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Trends in the incidence of births and multiple births and the factors that determine the probability of multiple birth after IVF treatment

Lawrence Engmann[1,2,5], Noreen Maconochie[3], Seang Lin Tan[4] and Jinan Bekir[1]

[1]The London Women's Clinic, 115 Harley Street, London W1N 2DG, [2]Department of Obstetrics and Gynecology, The University of Connecticut Health Center School of Medicine, Farmington, CT 06030–2947, [3]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT and [4]Department of Obstetrics and Gynaecology, Royal Victoria Hospital, Montreal, Canada

[5]To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, The University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030–2947. USA. E-mail: engmann@gme.uchc.edu

BACKGROUND: We aimed to review trends in the probability of birth and multiple birth before and after the legal restriction limiting the maximum allowable number of embryos transferred, and to examine factors that determine the probability of multiple birth following IVF treatment. METHODS: We analysed data relating to 7170 IVF and 530 intracytoplasmic sperm injection cycles reaching embryo transfer undertaken by 4417 women at a single tertiary referral assisted conception centre in the UK between 1984 and 1997. Probability of birth, and of proportion of multiple births among those who gave birth, was explored using logistic regression analysis. RESULTS: Between 1984 and 1997 there was a significant increase in probability of birth but no change in the probability of multiple birth. The trend in probability of birth was almost wholly explained by the significant increase in number of embryos created per cycle. Pooling all the data, risk factors for increased chance of birth and multiple birth were: younger age (<35 years), diagnoses other than tubal infertility, fewer than three previous unsuccessful cycles, previous IVF live birth and a large number of embryos created. Given these factors, increasing the number of embryos transferred did not increase the chance of a birth, but did increase the chance of a multiple birth. CONCLUSIONS: The probability of birth has increased and the probability of multiple birth has remained unchanged, despite legislation limiting the number of embryos transferred in the UK. Efforts should be made to reduce the incidence of multiple births by transferring fewer embryos, especially in the presence of good prognostic factors for birth.

Key words: birth/factors/IVF/multiple birth/prevention

Introduction

There is continuing concern about the high incidence of multiple births following IVF treatment. Every effort to reduce this incidence is justified, since multiple birth is an avoidable complication of treatment which results in a high perinatal morbidity and mortality (Petterson *et al.*, 1993; Dunn and McFarlane, 1996) as well as significant financial (Callahan *et al.*, 1994; Mugford and Henderson, 1995) and psychological (Garel *et al.*, 1997) consequences.

Until recently, a major problem with deciding on the optimal number of embryos to replace after IVF treatment has been the lack of reliable measures to predict the implantation potential for each individual embryo (Van Royen *et al.*, 1999, 2001). In view of the relatively low implantation rate overall, clinicians have resorted to increasing the number of embryos replaced to optimize the chances of success, with a concomitant rise in the multiple birth rate.

In 1991, the Human Fertilisation and Embryology Authority (HFEA) placed a legal restriction limiting the maximum allowable number of embryos transferred in the UK to three. The aim of this legislation was to minimize the risk of high order multiple births and reduce the incidence of multiple births resulting from IVF in general. Although this has undoubtedly resulted in the prevention of high order multiple births, there have been no published studies assessing the impact of the HFEA legislation on the probability of birth and multiple birth over time.

Previous studies investigating factors associated with the probability of multiple birth, and examining how limiting the number of embryos transferred affects the probability of both birth and multiple birth, have tended to be based either on relatively small data series (Nijs *et al.*, 1993; Staessen *et al.*, 1993; Bassil *et al.*, 1997; Elsner *et al.*, 1997) or on a pooling of heterogeneous data from several different clinics (Templeton and Morris, 1998; Schieve *et al.*, 1999).

The aim of this study was to examine trends over time in the probability of birth (single or multiple) and the proportion of multiple births among deliveries, using data from a single centre in the UK between 1984 and 1997, which spanned periods both pre- and post-HFEA legislation. We also used this large dataset to investigate risk factors affecting the probability of birth and multiple birth after IVF treatment, and to explore how these factors might be associated with any trends seen over time.

