CLINCAL STUDY

In vitro fertilisation and stage 3 retinopathy of prematurity

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Abstract

Purpose To re-examine the risk of children born by assisted conception developing stage 3 retinopathy of prematurity (ROP) and to define whether the risk of ROP varies with the method of assisted conception.

Methods This was a retrospective study carried out between December 1995 and December 1998 of infants in a single neonatal unit serving the Brent and Harrow area of North West Thames requiring screening and treatment of ROP. The infants screened were identified from the ROP screening database. Those conceived by _in vitro_ fertilisation (IVF) and other forms of assisted conception were identified by reviewing the neonatal notes and the maternal obstetric records. Birth weight, gestational age and the type of assisted conception were recorded. The presence or absence of any stage of ROP, its location and severity and the cases requiring treatment were recorded.

Results One hundred and seventy-nine infants fulfilled the screening criteria during this period. Acute ROP was detected in 32.4% (58 infants) and stage 3 ROP developed in 15.6% (28 infants). Twenty-one infants (11.7%) were born after assisted conception, with 12 (6.7%) being conceived by IVF. The others were conceived on clomiphene (8) or after intrauterine insemination (1). Assisted conception accounted for 21.4% of all those reaching stage 3 disease and 28.6% of those infants requiring treatment. Of the 12 infants conceived by IVF, 41.6% (5 infants) developed acute ROP which progressed to threshold ROP in all infants (100%). Of the assisted conception babies requiring treatment for ROP, 83.3% were conceived by IVF. The other child had been conceived on clomiphene. The gestational age and birth weight of the IVF infants reaching stage 3 ROP were 26.6 ± 0.89 weeks and 937 ± 170.2 g. The gestational age and birth weight in the rest of the infants reaching stage 3 ROP were lower than in those conceived by assisted conception (25.739 ± 1.13 weeks and 735.29 ± 117.70 g); however, this did not approach statistical significance ($p = 0.35$ and $p = 0.13$, respectively).

Conclusions In this study 11.7% of the group requiring screening were conceived by assisted conception. Of all babies requiring treatment for ROP, 28.6% were born after assisted conception. Of the assisted conception group, 83.3% were conceived by IVF. Assisted conception using IVF rather than other techniques appears to be the major risk factor for the development of threshold ROP. We would advise increased vigilance when screening babies conceived by the IVF methods of assisted conception.

Key words In vitro fertilisation, Prematurity, Retinopathy

During 1996 and 1997, 25 565 patients received *in vitro* fertilisation (IVF) treatment, which resulted in 5601 live birth events.[1] In 1993 McFaul *et al*.[2] reported that 8% of babies born from assisted conception were born with a birth weight of 1500 g or less, compared with 1% of those conceived naturally.[3] These infants would fulfil the criteria set out by the Royal College of Ophthalmologists and British Association of Perinatal Medicine for screening for retinopathy of prematurity (ROP).[4] In 1996 McKibbin and Dabbs[5] examined the workload imposed by treatment for infertility on the ROP screening programme and found that 16.5% of babies screened were born after assisted conception. They reported that, of the assisted conception infants, 23% developed some stage of ROP and 25% required treatment. However, they did not differentiate between the different forms of assisted conception and the development of retinopathy.

We had also noticed an increased workload with babies born after assisted conception and felt that the method of conception influenced the development and severity of ROP. We therefore identified those infants presenting to a neonatal intensive care unit in North West London who were conceived through assisted conception and observed the percentage of those infants developing acute ROP and their method of conception.

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Received: 19 April 1999
Accepted in revised form:
15 October 1999

Table 1. *Gestational age and birth weight data*

				Assisted conception		IVF	
	Total screened (n = 179)	Acute ROP (n = 58)	Stage 3 ROP (n = 28)	No ROP (n = 21)	Stage 3 ROP (n = 6)	Stage 3 ROP (n = 5)	No ROP (n = 7)
Gestational age, weeks Mean (range)	28.7 ± 2.5 (23–38)	26.5 ± 1.8 (23–32)	25.8 ± 1.1 (24–28)	29 ± 2.3 (25–36)	26.6 ± 0.8 (25–27)	26.6 ± 0.8 (25–27)	30 (0)
Birth weight, g Mean (range)	1129.1 ± 333.2 (540–2030)	857.4 ± 225.6 (540–1685)	771.7 ± 147.4 (540–1200)	1116.1 ± 251.2 (710–1725)	905.8 ± 170.3 (750–1200)	937 ± 170.2 (760–1200)	1212.1 ± 345.3 (710–1725)

Patients and methods

Between December 1995 and December 1998 the number of infants who fulfilled the Royal College of Ophthalmologists and British Association of Perinatal Medicine criteria for screening for ROP were identified from the ROP screening database. The infant's neonatal case notes and mother's obstetric case notes were reviewed.

