

Cognitive development of 12 month old Greek infants conceived after ICSI and the effects of the method on their parents

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BACKGROUND: ICSI is widely used as a method of assisted reproduction in Greece. Research shows that children conceived after the application of ICSI develop normally. However, Bowen et al. (1998) reported that children conceived after ICSI had lower scores in the Mental Development Index (MDI) of the Bayley Scales of Infant Development compared with infants conceived naturally or by standard IVF treatment. This finding raised concerns about the effects of ICSI on infants' cognitive development. The aim of the present study was twofold. First to compare the cognitive development of Greek infants conceived after ICSI treatment to a control group of infants conceived after IVF treatment and to a further control group conceived naturally (NC). Second, to investigate the psychological effects of ICSI compared to IVF on Greek parents. **METHODS:** The Bayley Scales of Infant Development were employed to assess cognitive development of infants. A 37 item semi-structured interview was devised to obtain demographic information and to assess and compare the psychological effects of ICSI and IVF on parents. **RESULTS:** The mental development of infants in all three groups was within the normal range (ICSI 101.4, IVF 95.7, NC 98.9). The differences between the three groups were not statistically significant. The duration of pregnancy and the birthweight differed in the three groups. Furthermore, mothers in the IVF and the ICSI groups experienced anxiety during pregnancy. IVF mothers differed in the mode of delivery and a smaller number of these mothers breastfed their infants. **CONCLUSIONS:** This study has shown that Greek infants, born after the application of ICSI, have mental and motor scores within the normal range. With regard to the psychological effects, it appears that mothers in the ICSI and IVF groups experience greater anxiety during their pregnancies than those in the NC group.

Key words: cognitive development/ICSI/IVF/psychological effects

Introduction

The technique of ICSI, as implemented in assisted human reproduction, has provided new possibilities for the treatment of severe male-factor infertility and $\geq 25\%$ of infertility is attributed to a male factor (Templeton, 1995). With this method, the spermatozoon is directly deposited into the oocyte cytoplasm and the fertilization rate is $\sim 50\text{--}70\%$ (Van Steirteghen *et al.*, 1993). The technique has proven to be a true revolution since it has decreased the number of people employing sperm donation in order to have children. Sperm donation, although simple as a technique, can be psychologically complicated for the couple, the child and the donor (Delaisi and Verdier, 1994).

It is interesting to note that no experimental phase preceded the introduction of ICSI. At first, only ejaculated sperm were

injected, but later, surgically obtained sperm, immature sperm and spermatids from the epididymis or testis were also used. In 1995 almost 50 000 ICSI cycles were undertaken globally. Tens of thousands of ICSI children have been born since the technique was introduced. The first four human pregnancies using ICSI were reported by Palermo *et al.* (1992). Since the birth of the first ICSI child and up to March 1997, in the Brussels Free University programme alone, 1672 children have been born after applying this technique. Research shows that the incidence of major malformations is no greater than that for IVF or naturally conceived children (Bonduelle *et al.*, 1996). It has been suggested, however, that there may be an increased risk from the use of abnormal sperm cells because the sperm are not selected by a process of natural selection. Increased prevalence of sex chromosomal abnormalities has been

reported (Veld *et al.*, 1995; Bonduelle *et al.*, 2002) together with a high prevalence of structural and numerical chromosomal aberrations which could be related to the presence of abnormal sperm (Bonduelle *et al.*, 1998).

The cognitive development of infants conceived after ICSI was reported in a study by Bowen *et al.* (1998) in which 92 infants conceived after ICSI were compared to 86 infants conceived after IVF and 82 infants conceived naturally. The results indicated that at 12 months infants conceived after ICSI had significantly lower scores in the Mental Development Index (MDI) of the Bayley Scales of Infant Development compared to scores of infants conceived after IVF or naturally. Furthermore, the mental development of boys was more delayed than that of girls. This study has been criticized mainly for two problems in methodology. First, the social background of the infants in the three groups was not matched; second, the researcher who administered the Bayley Scales of Infant Development to the children was aware of the method of conception employed in each case. In a series of studies, Bonduelle *et al.* (1998; 2002, 2003), assessed the mental development of a total of 439 ICSI children and 207 IVF children aged 24–28 months. The results indicated that the ICSI and IVF children had scores comparable to those of the general population. In subsequent studies, the Griffiths mental development scales were used to assess cognitive development in 208 infants conceived after ICSI and 221 naturally conceived infants. The results showed no differences between the two groups (Sutcliffe *et al.*, 1999, 2001).

Little is known regarding the psychological effects of ICSI on parents. It has been reported that couples undergoing ICSI experience higher anxiety during the days prior to oocyte retrieval than patients undergoing IVF (Boivin, 1998). In Greece the psychological effects of ICSI on couples undergoing treatment have not been studied. In a study concerning the psychological effects of IVF on Greek couples it was found that they abstained from sexual intercourse during the period of pregnancy and that the most common mode of delivery was the Caesarian section (Papaligoura, 1998).