Methods

Study Population

We obtained data on all IVF and intracytoplasmic sperm injection (ICSI) cycles undertaken in the London Women's Clinic between June 1984 and December 1997, the ICSI procedure being introduced in November 1994. A total of 11 740 cycles were initiated during the study period, but cycles were only included if at least one fresh embryo was transferred. A total of 3997 cycles were excluded because they did not result in embryo transfer, or because they involved oocyte donation, embryo donation or frozen embryo replacement. A further 15 cycles were excluded where a pregnancy was recorded, but the outcome was unknown. In addition, 28 cycles where two or more embryos were available but only one embryo was replaced were excluded from the analyses, as the exact reason for the single embryo transfer was not recorded in the dataset (e.g. previous multiple birth) and since the policy during the study period was to recommend transfer of at least two embryos if two or more were available. Cycles where only one embryo was available and replaced were, however, included in all analyses of birth, though not multiple birth. The dataset for analysis thus consisted of 7700 cycles undertaken by 4417 women, and 7170 (93%) of these cycles were IVF and 530 (7%) ICSI. All cycles undertaken by the same woman were linked using a unique personal identification number.

Factors that have been shown in previous studies to affect the probability of birth or multiple birth after IVF treatment were analysed (Tan *et al*., 1992; Templeton *et al*., 1996; Strandell *et al*., 2000). Number of embryos created and number replaced were recorded for each cycle. Age at commencement of each treatment cycle was measured using the woman's date of birth. Type of infertility was categorized as tubal factor, endometriosis, male factor, unexplained, other single cause or multiple causes. Most (91%) of the multiple causes mentioned two factors, the remainder three. A total of 72% of all multiple causes included tubal factor infertility, 54% included endometriosis, 54% included male factor and 20% included another single cause. All previous births resulting from IVF or ICSI were recorded. An unsuccessful IVF attempt was defined as a cycle from which no birth resulted. The variable was reset to zero on the first of each subsequent set of cycles (i.e. attempt for another baby) following an IVF birth.

Birth was defined as any pregnancy which led to at least one live birth or at least one stillbirth at $\geqslant$24 weeks gestation. Analyses relating to the probability of birth were carried out on all cycles resulting in at least one fresh embryo transfer.

Multiple birth was defined as the delivery of two or more babies (live or still) at $\geqslant$24 weeks gestation. Analyses relating to the risk of multiple birth were restricted to cycles where two or more embryos were replaced and where a birth resulted.

Statistical methods

All analyses were performed using the Stata statistical package (version 6.0). All *P*-values were two-sided and values < 0.05 were taken to indicate statistical significance. Age was analysed both as a continuous variable and as a categorical variable. For ease of presentation it was tabulated in categorical form, having first checked that the categorized variable gave an adequate fit to the data. Number of embryos created and number of embryos transferred were analysed as categorical variables.

The effect of various factors on the probability of birth and multiple birth were estimated using odds ratios (OR), by means of logistic regression analysis. Analyses included tests for statistical interaction, though judgement of evidence for interaction included examination of both estimates and *P*-values. Trends with categorical variables were performed using linear or logistic regression as appropriate, using the median value for each category in the analysis. Because of the correlation between cycles undertaken by the same woman, a robust method based on the sandwich estimate was used to compute standard errors in all regression analyses, with Wald tests to ascertain statistical significance of parameters (Huber, 1967; Rogers, 1993).

Results

Of the 7700 IVF and ICSI cycles reaching (fresh) embryo transfer, undertaken by 4417 women, 1889 (25%) resulted in pregnancy. A total of 1256 of these pregnancies continued to delivery (16% per transfer), and 355 (28%) of the resulting births were multiple: 292 (23%) twins, 58 (5%) triplets and five (0.4%) quadruplets. All the triplets and quadruplets resulted from the transfer of three or more embryos: 40 sets of triplets and two sets of quadruplets occurred after the transfer of three embryos, and 18 sets of triplets and three sets of quadruplets resulted from the transfer of four or more embryos. In all, 50 of these births (all singleton) resulted from 940 cycles (5% per transfer) where only one embryo was available and replaced. These cycles were excluded from analyses exploring risk factors for multiple birth, which were thus carried out on a total of 1206 cycles resulting in birth undertaken by 1122 women. The 50 women who achieved a live birth were significantly younger than the women with one embryo transfer who did not achieve a birth (32.5 versus 35 years, $P = 0.004$). They had similar diagnoses to those with a single embryo transfer who did not achieve a birth (P = not significant) but were almost half as likely to have had three or more previous unsuccessful attempts ($P = 0.06$).

