Article

Natural cycle IVF with and without terminal HCG: learning from failed cycles

Dr Lenton's career in reproductive endocrinology began in the Department of Obstetrics and Gynaecology in 1972. In 1987, she and Professor Ian Cooke established the Sheffield Fertility Centre, an IVF clinic with a significant bias towards natural cycle IVF, at least in those early years. Now, some 35 years and 150 publications later, the IVF clinic is part of the CARE group and Liz Lenton acts as a freelance advisor to other IVF clinics, as well as providing support.

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Abstract

Natural cycle IVF, without the use of LH down-regulation, is difficult because women start spontaneous LH surges at any time of the day and on any day of the week. This is not readily compatible with delivery of a routine IVF service and so historically the natural cycle has been modified by the use of human chorionic gonadotrophin (HCG) to make the natural cycle fit convenient clinical practice. This report re-evaluates data collected some years ago and seeks to determine whether the use of HCG is ultimately beneficial. Two large series of natural cycle IVF where only LH monitoring was performed (534 cycles) or where this was combined with HCG as necessary (241 cycles) were analysed. In essence, the use of HCG introduced as many problems as it overcame: there was no net benefit with respect to the number of eggs collected or clinical pregnancies generated. In fact there was an overall deterioration in all indices. The principle difficulties with natural cycle IVF are those associated with the prediction of follicle maturity and hence timing egg collection, and the conflict between costly and intrusively frequent monitoring with simpler but far less effective approaches.

Keywords: *HCG outcome, LH monitoring, natural cycle IVF*

Introduction

For a number of years natural cycle IVF was the principle type of IVF provided by the Sheffield Fertility Centre, Glen Road, Sheffield, S7 1RA. It initially operated as a 7-day service, making it easy for patients to undergo blood monitoring, egg collection and embryo transfer on any day of the week to fit their specific menstrual patterns. Ultimately, from a staffing perspective, this proved difficult and it was decided to pilot natural cycle IVF provision on the basis of a 6-day service, the clinic closing completely on Sundays. Although the IVF that had been provided was completely natural, i.e. no stimulation of any kind, and the timing of egg collection determined solely by the detection of a spontaneous LH surge, to accommodate Sunday closures meant the limited introduction of human chorionic gonadotrophin (HCG) injections to advance the time of egg recovery if it was anticipated that this might fall on a Sunday.

Thus the review described here re-evaluates the period when all procedures were available 7 days a week (1991–1992) and so could be optimally timed and a consecutive period (1992–1993) when HCG was used to advance 'ovulation' in a small number of subjects (Lenton *et al*., 1995) in order to better understand the factors associated with failed cycles. The specific issues evaluated are how easy it was to predict which subjects would need egg collection on a Sunday and how effective intervention was using HCG. The end-points assessed are follicle entry, egg recovery, embryo transfer and clinical pregnancy.

It should be noted that, despite operating a 7-day service, this was still restricted to reasonable working hours, namely about 07.00 to about 21.00 hours with egg collections scheduled between 09.00 and 17.00 hours. This necessitated two shifts of nursing staff while the embryologists frequently had to work

unsocial hours, staying to perform inseminations several hours after the last egg collection at 16.00 or 17.00 hours.

Materials and methods

The review consists of 775 cycles where natural cycle IVF was the intended treatment divided into two time periods: Group 1, containing 534 cycles from 335 subjects, was an 18-month period when a full 7-day service was available; Group 2, containing 241 cycles from 176 subjects, followed immediately on from Group 1, lasted 15 months, and was when Sunday working was abolished. Apart from a further 66 cycles (7.8%, not included) that were cancelled for reasons unrelated to the current evaluation (inaccessible ovaries, ovarian cysts, anovulation or for personal reasons), there was no subject selection. All patients attending the clinic and undergoing natural cycle IVF in these time periods, even if the cycle was ultimately cancelled, were included in the evaluation.

Subjects for whom natural cycle IVF is suitable need to have regular (25–35 day) ovulatory cycles; the small number of women whose cycles proved to be anovulatory have been excluded (see above). Subjects could be any age provided the ovulatory criterion was met and the age range in this series was 23–47 years, with 7.6% of cycles in women aged 40 years and above. At the time of the study, intracytoplasmic sperm injection (ICSI) was not available, so only male partners with mild or moderate fertility factors or where donor sperm was required were accepted. Apart from anovulation and severe male factor, all other causes of infertility were represented.