The details of the type of assisted conception, the birth history, the gestational age and birth weight details were recorded. The presence of singleton or multiple pregnancies and the details of the fundal examination were recorded.

The types of assisted conception utilised were IVF (which includes in vitro *fertilisation without micromanipulation (IVF) and the new technique of intracytoplasmic sperm injection (ICSI)), intrauterine insemination (IUI) and the use of clomiphene. Unless otherwise stated the term IVF includes techniques with and without micromanipulation.*

Statistical analysis was carried out using Microsoft Excel 97 for descriptive statistics and the SPSS software for significance testing.

Results

One hundred and seventy-nine infants met the screening criteria for ROP during the study period. The mean gestational age was 28.79 ± 2.51 weeks (range 23–38 weeks) and the birth weight 1129.15 ± 333.23 g (range 540–2030 g). Fifty-eight infants (32.4%) developed some stage of acute ROP. The gestational age and birth weight of the 58 patients who developed acute ROP were 26.55 ± 1.82 weeks (range 23–32 weeks) and 857.41 ± 225.65 g (range 540–1685 g). The data are given in Table 1.

Twenty-eight of these infants (15.6%) developed acute stage 3 ROP. There were 16 females and 12 males. Sixteen infants were Caucasian, 9 were Asian and 3 were Afro-Caribbean.

There were 21 infants conceived by assisted means. Twelve were conceived by IVF (7 with IVF without micromanipulation and 5 by ICSI), 1 by IUI and 8 with the help of clomiphene (Table 2). Acute ROP of any stage developed in 7 infants of the assisted fertilisation group; 1 reached stage 1 and 6 infants reached stage 3 ROP. One of these infants was conceived on clomiphene and 5 with IVF (3 with ICSI and 2 with IVF without micromanipulation). The latter 5 IVF infants all required treatment for threshold disease. Though the numbers were small there was a trend for the IVF infants with stage 3 ROP to have a higher gestational age and birth weight than the rest of the infants with stage 3 disease, but this did not approach statistical significance (p = 0.35 and p = 0.13, respectively) (Table 3).

There were 26 multiple pregnancies of which 23 were twin gestations and 3 were triplets. Eleven (1 from a triplet pregnancy and 10 from twin pregnancies) of the infants from multiple pregnancies died before screening for ROP could be undertaken. This left 44 infants (24.58%) from multiple gestations. Of the 21 infants conceived through assisted conception, 14 were from multiple gestations. Seven infants from multiple pregnancies (15.9%) reached stage 3 ROP, of which 5 were conceived through IVF treatment.

Discussion

The human fertilisation and embryology authority (HFEA) has licensed 114 clinics in the UK to carry out treatment and research in the various forms of assisted conception.[1] The assisted conception techniques offered consist of IVF (which unless otherwise stated includes other micromanipulation techniques of ICSI and subzonal insemination, or SUZI), gamete intrafallopian tube transfer (GIFT), donor insemination (DI), intrauterine insemination (IUI) and the use of gonadotrophins. In our study 5 babies were born after ICSI treatment, 7 after IVF without micromanipulation treatment, 1 after IUI and 8 after treatment with clomiphene.

Table 2. *Distribution of assisted conceptions and stage of ROP reached*

Type of assisted conception	No. of infants	No. with ROP	No. with stage 3 ROP
IVF	7	2	2
ICSI	5	3	3
IUI	1	0	0
Clomiphene	8	2	1

IVF, *in vitro* fertilisation without micromanipulation; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination. As ICSI is a form of IVF, for data analysis it is considered together with IVF without micromanipulation.

Table 3. *Birth weight and gestational age in infants reaching stage 3 ROP: IVF versus other assisted conception techniques*

	No. of infants	Sex	Race	Birth weight (g)	Gestational age (weeks)
Stage 3 ROP – not IVF (natural + *clomiphene)*	23	14F 9M	3AC 7A 13C	735.7 ± 117.7	25.7 ± 1.1
Stage 3 ROP – IVF	5	2F 3M	4C 1A	937 ± 170.2	26.6 ± 0.89

F, female; M, male; AC, Afro-Caribbean; A, Asian, C, Caucasian.