Trends over time

Trends in the age of women having treatment, the number of embryos produced and replaced and the birth and multiple birth rates are presented in Table I. Over the study period there was a strong trend of increasing age at treatment, taking the form of a total shift upwards in the age distribution. Women presenting for treatment at the end of the study period were on average two years older than in the 1980s, and there are now more than three times as many women starting cycles over the age of 40 years as there were prior to 1991 (18 versus 5%, $P < 0.001$).

There was a significant increasing trend with time in the number of embryos produced per cycle (Table I). By the end of the study period the majority of cycles resulted in three or more embryos being created, and the proportion of cycles resulting in five or more embryos had more than doubled, to just over half.

Table I. Trends over time (1984–1997)

	Year of treatment				
	Pre-HFEA legislation		Post-HFEA legislation		Test for trend over time
	1984–87	1988–91	1992–95	1996–97	
ALL CYCLES[a]	$n = 2190$	$n = 2871$	$n = 1787$	$n = 852$	
Age (years)					
<35	1406 (64%)	1691 (59%)	844 (47%)	408 (48%)	
35–39	744 (34%)	938 (33%)	615 (34%)	274 (32%)	
⩾40	40 (2%)	242 (8%)	328 (18%)	170 (20%)	
Median (5th–95th centiles)[b]	33 (26–38)	33 (26–40)	35 (28–43)	35 (28–43)	$P_{trend} < 0.0001$
No. of embryos produced per cycle					
1	361 (16%)	350 (12%)	161 (9%)	68 (8%)	
2	473 (22%)	449 (16%)	237 (13%)	106 (12%)	
3	493 (23%)	507 (18%)	277 (16%)	126 (15%)	
4	387 (18%)	614 (21%)	215 (12%)	92 (11%)	
⩾5	476 (22%)	951 (33%)	897 (50%)	460 (54%)	
Median (5th–95th centiles)[b]	3 (1–8)	4 (1–10)	5 (1–12)	5 (1–13)	$P_{trend} < 0.0001$
No. of embryos replaced per cycle					
1	361 (16%)	350 (12%)	161 (9%)	68 (8%)	
2	486 (22%)	505 (18%)	453 (25%)	283 (33%)	
3	571 (26%)	1 032 (36%)	1 173 (66%)	501 (59%)	
⩾4	772 (35%)	984 (34%)	–	–	$P_{trend} < 0.0001$[c]
No. of embryos transferred by number available[d]					
3 available					
2 replaced	8 (2%)	23 (5%)	32 (12%)	19 (15%)	$P_{trend} < 0.0001$
3 replaced	485 (98%)	484 (95%)	245 (88%)	107 (85%)	
4 available					
2 replaced	3 (1%)	7 (1%)	25 (12%)	19 (21%)	$P_{trend} < 0.0001$[e]
3 replaced	36 (9%)	126 (21%)	190 (88%)	73 (79%)	
4 replaced	348 (90%)	481 (78%)	–	–	
⩾5 available					
2 replaced	2 (0.4%)	26 (3%)	159.(18%)	139 (30%)	$P_{trend} < 0.0001$[e]
3 replaced	50 (11%)	422 (44%)	738 (82%)	321 (70%)	
⩾4 replaced	424 (89%)	503 (53%)	–	–	
Births					
n (%)	327 (15%)	461 (16%)	324 (18%)	144 (17%)	
Adjusted[f] OR (95% CI)	1.0[g]	1.1 (0.9–1.3)	1.4 (1.2–1.7)	1.3 (1.0–1.6)	$P_{trend} = 0.001$
Multiple Births					
n (%)	83 (4%)	137 (5%)	93 (5%)	42 (5%)	P_{trend} = NS
Adjusted[f] OR (95% CI)[h]	1.0[g]	1.2 (0.9–1.7)	1.2 (0.8–1.7)	1.1 (0.6–1.8)	
Multiple birth among deliveries					
Singleton	244 (75%)	324 (70%)	231 (71%)	102 (71%)	
Twin	70 (21%)	115 (25%)	71 (22%)	36 (25%)	
Triplet	13 (4%)	18 (4%)	21 (6%)	6 (4%)	
Quadruplet	– (0%)	4 (1%)	1 (0.3%)	– (0%)	