The IVF provided was completely natural in that no stimulation of any sort was used, the subjects were simply tracked from about day 8/9 of their spontaneous menstrual cycle using ultrasound scans and daily oestradiol assay. Twice-daily LH measurement was instituted once oestradiol concentrations had risen three-fold. Subjects attended the clinic between 07.00 and 09.00 hours for blood sampling and scanning and they collected their own evening blood sample by finger prick, approximately 12 h later. This small sample, typically 200 µl, was delivered to the laboratory when the subjects returned to clinic the following morning.

The start of an LH surge was determined from the pattern of LH in the serial samples obtained once a follicle was present (ultrasound) and producing significant amounts of oestradiol (venous blood assay). Blood samples were obtained at approximately 08.00 and 20.00 hours until it was clear the LH surge had commenced. An LH rise above 10 IU/l that was followed by further LH increases was used to interpolate the start of the LH surge, which had occurred at some time during the preceding 12 h (Zayed *et al*., 1997). The higher the LH concentration at first detection, the longer the LH surge had been underway before the time of the sample. Egg collection was then scheduled for between 25 h and 47 h following the time when the surge was estimated to have started. Although an interval of 35 h between the start of LH surge and egg collection was deemed ideal, this could only be achieved in those subjects whose LH surge started during the night (22.00 to 06.00 hours). Many subjects commenced LH surges at other times of the day and, because the clinic was constrained to undertake egg collections between 09.00 and 17.00 hours, some adaptation to idealised timing was necessary (**Table 1**). In approximately 50% of cycles, egg collection was timed for 35 h from the LH surge. All other egg collection timings had to be a compromise between taking place late (09.00 hours or later the following day, 39–47 h) or early (17.00 hours the same day, 25–33 h). With late egg collections there was a risk of prior spontaneous ovulation and with early ones that follicular fluid would be obtained but no egg would be found.

The majority of cycles scheduled for egg collection during the early part of the day were 'late' in that the interval between the start of LH surge and egg collection was >35 h, to reduce the chance of spontaneous ovulation (and consequent loss of the egg), indomethacin (as 50 mg orally in the morning and 100 mg rectally at night from the time that the decision to perform egg collection was taken) was given to most of these subjects (Athanasiou *et al*., 1996).

Details of the endocrine monitoring and the method of egg collection and embryo transfer (all single embryos) have been described elsewhere (Zayed *et al*., 1997). Clinical pregnancies were those where a fetal heart was seen using ultrasound.

Results

Despite the pretreatment selection criteria of regular 25–35 day cycles, presumptively 11–21 day follicular phases, follicular-phase length, defined as the onset of menses (day 1) to the scheduled day of egg collection, varied from 6 to 23 days (**Figure 1**) in the 530 (out of 534) Group 1 subjects where this could be determined with absolute precision. Some 6% of cycles had follicular phases shorter than or equal to 10 days. In these cycles, monitoring was seldom started early enough to detect the start of the LH surge some 48 h before ovulation.

Group 1 treatment cycles

A total of 534 eligible cycles were started in Group 1, of these 39 (7.3%) ended in cancellation before egg collection had been scheduled, because of poor oestradiol profiles, short follicular phases (so inadequately monitored) or small or ambiguous LH surges. This left 495 cycles for which egg collection was scheduled.

Day of the week

The 495 scheduled egg collections in Group 1 subjects were expected to fall randomly on any day of the week and, this being so, it can be estimated that about 14% (1/7) of all procedures should occur each day. In practice this situation was reasonably well observed (**Figure 2**) with between 11% and 16% of procedures occurring daily.

Time within the day

The effect of trying to adapt LH surges starting at any point in the 24 h period to egg collections within a discrete 9 h window meant some procedures were not well timed (**Table 1**). The consequence of this was that, instead of a steady 11% (1/9) of all procedures taking place each hour during the 9 h, there was

Table 1. Scheme for scheduling egg collection[a] depending on the hour in the day when the LH surge was deemed to have started.

