was answered freeform. The median responses for patients, embryologists and clinicians were ‘any’, 5% and 5% (ranges any−50%, any−10% and any−100%) respectively.

Responses to Question 4 showed that 59% of patients and 72% of healthcare professionals would not be deterred from the trial by a 10% risk of no blastocyst transfer (Table III).

A variety of responses were received on the risks of multiple

| Table I. Positive and negative comments volunteered concerning blastocyst culture |
|----------------------------------|-----------------|-----------------|
|                                  | Patients (%)    | Embryologists (%) | Clinicians (%) |
| **Good points**                  |                 |                 |                |
| Higher chance of pregnancy/birth | 9 (41)          | 15 (23)         | 3 (14)         |
| Lower multiple pregnancy rate    | 0               | 17 (26)         | 5 (24)         |
| ‘Good idea’                      | 5 (23)          | 5 (8)           | 5 (24)         |
| Information on embryo development/selection | 4 (18) | 11 (17) | 2 (10) |
| Embryo in more mature state/better synchrony with uterus | 1 (5) | 6 (9) | 3 (14) |
| Various benefits to patients⁴ | 1 (5)           | 12 (18)         | 2 (10)         |
| Benefits relating to ‘progress’  | 2 (9)           | 0               | 1 (5)          |
| **Total good**                   | 22 (82)         | 66 (51)         | 21 (62)        |
| **Bad points**                   |                 |                 |                |
| Increased chance of failed embryo transfer | 1 (20) | 19 (30) | 4 (31) |
| Increased multiple pregnancy risk | 1 (20)          | 1 (2)           | 0              |
| (if number of embryos not reduced) |                 |                 |                |
| Need for follow-up info. on children | 2 (40) | 2 (3) | 5 (38) |
| Lack of knowledge               | 1 (20)          | 5 (8)           | 0              |
| Uterine environment may be better for embryo development | 0 | 20 (32) | 3 (23) |
| Workload, cost and resources    | 0               | 10 (16)         | 0              |
| Various technical problems⁶      | 0               | 6 (10)          | 0              |
| Emotional trauma                | 0               | 0               | 1 (8)          |
| Overhyped procedure             | 0               | 0               | 1 (8)          |
| **Total bad**                    | 5 (18)          | 63 (49)         | 13 (38)        |

⁴e.g. moved patients through to the outcome of their treatment more quickly; treatment option for patients with multiple previous treatment failures; additional information on embryo development may help to dissuade patients with very poor prognosis from continuing with treatment.

⁵P < 0.05, pxq contingency table.

⁶e.g. increased complexity of culture system, problems with freezing blastocysts, unpredictable process.

| Table II. Who should have blastocyst culture? |
|----------------------------------------------|-----------------|-----------------|
|                                              | Patients (%)    | Embryologists (%) | Clinicians (%) |
| **Age**                                      |                 |                 |                |
| Anyone                                       | 6 (46)          | 10 (40)         | 9 (56)         |
| Young/good prognosis                         | 1 (8)           | 12 (48)         | 2 (12)         |
| Older/poor prognosis                         | 6 (46)          | 3 (12)          | 3 (19)         |
| Don’t know                                   | –               | –               | 2 (12)         |
| **Total**                                    | 13              | 25              | 16             |
| **Number of previous attempts**              |                 |                 |                |
| Anyone                                       | –               | 5 (19)          | 4 (33)         |
| >0–1                                        | 3 (11)          | 1 (8)           |                |
| >1–2                                        | 5 (38)          | 3 (11)          | 1 (8)          |
| >2–3                                        | 3 (23)          | 9 (35)          | 4 (33)         |
| >3                                           | 1 (8)           | 1 (4)           | 2 (17)         |
| Several                                     | 3 (23)          | –               | –              |
| Non-specified                                | 1 (8)           | –               | –              |
| **Total**                                    | 13              | 26              | 12             |
and clinicians who thought that no more than two embryos should be replaced were 61, 85 and 82% respectively.

Question 7, on how best to start a new treatment, was ambiguous. Some patients thought it asked how they could best prepare themselves for a treatment cycle, whereas other patients and all the professionals who answered, interpreted the question as intended by the authors, in terms of how a new treatment procedure should be worked-up and introduced. No consensus was evident, but some examples are presented in Table VI.