[a]Reaching (fresh) embryo transfer; [b]central 90% of distribution; [c]three or more versus two or more; [d]cycles with one embryo replaced when more than one embryo available excluded from all analyses, hence 100% replaced when two or more available; [e]two versus three or more; [f]adjusted for age, diagnosis, number of previous unsuccessful cycles and previous IVF birth; [g]baseline group; [h]among those having a birth only; OR = odds ratio.

The impact of the HFEA legislation limiting the number of embryos transferred can clearly be seen in Table I. Not only was the maximum number replaced reduced to three after 1991, but there was a general shift over time towards transferring fewer embryos. On average, prior to 1991 just 2% of women with three or more embryos available had only two embryos transferred. After 1991 this figure rose to 18% ($P < 0.001$).

There was a significant increase in the probability of birth over the period of study (Table I). After adjusting for age, diagnosis, number of previous attempts and previous IVF birth, the chance of achieving a birth after 1991 was 34% higher (OR 1.3; 95% CI 1.2–1.6; $P < 0.0001$). In statistical terms, the trend in probability of birth was, however, almost wholly explained by the increase in number of embryos created per cycle. When the number of embryos created was added to the model, year of treatment lost its statistical significance ($P = 0.48$).

Despite the increasing trend in probability of birth, there was no significant change in the risk of multiple birth over time among those achieving a birth; the proportion of births which were multiple remained fairly constant at ~30% (Table I).

Factors associated with probability of birth and multiple birth

Overall, factors intrinsic to the woman which influenced probability of birth tended to increase or decrease risk of multiple birth in a similar way.

Age was an important determinant of both birth and multiple birth (Table II). There was a marked decrease in probability of both birth and multiple birth with age, this decrease being most marked over the age of 35 years. On average, at age ⩾35 years the chance of a birth was 35% lower than among younger women (OR 0.7; 95% CI 0.6–0.7), and the chance of a multiple birth was 32% lower (OR 0.7; 95% CI 0.5–0.9).

Probability of both birth and multiple birth declined with the number of previous unsuccessful attempts (Table II). After three unsuccessful attempts, the probability of birth was 30% lower than those just starting IVF treatment, with risk of multiple birth among those giving birth being reduced by 40%. If a live birth was achieved through IVF, the chance of success in subsequent IVF attempts was greatly increased. Among women with a previous IVF live birth, the chance of another birth was 50% higher, though risk of multiple birth was also increased by ~60% (Table II).

Probability of birth varied significantly with diagnosis of infertility (Table II). Women with tubal factor infertility (single cause) were the least likely to achieve a birth. Compared with those with other diagnoses (combined), they had a 20% lower chance of a birth (OR 0.8; 95% CI 0.7–0.9; $P < 0.0001$). Similar variation in risk was seen for multiple birth, though overall the differences between diagnostic categories were not statistically significant (Table II). Among women achieving a birth, it was again those with tubal factor infertility who had a lower risk of multiple birth, the probability being 20% lower than those with other diagnoses (OR 0.8; 95% CI 0.6–1.1; P = not significant).

Unlike factors intrinsic to the woman, factors relating to treatment (number of embryos produced, number of embryos replaced) tended to influence probability of birth and multiple birth in slightly different ways.