Time of start of LH surge	*LH surge in morning blood*	*LH surge in afternoon blood*	*Interval from LHS (h)*	*Time of egg collection*	*Interval from LHS (h)*	*Time of egg collection*
20.00	+	+	37	09.00		
22.00	+	+	**35**	**09.00**		
00.00	+	+	**35**	**11.00**		
02.00	+	+	**35**	**13.00**		
04.00	+	+	**35**	**15.00**		
06.00	+	+	**35**	**17.00**		
08.00		+	33	17.00		
10.00		+	31	17.00	47	09.00
12.00		+	29	17.00	45	09.00
14.00		+	27	17.00	43	09.00
16.00		+	25	17.00	41	09.00
18.00		+			39	09.00

LHS: LH surge; +: LH surge detected.
[a]Ideally egg collection was timed for 35 h from the start of the LH surge, but in practice this timing could only work for those approximately 50% of cycles with surges starting between 22.00 and 06.00 (shown in bold).

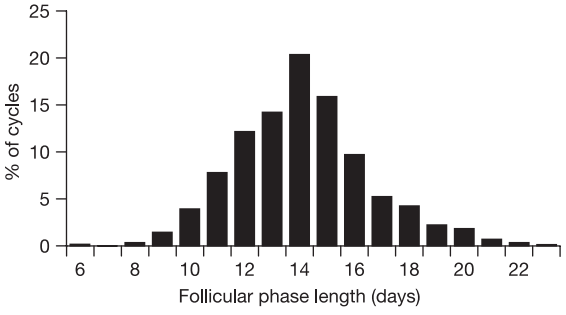

Figure 1. Variation in follicular-phase length in 530 cycles in regularly ovulating women (Group 1), defined as the interval between the last menstrual period (day 1) and the presumptive day of egg collection based on detection of the spontaneous LH surge. Egg collection was scheduled in 93% of cycles; 7% were cancelled due to short follicular phase, poor follicle dynamics (small follicle or low oestradiol concentration) or short duration LH surge (±24 h). Eggs were actually obtained in 403 cycles (76%).

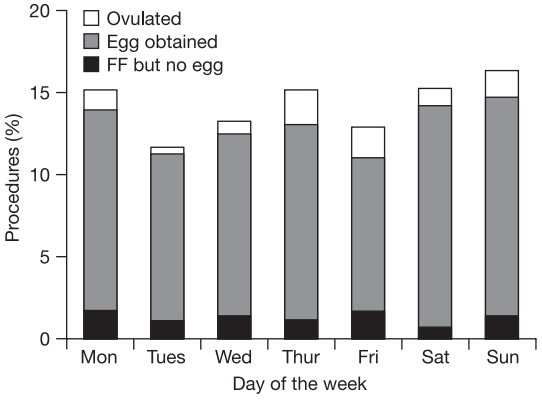

Figure 2. In natural cycle IVF, the distribution of scheduled procedures across each day of the week was approximately constant, at about 14% for 495 cycles monitored by identifying the start of the spontaneous LH surge. Similarly the distribution of cycles wrongly classified, so that they were either timed too early (follicular fluid (FF) obtained but no egg) or too late (follicle already ovulated), was also constant.

significant variation. Rather more egg collections were scheduled between 15.00 and 17.00 hours (15% and 25%), as cycles where ovulation was expected during the evening or night were brought forward (**Figure 3a**), so that the interval between the start of LH surge and egg collection was less than 35 h. Further, although only 12% of egg collections took place between 09.00 and 10.00, about 20–24% could have been expected to be ready at this time (**Table 1**). However as only one egg collection could take place at a time (one theatre), the most urgent cycles were put in first, pushing to later, particularly on a busy morning, some cycles that might have actually been well timed for 09.00, but which were late by 11.00. Since the majority of these 09.00 and 10.00 cycles had had ovulation 'blocked' by indomethacin, this was not of immediate concern. Thus both the beginning and the end of the day contained egg-collection procedures that were less optimally timed relative to the start of the LH surge, and might thus be expected to result in a less good outcome.

The impact of poor timing is clearly shown in **Figure 3b,** in which a high proportion of the 48 cycles with 'no egg' occurred at 17.00 hours. In these cases, the follicle was clearly present, was entered by the needle and follicular fluid aspirated, however no oocyte was found despite vigorous flushing. This suggests that, in at least 27% of the cycles scheduled for egg collection at 17.00, the procedure was timed too early relative to the LH start. Conversely, the 43 egg collections that were timed too late had either ovulated shortly prior to the procedure or the follicle 'exploded' as the needle touched it. As shown in **Figure 3c**, these cycles were commonest between 09.00 and 11.00 and were particularly marked (24%) in the 11.00 egg collections. This was principally due to the lower indomethacin cover in the 11.00 egg collections.