### Quantitative questions

A summary of the responses to quantitative Questions 1–5 and 7 are presented in Table VII and responses to Question 6 are shown in Figure 1. No significant differences in opinion were detected in responses to Questions 1, 4, 5 and 7. There was no significant difference in the percentage pregnancy increase at which the groups would consider blastocyst culture worthwhile, despite a wider range of opinion among the patients and embryologists than the clinicians. The median results obtained appeared different and less spread when the relative risks associated with blastocyst culture were made explicit (compared with qualitative Question 3). Question 4 showed that a similar number of fertilized oocytes would be regarded by all groups as an appropriate start point for blastocyst culture treatment. This suggests that respondents had a reasonable grasp of the technology. Question 5, concerning the proposal to restrict numbers of embryos transferred to two, was rejected by 40% of patients, and a similar proportion of clinicians and embryologists, which would suggest that some difficulty might be encountered in trying to recruit patients to a trial including this restriction. Interestingly, Question 7 showed that all groups would require a pregnancy rate of ~30% on average before considering single embryo transfer for preference.

Questions 2, 3 and 6 demonstrated significant divergence of opinion among groups. Most notably, Figure 1 shows the response to Question 6, balancing the potential risks of multiple pregnancy against the potential of a higher pregnancy rate occasioned by an increased implantation rate per embryo transferred which may arise from blastocyst transfer. Nearly 80% of patients preferred options that increased the chances of pregnancy, with nearly half of these accepting an increased risk of multiple pregnancy. By contrast, the option including an increased risk of multiple pregnancy was preferred by <5% of the health care professionals. Questions 2 and 3 also related to the acceptability of multiple pregnancies and the responses again indicated that patients were significantly more accepting of this prospective outcome than health care professionals.

### Discussion

The data presented were collected in preparation for a randomized controlled clinical trial (RCT) of blastocyst culture in comparison with cleavage stage embryo transfer. A multicentre RCT will be crucial to provide unbiased data on the potential benefits and concerns of blastocyst culture as outlined in the introduction. It would also help to quantify the outcome to be

### Table III. Would a 10% risk of all the embryos dying before transfer put you off?

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Embryologists</th>
<th>Clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>5 (23)</td>
<td>7 (21)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>No</td>
<td>13 (59)</td>
<td>24 (73)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Other*</td>
<td>4 (18)</td>
<td>2 (6)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>33</td>
<td>18</td>
</tr>
</tbody>
</table>

*e.g. ‘maybe’.
Figures in parentheses are percentages.

### Table IV. Representative examples of comments on the risks of multiple pregnancy

**Patients**

A chance we’re prepared to take
Quite scary, but people who conceive normally have multiple births, therefore it’s not unnatural
The aim should be for a singleton, twins are OK, but the risks with triplets are too high
Would rather have multiple pregnancy than none. Two would perhaps be ideal

**Embryologists**

Blastocyst culture opens the possibility of doing one-embryo-transfer thereby reducing the risk of multiple pregnancy dramatically
Generally we transfer two embryos but future reductions in multiple pregnancy would be beneficial
Risk of triplet (+ twin) pregnancy should be minimized

**Clinicians**

Should eliminate if possible, even twins
Accepted as of overriding importance
I’d prefer the ‘gold standard’ of working towards a single live healthy baby

### Table V. How many embryos should be transferred?

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Embryologists</th>
<th>Clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5 (29)</td>
</tr>
<tr>
<td>1–2</td>
<td>14 (61)</td>
<td>28 (85)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>3 exceptionally</td>
<td>2 (7)</td>
<td>3 (9)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>3</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>–</td>
</tr>
<tr>
<td>at least 3</td>
<td>2 (7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>no specific answer</td>
<td>3 (13)</td>
<td>1 (3)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>33</td>
<td>17</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages.

The tone of responses from patients was different to that from embryologists and clinicians. Some representative examples are given in Table IV. Overall, 45% of patients, 6% of embryologists and no clinicians gave responses that indicated acceptance of multiple pregnancy. A quarter (22–28%) of responses in each group indicated a cautious approach to multiple pregnancy. Answers from ~50% (44–54%) of respondents in all groups indicated awareness of the risks of multiple pregnancy, however an absence of this aspect in their answer may not infer a lack of awareness. In line with this, the responses to Question 6 (Table V) show that a quarter of responding clinicians, but no patients or embryologists, indicated that embryos should be transferred singly. Similarly, the percentages of patients, embryologists
Table VI. What is the best way to start a new treatment?