There was strong evidence from this data that, having controlled for all other factors, it was the number of embryos available for transfer rather than the number transferred which had the greater influence on probability of birth. Overall there was a strong increasing trend of odds of birth with number of embryos available for transfer ($P < 0.0001$) but, having adjusted for this, there was no evidence that increasing the number of embryos transferred increased the chance of birth (P for trend = not significant), nor was there evidence of statistical interaction between the two factors (P = not significant). The overall effect of these two factors combined is summarized in Table III where it may be seen that probability of birth increases with number of embryos available, but that

Table II. Factors relating to probability of birth per embryo transfer, and of multiple birth per delivery[a]

	No. of births	Adjusted[b] OR birth (95% CI)	No. of multiple births	Adjusted[b] OR multiple birth (95% CI)[c]
TOTAL	1256	–	355	–
Age (years)				
<30	267	1.0[d]	83	1.0[d]
30–34	571	0.9 (0.8–1.1)	176	1.0 (0.7–1.4)
35–39	364	0.7 (0.6–0.8)	92	0.8 (0.5–1.1)
⩾40	54	0.3 (0.2–0.4)	4	0.2 (0.1–0.6)
		$P_{trend} < 0.0001$		$P_{trend} = 0.003$
No. of previous unsuccessful attempts				
0	616	1.0[d]	200	1.0[d]
1	330	0.9 (0.8–1.1)	91	1.0 (0.7–1.3)
2	162	0.8 (0.7–1.0)	41	0.9 (0.6–1.3)
3	67	0.7 (0.5–0.9)	13	0.7 (0.3–1.3)
⩾4	81	0.7 (0.5–0.9)	10	0.4 (0.2–0.9)
		$P_{trend} = 0.001$		$P_{trend} = 0.01$
Diagnosis				
Tubal factor	400	1.0[d]	105	1.0[d]
Endometriosis	72	1.6 (1.2–2.1)	26	1.7 (0.9–3.0)
Male factor	265	1.3 (1.1–1.6)	80	1.5 (1.0–2.2)
Unexplained	240	1.3 (1.1–1.6)	58	1.0 (0.7–1.4)
Other single cause	89	1.6 (1.3–2.1)	25	1.2 (0.7–2.1)
Multiple causes	190	1.1 (0.9–1.4)	61	1.4 (0.9–2.1)
		$P_{heterogeneity} = 0.0001$		$P_{heterogeneity}$ = NS
Previous IVF live birth				
No	1164	1.0[d]	323	1.0[d]
Yes	92	1.5 (1.2–2.0)	32	1.6 (1.0–2.5)
		$P_{heterogeneity} = 0.001$		$P_{heterogeneity} = 0.07$

[a]Live or stillbirth; excludes births resulting from cycles where only one embryo was transferred.
[b]Adjusted for all other factors in the table and for number of embryos available and number of embryos replaced.
[c]Among those having a birth only.
[d]Baseline group.
OR = odds ratio.

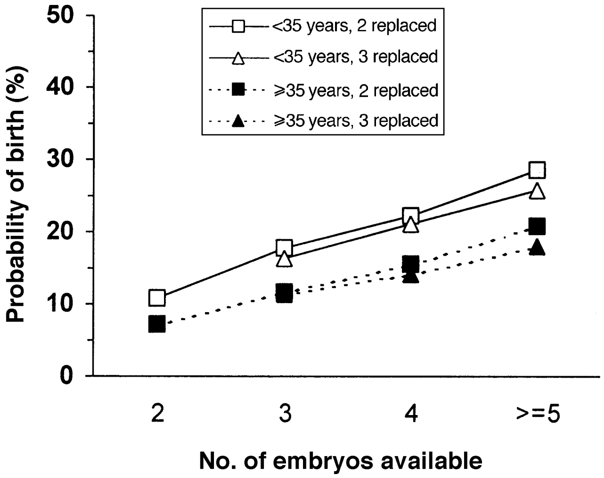

Figure 1. Predicted probability of birth by number of embryos available, number replaced and age at treatment.