The impact of timing of egg collection (and hence the age of the egg at insemination) was still apparent even when eggs had been successfully recovered. Fertilization rates were lower (53.1%) at 17.00 hours compared with 67.6% over the remainder of the day (data not shown). While the overall clinical pregnancy rate was 15% per embryo transfer, timing also affected the clinical pregnancy rates, demonstrating a slightly better chance of pregnancy (17% per embryo transfer) when egg collection took place between 11.00 and 14.00 than when the egg collection was performed at other times (11%) (**Figure 3d**). The most successful egg collections were those accurately timed to about 35 h from the start of the LH surge (**Table 1**).

The value of indomethacin

The protocol dictated that all subjects scheduled for egg collections at 09.00 and 10.00 should be given indomethacin cover as a precaution. Similarly, where there was concern that the egg collection might be late relative to the LH rise, indomethacin was used to cover procedures timed for 11.00. Coverage was not perfect at 93%, 90% and 55% for procedures starting 9.00–10.00, 10.00–11.00 and 11.00–12.00, respectively. However ovulation prior to or during egg collection occurred, respectively, in only 6%, 10% and 0% of cycles covered with indomethacin compared with 50%, 33% and 42% of

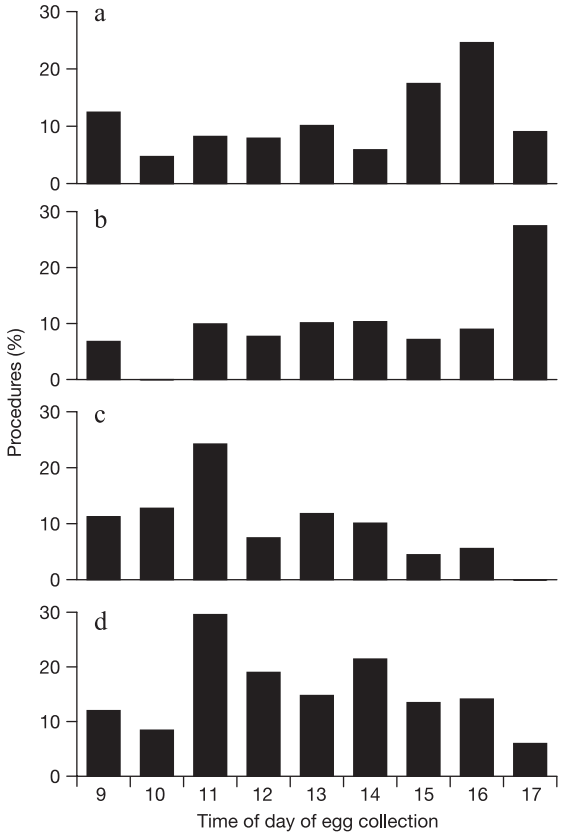

Figure 3. (**a**) The distribution of 495 scheduled natural-cycle egg collections throughout the working day. An even distribution would result in approximately 11% of procedures in each interval. There were relatively more procedures than expected towards the end of the day. (**b**) The distribution of 48 cycles in which the follicle was entered, follicular fluid aspirated but no egg found despite vigorous flushing. (**c**) The equivalent distribution of 43 cycles in which ovulation occurred prior to or during needle entry. (**d**) The distribution of 38 clinical pregnancies per single embryo transfer that were relative to the time of day at which the eggs were collected.

equivalently timed cycles where indomethacin was not given. Expressed another way, eggs were successfully recovered from 80/90 (89%) of egg collections performed between 09.00 and 12.00 where indomethacin was given compared with 17/35 (49%) where it was omitted ($P < 0.001$).

Group 1 overall outcomes

A total of 495 cycles were scheduled for egg collection on the basis of twice-daily LH monitoring. In 403 cycles (81%), an egg was collected. The 18% cycle-failure rate consisted of 48 cycles (9.7%) that were thought to have been performed too early, in which follicular fluid only was recovered, and 43 cycles (8.7%) thought to have been performed too late, where follicle rupture occurred shortly before or during egg collection. Fertilization rates were low in comparison with stimulated IVF; only 257 (64%) single embryo transfers were achieved. Similarly there were only 38 clinical pregnancies, 14.8% per embryo transferred, 9.4% per egg collected and 7.7% per cycle scheduled for egg collection.