Patients
Get fit, body mass index at optimum, counselling provided
Offer to a sample of women, maybe 100 or more, as a research group. Charge slightly less for first year of trials
With as much information as possible
Clinical trial with volunteers for whom IVF/ICSI is not working

Embryologists
Start with the good responders to make sure blastocysts will be available for embryo transfers. It is essential to have confidence in the system we are using the lab
Try on patients with multiple transfer failures
Give the added treatment at no extra cost
Trial basis with patient consent (informed)

Clinicians
Offer as buy in extra for patient to choose whether it is of value to them
Randomized prospective centrally funded trial
Randomized controlled trial in poor responders
Research on those with good quality embryos and good numbers of eggs i.e. rather than the ‘poor responders’

Table VII. Summary data on responses of patients, scientists and clinicians to quantitative questions.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Patients</th>
<th>Embryologists</th>
<th>Clinicians</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 % increase pregnancy rate required to make blastocyst culture worthwhile</td>
<td>Median 11</td>
<td>10</td>
<td>5</td>
<td>NS^b</td>
</tr>
<tr>
<td></td>
<td>Range 1–30</td>
<td>0.5–27.5</td>
<td>3–11</td>
<td></td>
</tr>
<tr>
<td>2 Additional % point increase in rate of twin pregnancies acceptable (at 7% increased pregnancy rate)</td>
<td>Median 10</td>
<td>6</td>
<td>6</td>
<td>&lt; 0.05^a</td>
</tr>
<tr>
<td></td>
<td>Range 20</td>
<td>30</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>3 Additional % point increase in rate of triplet pregnancies acceptable (at 7% increased pregnancy rate)</td>
<td>Median 2.5</td>
<td>0</td>
<td>0.003</td>
<td>&lt; 0.01^a</td>
</tr>
<tr>
<td></td>
<td>Range 20</td>
<td>31</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>4 No of zygotes needed to embark on blastocyst culture</td>
<td>Median 7</td>
<td>7</td>
<td>5.5</td>
<td>NS^a</td>
</tr>
<tr>
<td></td>
<td>Range 19</td>
<td>31</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>5 % still wanting the choice of three embryos transferred</td>
<td>% 40</td>
<td>51.6</td>
<td>44.4</td>
<td>NS^b</td>
</tr>
<tr>
<td></td>
<td>n 20</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>7 % chance of pregnancy expected before choosing single embryo transfer</td>
<td>Median 30</td>
<td>30</td>
<td>27.5</td>
<td>NS^a</td>
</tr>
<tr>
<td></td>
<td>n 20</td>
<td>31</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

^aKruskall Wallis test.
^bPxq contingency table.

expected if blastocyst transfer were to be widely introduced.
The solicitation of views of service users and providers is a crucial part of the recommended work-up (Hanley et al., 2000).
We have previously involved patients in many aspects of planning our service, to good effect, and have found their opinions to be informed with a unique and well-reasoned perspective, which has been helpful, for example, in prioritizing developments in our unit. The numbers of patients and specialists providing responses were relatively small, explained by the limited availability of opportunities to target appropriate audiences. Moreover, it is highly likely that views regarding blastocyst culture, multiple embryo transfer and multiple pregnancy in all groups are evolving. Indeed, since the data were collected, professional opinion may already have shifted (Royal College of Obstetricians and Gynaecologists, 2000; Human Fertilisation and Embryology Authority, 2001). It was therefore important to ensure that our data were presented promptly to provide a snapshot of current opinion.

The present study has confirmed that patients are more willing to accept the risks of multiple pregnancy in prospect than their carers (Gleicher et al., 1995). This significant difference was found notwithstanding a lack of difference on several other questions. Infertile patients are clearly aware of the risks of multiple pregnancy but many choose to accept them, on behalf of themselves and their potential children. It is debatable whether patients may be considered fully able to take an objective view upon this point as their perception of multiple pregnancy may be affected by their personal situation. Whether the same view would be taken in retrospect is not known. However, these patients would be considered competent to take responsible decisions in other respects, including consent or otherwise to medical treatment for themselves and any young children they may already have.