As a result of the activity of various units offering assisted conception, the outcome of these pregnancies has seen an increase in the number of premature infants (24% for assisted conceptions compared with 6% of those naturally conceived) and low birth weight infants (32% conceived by assisted conception compared with 7% conceived naturally).[3] This is largely due to the high frequency of multiple births in assisted conceptions compared with natural conceptions (23% vs 1%).[3] About 8% of assisted conception babies, compared with 1% of those conceived naturally, weigh less than 1500 g,[2] and hence would merit screening for ROP. This will underestimate the number of assisted conception babies requiring screening as it does not include those born before 32 weeks who weigh more than 1500 g. In 1996 McKibbin and Dabbs[5] reported that 16.5% of infants who fulfilled the ROP screening criteria were born after assisted conception. Screening data were available on 29 of these infants. Ten infants developed ROP of any stage, and 3 infants progressed to stage 3, of whom 2 required treatment for threshold disease. The mode of assisted conception for these infants was not recorded. Our data concur with McKibbin and Dabbs' findings in some aspects. Of their cohort 29.6% had any stage of ROP, whilst we found 32.4% in our series. Twenty-three per cent of their assisted conception cohort developed some form of retinopathy whilst the figure was 33.3% in our series. Twenty-five per cent of their series requiring treatment were born after assisted conception compared with 28.6% in our cohort.

In our series 11.7% of the infants screened for ROP were born after assisted conceptions. Of these infants 33.3% (7 infants) developed some stage of ROP, of whom 87.5% (6 infants) reached stage 3, and 71.4% (5 infants) required treatment for threshold disease. The remaining infant did not progress beyond stage 1 ROP.

The IVF infants accounted for 57.1% (12 infants) of assisted conceptions, with 41.6% progressing to stage 3 threshold disease compared with 9.37% of those born naturally. All IVF infants who developed any stage of ROP progressed to threshold disease. Those IVF infants with ROP had a lower gestational age (26.6 ± 0.89 weeks) and birth weight (937 ± 170.2 g) than those IVF infants who did not develop ROP (gestational age 30.25 ± 0.7 weeks, birth weight 1206.87 ± 320.04 g). Of the assisted conception babies needing treatment, 83.3% were born after IVF treatment.

Amongst the 179 infants in our series, 29.5% of the infants born of multiple gestations had some stage of ROP, with 13.6% reaching stage 1 and 15.9% reaching stage 3 ROP. Some stage of ROP was present in 33.3% of singleton pregnancies; stage 1 ROP was present in 12.5%, stage 2 ROP in 5.18% and stage 3 in 15.5%. These percentages represent the maximum stages of ROP reached before either regression was noted or treatment initiated.

The development of ROP in infants conceived from assisted conceptions is largely a result of these infants being born prematurely with very low birth weights and low gestational ages. This is to a large extent related to the high frequency of multiple pregnancies associated with assisted conceptions. Blumenfeld *et al.*[6] found in a large series that there was no difference in the incidence or the severity of ROP between singleton and multiple gestation babies. Although the number of infants conceived through IVF treatment compared with those conceived naturally is small, multiple pregnancies alone do not account for the increased percentage of infants reaching threshold disease in this group. The difference in outcomes of assisted conception has been postulated to be due to the fact that the gametes were exposed to a variety of drugs, physically manipulated, nurtured in potentially hazardous conditions, and perhaps placed in an inappropriate uterine environment.[2] This, in addition to immaturity, may have some relevance in the development of their eye disease. It certainly appears that infants conceived with the aid of clomiphene, a gonadotrophin which causes ovarian stimulation, have a lower risk of developing threshold ROP.

Conclusions

Our data support previous suggestions that babies born after assisted conception have a higher incidence of acute ROP. This is particularly so for the children conceived by IVF. It appears that IVF-assisted conception is the major risk factor rather than gonadotrophin stimulation. We would advise greater vigilance when screening these very precious babies conceived by IVF as they appear to be at greater risk of developing acute sight-threatening retinopathy. This association of IVF and ROP has not been previously documented.

The authors wish to thank Catey Bunce (Medical Statistician, Glaxo Department of Epidemiology, Moorfields Eye Hospital), Rachel Abraham and Ann Tubritt (Clinical Audit Department) and Lis Temple (Neonatal Unit, Northwick Park Hospital) for their help in this study.

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