Group 2 treatment cycles

A total of 241 eligible cycles was started in the second time period. Of these, 19 (7.9%) ended in cancellation before egg collection because of poor oestradiol profiles, short follicular phases (so inadequately monitored) or small or ambiguous LH surges. This left 222 cycles for which egg collection was scheduled. With a 7-day service, about 14% or 32 egg collections would be expected each day. Thus, to reduce to a 6-day service meant rescheduling (advancing) about 32 cycles. While theoretically this could be done quite simply by giving an injection of HCG in advance of the spontaneous LH surge, in practice it was rather more problematic.

Firstly, to simply advance Sunday egg collections to Saturday meant that the Saturday workload doubled. Thus to be effective any policy would need to redistribute some of the potential Saturday egg collections to Friday in order to be able to accommodate the Sunday procedures on Saturday. The decision process was as follows:

If the oestradiol was high by Wednesday morning, HCG was given at night for Friday egg collection.

If the oestradiol was high by Thursday morning, HCG was given at night for Saturday egg collection.

If the oestradiol was high by Friday morning, there was a problem. It was too late, unless the LH had also risen, to undertake egg collection before Monday. The best that could be achieved was to monitor on Saturday morning, and if the LH surge had not yet begun, to give HCG on Saturday night for a pretimed egg collection on Monday morning. If the LH had started to rise, the chances the subject would have ovulated by Monday morning were high.

If the oestradiol was high by Saturday morning, HCG was given at night for Monday egg collection.

There are two sources of cycle failure in this scheme. Those cycles that were clearly destined to ovulate on Sunday, but which were not predicted sufficiently early (by Thursday am) for intervention, were inevitably lost. Secondly, all those cycles where HCG was given at night and egg collection pretimed for 35 h later, but where the LH surge started between the 08.00 hours blood test and the time HCG was administered some 15 h later, were also mis-timed. These cycles might have been detected if the subjects had collected a further blood sample just before giving themselves HCG. This sample would have needed to be analysed the following morning and the time of egg collection rescheduled to compensate.

In practice, HCG was given in 53 cycles, rather than the predicted minimum of 32. This demonstrates the degree to which Saturday procedures were allocated to Friday as well as those subjects given HCG who did not actually require it because they were naturally destined to ovulate on Monday.

The effectiveness of the policy to avoid Sundays is shown in **Figure 4**. Tuesday, Wednesday and Thursday egg collections were identical to Group 1 cycles, i.e. based entirely on LH monitoring, and approximately met the expected 14% distribution. A small number (3%) of potential Saturday egg

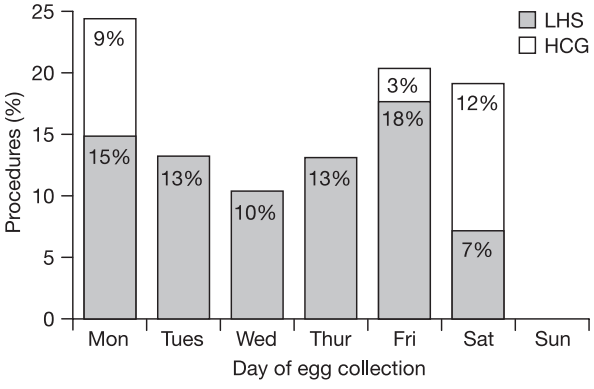

Figure 4. Distribution of 226 scheduled IVF procedures (169 with LH and 53 with human chorionic gonadotrophin (HCG) induced ovulation) across the days of the week where the objective was to avoid Sunday procedures. All cycles where ovulation was expected on Sunday were advanced to Saturday by the injection of HCG on Thursday night. To avoid excessive numbers of procedures, some cycles where ovulation was expected on Saturday were advanced to Friday by injection of HCG on Wednesday night. A smaller number of cycles that were less advanced but where Sunday monitoring would have been required, were arbitrarily given HCG on Saturday night so that a planned egg collection could take place on Monday morning. If no redistribution had taken place, about 14% of procedures would have fallen on each day (see **Figure 2**). HCG: human chorionic gonadotrophin; LHS = LH surge.

collections were deliberately advanced to Friday, and some Sunday procedures (12%) advanced to Saturday. HCG and indomethacin were given to 9% of cycles for Monday egg collection as a precaution. In addition the expected normal number of LH-surge managed cycles occurred on all 3 days (with some variation).