Clinicians may be affected by the perinatal prognosis of multiple pregnancies. In addition, it is possible that health care providers in general and clinicians in particular may be more
Whether these risks are acceptable to society is another matter, when considerable public expenditure is required to care for iatrogenic multiple pregnancies (Dunn and McFarlane, 1996; Hidlebaugh et al., 1997; Wolner-Hanssen and Rydstroem, 1998). Moreover, the legal requirement to consider the welfare of the child places an additional responsibility on the service provider (Human Fertilisation and Embryology Act, 1990). Clinicians and embryologists both demonstrated concern about the outcome of pregnancy, and it is important that we should work for future improvements. However, the main issue for patients facing treatment remains their chance of a pregnancy, and philosophically we are uneasy in the notion that parents should be coerced to accept societal or professional limitation on all but the most extreme actions they may choose.

The input of results from the questionnaire produced a well-informed discussion and resulted in our moving towards a pragmatic trial design. As shown in Table II, patients felt that those with previous attempts and older/poor prognosis patients should be included, and were more relaxed about transfers of more than two embryos than the other groups (Table V). A quarter of clinicians supported the transfer of embryos singly (Table V) whilst requiring a pregnancy rate of at least 20% to be maintained (Table VII).

It has been previously suggested that a reduction from three to two embryos transferred in patients for whom there is a choice will not affect pregnancy rates (Templeton and Morris, 1998; Royal College of Obstetricians and Gynaecologists, 2000). This retrospective interpretation of national statistics has not been challenged by a prospective randomized controlled trial, and some evidence is contradictory (Gerris et al., 1999). The number of embryos transferred beyond which no further increase in pregnancy rate would occur has not yet been established with certainty, but may be at least three (Fishel et al., 1985; ASRM/SART, 2000). Fewer embryos are normally transferred to patients perceived to be more fertile in view of a younger age, previous history of pregnancy, aetiology of infertility and lower likelihood of age-related reduction in embryo viability, rendering the national data uncontrolled, and tending to equalise the pregnancy rates of two embryo transfers (good prognosis patients) and three embryo transfers (poor prognosis patients). Changes in the implantation rate due to, e.g. blastocyst culture, would also affect such calculated predictions, i.e., if the theory that blastocysts have higher implantation rates per embryo is confirmed, then the alteration in pregnancy rate effected by each additional embryo transferred would be more marked.

An interesting variety of responses was received on the best method of starting a new treatment, indicating broad diversity of opinion on a topic of some importance and perhaps reflecting the complexity of balancing the needs of the individual patient who may be paying for their own treatment against the need to design appropriate trials. Assisted conception is noted for the lack of control with which new methods are often introduced (Vandekerckhove et al., 1993), and the current legislative arrangements in the UK require that any new technique is shown to be safe before its introduction to patient treatment. As a result, equipoise may be lost before the treatments are

![Figure 1](image-url). Outcome preferences of patients and health care professionals in terms of the balance between pregnancy rates and multiple pregnancy rates. Question 6: Blastocysts are believed to have a higher chance of implanting than cleaving embryos. Depending upon the number of embryos replaced, this could result in: A = The same chance of pregnancy as now, but a lower risk of multiple pregnancy. B = A higher chance of pregnancy than now, with the same risk of multiple pregnancy. C = An even higher chance of pregnancy, together with an increased risk of multiple pregnancy. D = The possibility of nearly eliminating multiple pregnancy (except identical twins) by replacing only one embryo, which would be associated with a lower chance of pregnancy. Would you prefer A, B, C or D?

Figure 1. Outcome preferences of patients and health care professionals in terms of the balance between pregnancy rates and multiple pregnancy rates. Question 6: Blastocysts are believed to have a higher chance of implanting than cleaving embryos. Depending upon the number of embryos replaced, this could result in: A = The same chance of pregnancy as now, but a lower risk of multiple pregnancy. B = A higher chance of pregnancy than now, with the same risk of multiple pregnancy. C = An even higher chance of pregnancy, together with an increased risk of multiple pregnancy. D = The possibility of nearly eliminating multiple pregnancy (except identical twins) by replacing only one embryo, which would be associated with a lower chance of pregnancy. Would you prefer A, B, C or D?


day.
ready and available for trial in this country. It is unfortunate that our application for a multicentre RCT was rejected, rendering more likely the introduction to the UK of another assisted conception technique before its scientific evaluation.