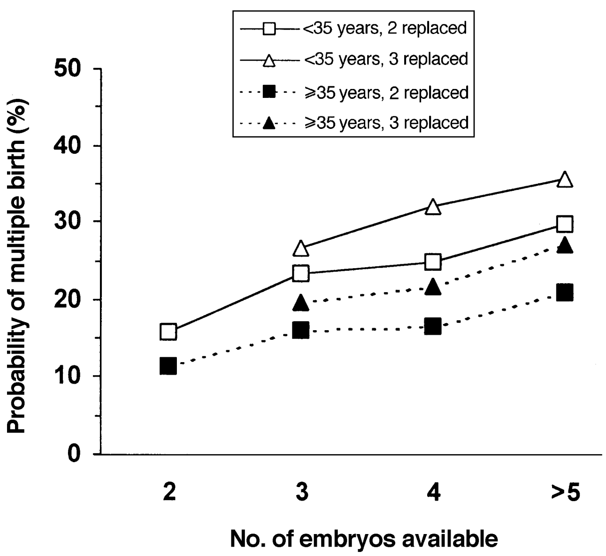

Figure 2. Predicted probability of multiple birth by number of embryos available, number replaced and age at treatment.

for a given number of embryos available the number replaced makes no difference.

In contrast to probability of birth, the risk of multiple birth among deliveries increased independently with both number of embryos available ($P = 0.01$) and number of embryos transferred ($P = 0.04$), with no evidence of an interaction between the two factors (P = not significant). The overall effect of the two factors combined is presented in Table IV.

Using the models documented above, predicted probability of birth adjusted for diagnosis, number of previous unsuccessful attempts and previous IVF live birth was calculated by number of embryos available, number replaced and age. This is presented in Figure 1 for those where two or three embryos were transferred. The difference in probability of birth between younger (<35 years) and older women is very clear, and replacing two rather than three embryos appears to have little effect on this age difference. In both groups, probability of birth increases with increasing number of available embryos, women aged >35 years with five or more embryos available having a similar chance of success as younger women with around three embryos available.

Similar broad patterns with age and number of available embryos are seen in Figure 2, where predicted adjusted probability of multiple birth is presented for those who achieved a birth, but here the 30% increased risk associated with replacing three rather than two embryos may also be seen. For younger women having five or more embryos available, the risk of multiple birth reaches >35% when three embryos are replaced, the corresponding figure for women aged ⩾35 years also being high at 27%.

Discussion

To our knowledge, this is the first study to be conducted in a single centre in the UK which spans periods both before and after the HFEA legislation limiting the maximum number of embryos transferred to three. The results show clearly that despite the HFEA legislation the likelihood of birth increased significantly over the period of the study, whilst the likelihood

Table III. Probability of birth per embryo transfer by number of embryos available and transferred

No. of embryos transferred	No. of embryos available				
	1 Adjusted[a] OR birth (95% CI) (no. of births in brackets)	2	3	4	⩾5
1	0.2 (0.1–0.3) (50)	–	–	–	–
2	–	0.3 (0.3–0.4) (114)	0.5 (0.4–0.8) (12)	0.7 (0.5–0.8) (9)	1.0 (0.8–1.3) (92)
3	–	–	0.5 (0.4–0.6) (189)	0.7 (0.6–0.8) (78)	1.0[b] (356)
⩾4	–	–	–	0.7 (0.5–0.8) (144)	0.9 (0.8–1.1) (212)

[a]Adjusted for each other and for age, number of previous unsuccessful attempts, diagnosis and previous IVF live birth.
[b]Baseline group.
OR = odds ratio.

Table IV. Probability of multiple birth per delivery[a] by number of embryos available and transferred

No. of embryos transferred	No. of embryos available				
	1	2	3	4	⩾5
	Adjusted[b] OR multiple birth (95% CI) (no. of multiple births in brackets)				
1	–	–	–	–	–
2	–	0.3 (0.2–0.6) (16)	0.5 (0.2–0.9) (3)	0.5 (0.3–1.0) (1)	0.7 (0.4–1.1) (27)
3	–	–	0.7 (0.5–1.0) (45)	0.8 (0.6–1.1) (21)	1.0[c] (121)
⩾4	–	–	–	0.9 (0.6–1.4) (46)	1.2 (0.8–1.7) (75)

[a]Live or stillbirth; excludes births resulting from cycles where only one embryo was transferred.
[b]Adjusted for each other and for age, number of previous unsuccessful attempts, diagnosis and previous IVF birth.
[c]Baseline group.
OR = odds ratio.

of multiple birth remained high and stable at ~30% of all births.