While clearly all procedures had been relocated, the effectiveness of the strategy can only be assessed by whether egg recovery was successful. Unfortunately it was not as successful as hoped; in the LH only group, 36% cycles had already ovulated by Monday, i.e. the missed Sunday cycles, compared with only 8% in Group 1 ($P < 0.001$), and 16% of cycles on a Friday or Saturday were potentially scheduled too early compared with 9% in Group 1 (**Figure 5**). In the HCG-treated group, although relatively few egg collections were timed too early, many were still timed too late, 14% on Monday and 22% on Friday and Saturday (Group 1, 8% and 10% respectively) as a consequence of the spontaneous LH surge starting unnoticed in the 15 h prior to HCG administration. Indomethacin was again given to those cycles which were being left to Monday, and was partially effective in that eggs were obtained in 12/15 (80%) cycles given indomethacin but in only 2/6 (33%) where it was omitted. The result was that although 81% of Group 1 cycles yielded eggs, only 76% of Group 2 did so. In practice, if all the cycles expected to ovulate on Sunday had simply been cancelled, egg recovery rates would only have been slightly lower at 69%.

Group 2 overall outcomes

A total of 222 cycles were scheduled for egg collection, 169 on the basis of twice-daily LH monitoring and 53 following HCG injection. In 168 cycles (76%), an egg was collected. The 24% cycle-failure rate consisted of 19 cycles (8.6%) that were thought to have been performed too early, in which follicular fluid only was recovered, and 35 cycles (15.8%) thought to have been performed too late, where follicle rupture occurred shortly before or during egg collection. Fertilization rates were similar in comparison with Group 1; 111 (66%) single embryo transfers were achieved. However there were only 15 clinical pregnancies, 13.5% per embryo transferred, 8.9% per egg collected and 6.7% per cycle scheduled for egg collection, figures that were slightly, but not significantly, lower than those achieved in Group 1.

Conclusions

Natural cycle IVF has over the last couple of decades been held up as the ideal for simplicity, economy (Daya *et al.*, 1995) and safety (Nargund *et al.*, 2001). There have been numerous attempts to establish flourishing natural cycle programmes (Pelinck *et al.*, 2006). Despite the optimism, most have been of limited success (Nargund *et al.*, 2001, Pelinck *et al.*, 2006) although the reasons for this have never been clearly described. This evaluation was undertaken to demonstrate just why such programmes frequently fail. Essentially, the natural cycle is a complex series of endocrine signals that result ultimately in the timely rupture and release of a mature oocyte (egg). The process occurs smoothly across the 24 h and the days of the week and, as such, is poorly suited to the demands of an IVF programme, although intrauterine insemination or donor insemination may be more successful.

The endocrine signalling can be measured and interpreted, but not continuously over the 24 h, so interpolation between measurement episodes, e.g. twice-daily LH sampling, has to be introduced. This is the first compromise. In practice this is probably the least problematic part of the process provided two blood tests daily are acceptable. It should, however, be noted that while detection of the LH peak is easy (e.g. LH dipsticks and other urine-based technology: O'Connor *et al.*, 2006), for IVF, it is the start of the LH rise that is critical and this is a great deal more difficult to measure accurately (de Ziegler *et al.*, 1999).

The second compromise follows from IVF clinics' need to collect eggs before spontaneous ovulation occurs. In this respect natural cycle IVF becomes vastly more difficult than, for example, intrauterine insemination or donor insemination, where absolute timing is not critical. Naturally, many subjects ovulate during the night, a time when an IVF clinic is normally closed. Attempts to modify the optimum time for egg collection (about 35 h after LH surge in this study) to fit clinic opening times results in significant treatment failures due to an inability to recover eggs in both early- and late-timed procedures. Thus inevitably egg yields, which with stimulated IVF are close to 100%, cannot improve much on the 81% reported here for the pure natural cycle without the wider use of follicular rupture suppressants, such as indomethacin (Daya *et al.*, 1995, Nargund