A further concern is the paucity of long-term follow-up data on children resulting from various in-vitro procedures, including blastocyst culture. Funding of such expensive studies is a major issue for a discipline where state funding is restricted and most patients are paying for their own treatment.

Blastocyst culture is unlikely to be a suitable treatment for every infertile couple, and many questions persist about its most useful application and the reality of the benefits that it promises. Nevertheless, our investigation has shown that patients and centres would be willing to participate in a trial and the majority would not be put off by a 10% risk of all embryos failing to survive, though a substantial minority would wish to retain the option of three embryos transferred, despite the elevated risks of multiple pregnancy.

In conclusion, our questionnaire has highlighted differences among patients, embryologists and clinicians in their perceptions of the desirability of multiple pregnancy, their preferences in certain practical aspects of treatment such as embryo transfer numbers, and their ideas on blastocyst culture and its prospective outcomes and risks.

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References


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Appendix

Summary of questions

(A copy of the full questionnaire is available from the corresponding author.)

Personal information (confidential—no names will be attributed)
For patients:
Your name:
Your age:
Your number of previous attempts:
Any special comments:
For symposium delegates:
Your name:
Your job title:
Has your unit attempted blastocyst culture?
Any special comments:
For BFS delegates:
Your name:
Your job title:
Do you practise assisted conception?
If so, has your unit attempted blastocyst culture?
Do you practise obstetrics?
Any special comments:

Open questions—Please answer in your own words

(1) What do you think of the idea of blastocyst culture? Good and bad points?
(2) Who should have blastocyst culture? Age
No of embryos needed to start blastocyst culture treatment
No of previous attempts?
(3) What % increase in pregnancy rate would make blastocyst culture worthwhile?
(4) Would a 10% risk of all the embryos dying before the transfer put you off this service?
(5) What do you think about the risks of multiple pregnancy?
(6) How many embryos should be transferred?
(7) What is the best way to start a new treatment?

Quantitative questions

1. If we assume (once fertilization is assured) that a normal IVF or ICSI cycle has a 99% chance of embryos being transferred on day 2 or 3 and that blastocyst culture has about a 90% chance of embryos being transferred on day 5 or 6, please indicate the percentage increase in pregnancy rate (i.e. in addition to the standard IVF/ICSI pregnancy rate of about 25%) which you would expect before preferring blastocyst culture.

2. If blastocyst culture offered a 7% increase in pregnancy rate, what additional risk of a twin pregnancy would you be prepared to accept? (Average risk of a pregnancy being twins with current practice is about 28%).

3. If blastocyst culture offered a 7% increase in pregnancy rate, what additional risk of a triplet pregnancy would you be prepared to accept? (Average risk of a pregnancy being triplets with current practice is about 3%).

4. Patients will be asked to choose how many fertilized embryos they would want to have before they decide whether to enter the trial. A higher number gives a better chance of getting blastocysts for transfer (on average about 50% will become blastocysts but this is very variable). However, because not all of the embryos are likely to become blastocysts, the chances of having enough for a cryopreservation cycle are reduced. How many embryos would you choose as a starting point?

5. The legal maximum number of embryos which can be transferred is three, but recent guidelines from the Royal College of Obstetricians and Gynaecologists advise not more than two, to reduce the chance of multiple pregnancy which carries risks to babies and their mothers. Patients entering the trial will receive not more than two cleaving embryos or two blastocysts. Would you still want the choice of having three embryos transferred? YES/NO

6. Blastocysts are believed to have a higher chance of implanting than cleaving embryos. Depending upon the number of embryos replaced this could result in:
A: The same chance of pregnancy as now, but a lower risk of multiple pregnancy.
B: A higher chance of pregnancy than now, with the same risk of multiple pregnancy.
C: An even higher chance of pregnancy, together with an increased risk of multiple pregnancy.
D: The possibility of nearly eliminating multiple pregnancy (except identical twins) by replacing only one embryo, which would be associated with a lower chance of pregnancy. Would you prefer A, B, C or D?

7. What chance of pregnancy would you expect before you would choose single embryo transfer?