The goals of the present study were: first, to examine whether Greek infants conceived after the application of the ICSI technique differ in their cognitive development from Greek infants conceived through IVF or infants conceived naturally; second, to investigate and compare the psychological effects of ICSI and IVF on Greek couples.

Materials and methods

Population

Three groups of infants participated in the study. The experimental group included 34 infants [26 singletons and eight twins (23%); 15 boys, 19 girls] conceived after the application of the ICSI technique. The first control group was comprised of 26 infants [14 singletons, 12 twins (46%); 14 boys, 12 girls] conceived after the application of IVF. The second control group consisted of 29 infants [23 singletons, six twins (21%); 10 boys, 19 girls] conceived 'naturally'. All participants gave informed consent.

Recruitment of infants

The method for sample collection was retrospective enrolment. Infants conceived after ICSI and IVF were recruited through the Euromedica IVF Centre from September 1998 to January 2000. The Euromedica IVF Centre has been operating in Athens since 1989. It is one of the oldest and largest centres operating in Greece with an annual average of 700 cases and 2500 children have been born during the continuous 14 years of its operation. The ICSI method has been available in the centre since 1994 and ~40% of all the cycles use this technique while the rest use the IVF method. Parents of infants conceived naturally were approached through paediatricians associated with the two largest children's hospitals in the Athens area. Since all infants in the experimental group were first-borns, only first-born infants were included in the two control groups. All participants were contacted by telephone when the infants were 10 months old and the purpose of the study was explained to them. Those who agreed to participate were then contacted by the first researcher who explained the details of the study and arranged the date for the child's assessment. There was one refusal in the ICSI group, two in the IVF and none in the natural conception (NC) group.

Assessment of infant cognitive development

The Bayley Scales of Infant Development (Bayley, 1993), which are especially suitable for assessing the development of infants aged 12 months, were employed. The researcher who administered the test was a psychologist trained to employ the Bayley Scales and was blind regarding the group to which each infant belonged. All mothers gave their informed consent and the infants were visited at home, around their first birthday, at a time suitable for the families. Once the test had been completed and scored, the mothers were interviewed.

Interviews with mothers

A 37 item semi-structured interview was used to collect information on maternal age, years of education, years of marriage, duration and aetiology of infertility and the number of cycles mothers had undergone. In addition, questions on the mode of delivery, breastfeeding and the sleeping routine of the infants were included. In order to assess psychological issues concerning ICSI and IVF, questions were also asked about the revelation of the method of conception to relatives, precautions during pregnancy and frequency of sexual relations during pregnancy. Responses were rated as yes/no.

Statistical analysis

Statistical analysis was conducted using the statistical package SPSS for Windows 10.0. Between-group differences were analysed with one-way analysis of variance (ANOVA) for continuous variables and χ^2 was used for categorical variables. Differences between the ICSI and the IVF group in skewed variables (years of infertility, number of cycles) were examined by the non-parametric Mann-Whitney test. When the ANOVA revealed a difference between the three groups, the Bonferroni multiple comparisons procedure was used to determine which means were significantly different from each other. Two-way multivariate ANOVA was used to test for group differences in Bayley scores and gender effect. Analysis of covariance was also used to test between-group differences in Bayley scores after adjustment for differences in maternal age and infant birthweight. Estimates of effect size were calculated using the partial η^2 value, which describes the proportion of total variability of a characteristic attributable to a certain factor (e.g. groups).

Table I. Sociodemographic characteristics of parents

	ICSI (<i>n</i> = 30)	IVF (<i>n</i> = 20)	NC (<i>n</i> = 26)	Test	<i>P</i>
Education > 12 years, <i>n</i> (%)					
Father	23 (76.6)	15 (75.0)	22 (92.3)	$\chi^2 = 3.049$	0.218
Mother	20 (66.7)	14 (70.0)	18 (69.2)	$\chi^2 = 0.074$	0.964
Mothers not employed, <i>n</i> (%)	4 (13.8)	3 (15.0)	4 (16.0)	$\chi^2 = 0.052$	0.974
Mother's age ^a	34.2 ± 3.7	36.3 ± 3.5	31.5 ± 4.1	<i>F</i> = 9.483	< 0.001
Years of marriage ^a	8.1 ± 2.6	8.3 ± 3.7	4.4 ± 2.6	<i>F</i> = 13.851	< 0.001

^aMean ± SD.

NC = natural conception.

Results

Description of the sample

Sociodemographic characteristics of parents are shown on Table I.