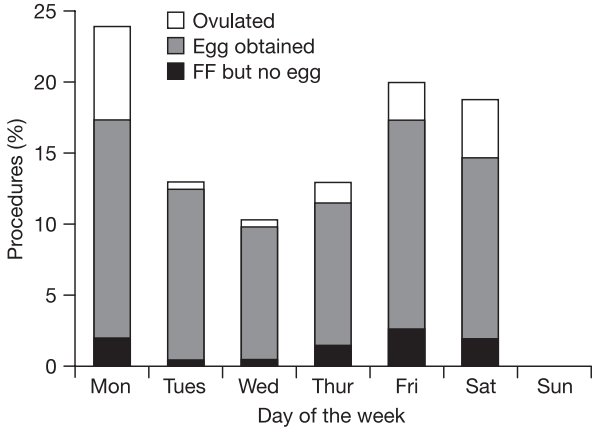

Figure 5. The outcome of IVF cycles during the time that Sunday procedures were not performed. In comparison with **Figure 2** it is clear that more cycles ended in failure to recover an egg, either because they were timed too early (worst on Friday) or because the scheduled procedure occurred too late and the follicle had already ovulated (particularly marked on Monday). Cycles on Tuesday, Wednesday and Thursday, which were planned normally following detection of the LH surge, did well. FF = follicular fluid.

et al., 2001, Pelinck *et al*., 2006, Kadoch *et al*., 2007). This second compromise does not just the ability to collect an egg but may well also impact on outcomes even if an egg is recovered. From the data evaluated here, there is a suggestion that fertilization rates are compromised if the egg is recovered too early and certainly clinical pregnancy rates seem highest when the eggs are collected at the most optimum time, irrespective of the use of indomethacin (**Figure 3d**).

Finally, the third compromise occurs when the dictates of staffing and economic management of an IVF programme come into play. Whether this is due to simply the advancement of Sunday egg collections as described here or the wide-scale use of HCG to induce oocyte maturity to schedule all egg collections at social times, efficacy is inevitably further reduced. There are a number of factors involved here. Firstly, it is difficult for clinic staff to manage patients using several protocols (e.g. LH monitoring and HCG-timed egg collection, or natural versus stimulated IVF). Secondly, there is a tendency to set up the HCG injection and sit back, confident that all will be well on the day. This is, of course, what happens with down-regulated stimulated IVF but, in the natural cycle, there is no such luxury. As shown here, a significant number of patients [perhaps as many as 20% (Kadoch *et al*., 2007)] will start LH surges between the decision to give HCG and the actual injection. This is because the last LH measurement can be more than 47 h, but the HCG injection only 35 h, before egg collection. The window of more than 12 h is sufficient to bring about a further increase in the number of cycles that unexpectedly fail due to spontaneous ovulation.

The problem is that daily assessment of oestradiol concentrations and/or daily ultrasound scans are not sufficiently predictive of impending LH rises to enable the consistent preventative administration of HCG. Some patients have an oestradiol rise limited to only a day or two before the LH surge starts (particularly in the short follicular-phase cycles where monitoring may be implemented too late anyway). There is much variation in the oestradiol concentration at which the LH surge is triggered and the decision to give HCG is often just too early for a confident prediction of follicular maturity.

All women, even those undergoing natural cycle IVF, will have invested significant time, effort and emotional energy in the process; the high rate of cycle 'losses' and commensurate low success rates may prove too debilitating. There is the added disadvantage that IVF clinic staff, accustomed to the availability of large numbers of eggs per patient, will find practising natural cycle IVF demoralizing, particularly if they do not appreciate the difficulties and understand the reasons for the inevitable failures.

The future of natural cycle IVF, and its undoubted benefits, will rely on technological developments in the arena of home-based endocrine monitoring that are both accurate and sufficiently predictive to allow late-stage intervention with HCG or, preferably, an orally active oocyte maturation inducer such as progesterone. This, in combination with an ovulatory blocking drug (such as indomethacin, see Kadoch *et al*., 2007), should facilitate a more successful rate of egg collection. These modifications will not however solve the problem of 50% of cycles needing oocyte retrieval first thing in the morning. Varying the time of insemination to match oocyte maturity might help, as might performing ICSI on all eggs irrespective of the presence or absence of male factor infertility. Meanwhile, with the impetus towards single embryo transfer, it is likely that there will be increasing interest in using low dose or modified stimulated IVF but these treatment modalities are likely to suffer from similar problems to the completely natural cycle. Development of specific expertise will be required before acceptable success rates can be achieved.

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