Pooling all the data, we confirmed the relationship between probability of birth and multiple birth and age of the woman at treatment, diagnosis, number of previous unsuccessful attempts and previous history of IVF live birth. In addition, we found that the number of embryos produced was an important determinant of the probability of both birth and multiple birth. Once adjusted for the other variables, however, number of embryos transferred did not increase the chance of a birth, only the probability that if a birth occurred it would be multiple.

Our study has several characteristics which distinguish it from other large retrospective studies in this area (Templeton and Morris, 1998; Schieve *et al.*, 1999). Although presentation of results based on large populations is valuable, the pooling of data from different clinics using different assisted reproductive techniques may conceal important sources of variation and the potential presence of unknown confounding variables may affect the results (Walters, 1994). In taking our data from a single clinic we do not have this problem. Secondly, our study covered periods both before and after 1991 and we were therefore able to assess the impact of the HFEA legislation on the probability of birth and multiple birth. Thirdly, cycles undertaken by the same woman are linked in this study, so that (unmeasured) factors intrinsic to the woman which might affect her probability of success were accounted for when assessing statistical significance. Lastly, we analysed probability of multiple birth only among cycles resulting in birth and not among all embryo transfer cycles, hence separating out the probability of a birth itself from the probability of a multiple birth.

The increase over time in probability of birth at this clinic occurred despite a background increase in the age of the woman undergoing treatment over the same time period. Several factors may explain these findings. Over the years, there have been changes in clinical protocols ranging from natural cycle IVF in the 1980s to the use of controlled ovarian stimulation with gonadotrophins in combination with pituitary desensitization in the 1990s. There have also been improvements in laboratory procedures such as culture techniques and introduction of ICSI over the years. Consequently, there has been a consistent increasing trend over time in the number and quality of embryos created. In comparing results and outcomes over a period of time, it is difficult to factor the gradual changes in technology into the analyses. However, we indirectly took into consideration the changes that have occurred over time by including the number of embryos created in our analysis. When this variable was added to models relating to birth, trends with calendar period of treatment lost their significance.

Previous studies have shown that when several embryos are created, there is an increase in the likelihood of selecting good quality embryos to be replaced (Devreker *et al.*, 1999). We may thus postulate that the number of embryos available may be an indirect measure of quality of embryos created. The increase in number of embryos created over the years may have improved the probability that at least one embryo with a high implantation potential would be transferred and subsequently implant. Hence, although there was a general trend towards transferring fewer embryos, the overall birth rate increased. The lack of change over time in the multiple birth rate is perhaps due to the effect of reducing the number of embryos transferred being offset by the effect of increasing numbers of embryos being created over time (hence the probable greater quality of those transferred).

The number of embryos created was thus found to be a very important determinant of the probability of birth and multiple birth. This is consistent with the findings of previous studies (Templeton and Morris, 1998; Schieve *et al.*, 1999). There is a suggestion from the findings of our study that, for birth, it may be even more important than the number of embryos transferred. Having adjusted for number available, increasing the number of embryos transferred did not alter the probability of birth though, as might be expected, the probability of multiple birth increased with the number of embryos transferred.

Edwards and colleagues suggested that it was time to consider milder forms of ovarian stimulation protocols to create fewer embryos (Edwards *et al*., 1996). This is essential in view of the move towards the transfer of fewer embryos and the advent of gonadotrophin-releasing hormone (GnRH) antagonists. It is without doubt that milder forms of ovarian stimulation protocols will reduce the risk of ovarian hyperstimulation syndrome and the cost of IVF treatment, as well as the controversial potential risk of ovarian cancer. However, embryo cohort size is an important predictor of the quality of embryos transferred (Devreker *et al*., 1999) and as shown in this study, of birth. It may therefore be argued that even with the current shift in policy towards elective single embryo transfer, a large embryo cohort size is still essential to ensure that at least one good quality embryo is available for transfer in order to achieve an acceptable birth rate. Further, it has been shown that cryopreservation of supernumerary embryos improves the cumulative birth rate after elective single embryo transfer (Tiitinen *et al*., 2001).

Several studies have shown the effect of age on the probability of birth (Tan *et al.*, 1992; Hull *et al.*, 1996; Engmann *et al.*, 1999) and multiple birth (Templeton and Morris 1998; Schieve *et al.*, 1999). This was confirmed in our study. The probability of multiple birth in women aged <35 years when excess embryos were created was particularly high, and probably unacceptable even in women who had only two embryos replaced.

Increasing the number of embryos transferred in older women is controversial since no studies have showed convincingly that this improves the chances of success. Moreover, probability of multiple birth is affected by the number of embryos transferred, and although 30% lower than for women aged <35 years, the risk of multiple birth for women in this age group who had three embryos replaced was still high, varying from ~20% to almost 30%.

There have been suggestions that further legislation to limit the number of embryos transferred to two in the UK is necessary. However, the results of our study indicate that this might have little impact on the probability of multiple birth overall, although it would reduce the incidence of triplets, since it is likely that clinical protocol and laboratory techniques will continue to improve, bringing consequent improvement in implantation rates and the chance that both embryos would implant. A blanket policy would only be justified if a high twin rate were acceptable, and in considering this the high incidence of perinatal morbidity and mortality among twins must be borne in mind. The incidence of late intrauterine death is three times higher in twins than in singletons (Office of National Statistics, 2001). Furthermore, the chance of twin pregnancy resulting in a baby with cerebral palsy is eight times that of a singleton birth (Petterson *et al.*, 1993). Although patients often express a preference for multiple birth after IVF treatment (Gleicher *et al.*, 1995; Murdoch, 1997), these statistics make it medically undesirable.

The evidence from our study, suggesting that increasing the number of embryos transferred has little or no effect on probability of birth, but merely increases the probability of multiple birth, is important. The chance of a birth thus depends almost solely on the characteristics of the woman and how successful the treatment is in terms of number of embryos created, and hence the ability of the laboratory to select high quality embryos for transfer. Women undertaking their first three cycles, aged <35 years, with non-tubal factor infertility, a previous IVF live birth and five or more embryos created in the cycle have the greatest chance of success; older women undergoing their fourth or higher cycle, with tubal factor infertility, no previous IVF live birth and three or fewer embryos created, have the worst chance of success.

Recent randomized prospective studies have suggested that elective single embryo transfer using strict embryo criteria in selected women is feasible and a reasonable birth rate can be achieved with a significant reduction in the multiple birth rate (Gerris *et al.*, 1999). Further studies have confirmed these findings and pregnancy rates equal to or even slightly higher than the natural pregnancy rate in normally fertile couples is possible (Vilska *et al*., 1999; ESHRE Campus Course Report, 2001). It has also been shown that an acceptable cumulative delivery rate can be achieved after elective single embryo transfer with a good cryopreservation programme (Tiitinen *et al*., 2001). Studies involving blastocyst culture in selected groups of patients have also shown that high implantation rates can be achieved with transfer of relatively fewer numbers of embryos (Gardner *et al.*, 1998; Milki *et al.*, 1999; Schoolcraft *et al.*, 1999). Evidence from these studies suggests that a move towards elective single embryo transfer in selected women should be encouraged. However, for elective single embryo transfer to be successful it is essential that the embryo with the highest implantation potential is identified and transferred. Recent studies have shown that a top quality embryo can be identified using strict criteria allowing reasonable pregnancy rates after elective single embryo transfer (Van Royen *et al*., 1999, 2001).

In summary, despite legislation introduced in 1991 to limit the maximum number of embryos transferred in the UK, at the clinic under study the likelihood of multiple birth remained stable between 1984 and 1997, though the probability of birth increased. This was largely due to a concomitant increase in the number of embryos created, which reflect improvements in clinical protocol and laboratory techniques. Younger age (<35 years), diagnoses other than tubal infertility, fewer than three previous unsuccessful cycles, previous IVF live birth and a large number of embryos created were all associated with increased chance of birth and multiple birth. Given these factors, increasing the number of embryos transferred did not increase the chance of a birth, but did increase the chance of a multiple birth. This should be borne in mind before any alteration in current policy for IVF treatment. A further reduction in the number of embryos transferred should also be encouraged, especially in patients with good prognostic factors for birth.

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