There was no between-group difference in parental education ($P = 0.96$ for mother, $P = 0.22$ for father). There was a significant difference and a large effect in maternal age ($P < 0.001$, $\eta^2 = 0.21$). Multiple comparison testing, after Bonferroni adjustment, showed that mothers in both the ICSI group and in the IVF group were older than mothers in the natural conception group ($P = 0.03$ and $P < 0.001$ respectively), while the age difference in the first two groups was not significant ($P = 0.15$). Mothers in the ICSI group had a mean age of 34.2 years (SD 3.7), and those in the IVF group had a mean age of 36.3 years (SD 3.5), while mothers in the natural conception group had a mean age of 31.5 years (SD 4.1). Another significant difference between the groups was the years of marriage ($P < 0.001$) and the effect was large ($\eta^2 = 0.27$). Mothers in the ICSI group were married for a mean of 8.1 years (SD 2.6), mothers in the IVF group were married for a mean of 8.3 years (SD 3.7), while mothers in the natural conception group were married for a mean of 4.4 years (SD 2.6). Most mothers in all three groups were employed and the between-groups difference in the percentage of maternal employment was not significant ($P = 0.95$).

Infertility in the ICSI group ranged from 1 to 10 years (median 4 years) and in the IVF group it ranged from 1 to 13 years (median 2 years) (Table II). The difference in the duration of infertility was not significant ($P = 0.531$). As far as aetiology of infertility was concerned: as was expected, in the ICSI group most couples (65.5%) had a male infertility problem. The corresponding percentage in the IVF group was 10.5%. In the ICSI group, 24.1% had an infertility problem which was due to a combination of a male and female factors. In the IVF group the most usual infertility problem was due to abnormal Fallopian tubes (21%). There was also a high percentage of unexplained infertility in the IVF group (26.3%) whereas in the ICSI group this was only 3%. Regarding the number of cycles, the difference between the two groups was not statistically significant ($P = 0.15$). Seventy-seven per cent of women in the ICSI group were in their first three cycles while in the IVF group 85% of the participants were in their first three cycles.

Table II. Infertility

	ICSI (<i>n</i> = 30)	IVF (<i>n</i> = 20)
Duration of infertility	Median 4 years Range (1–10)	Median 2 years Range (1–13)
Revelation of infertility to relatives (%)	76.7	65
No. of cycles (%)		
1–3	76.7	85
4–7	16.7	5
>7	6.6	10
Aetiology (%)		
Semen abnormality	65.5	10.5
Endometriosis	3.4	5.3
Abnormal Fallopian tubes	0	21.1
Male and female factor	24.1	5.3
Unexplained infertility	3.4	26.3

No between-group difference was found regarding the revelation of the method of conception to relatives ($\chi^2 = 0.81$, $P = 0.37$). More couples (76.7%) in the ICSI group than in the IVF group (65%) revealed to their family members the method of conception.

Infants' characteristics

All infants were seen for assessment at the age of 12 months ± 6 days.

Table III shows the characteristics of infants in the three groups. There were no significant differences between the groups in percentage of male infants ($P = 0.35$) or twins ($P = 0.08$). Significant differences were found regarding the mode of delivery ($P < 0.001$) and the percentage of children with low birthweight ($P = 0.03$). Infants in the ICSI and IVF groups were more often delivered by Caesarean section than infants in the NC group (ICSI = 85.3%, IVF = 92.3%, NC = 44.8%). Infants in the IVF group and in the ICSI group were more often of low birthweight compared to infants in the NC group (ICSI = 20.6%, IVF = 30.8%, NC = 3.4%). Although differences in the proportion of infants born prematurely were not significant, there was a significant difference and a rather large effect in gestational length ($P = 0.002$, $\eta^2 = 0.14$) and in birthweight ($P = 0.011$, $\eta^2 = 0.10$). Multiple comparisons after Bonferroni adjustment showed that IVF infants were born earlier, in comparison both to ICSI infants ($P = 0.04$) and to the NC group

Table III. Infants' characteristics

Infants' characteristics	ICSI (<i>n</i> = 34)	IVF (<i>n</i> = 26)	NC (<i>n</i> = 29)	Test	<i>P</i>
Males	15 (44.1)	14 (53.8)	10 (34.5)	$\chi^2 = 2.09$	0.352
Twins	8 (23.5)	12 (46.1)	6 (20.7)	$\chi^2 = 5.16$	0.076
Caesarean section	29 (85.3)	24 (92.3)	13 (44.8)	$\chi^2 = 19.69$	< 0.001
Premature ^a	19 (57.6)	18 (69.2)	11 (42.3)	$\chi^2 = 3.86$	0.145
Low birthweight (<2500 g)	7 (20.6)	8 (30.8)	1 (3.4)	$\chi^2 = 7.19$	0.027
Colic pains	21 (63.6)	13 (50)	13 (44.8)	$\chi^2 = 2.37$	0.306
Breastfed	31 (91.2)	14 (53.8)	25 (86.2)	$\chi^2 = 13.69$	< 0.001
Feeding problems	7 (20.6)	6 (23.1)	10 (34.5)	$\chi^2 = 1.72$	0.422
Sleeping problems	13 (38.2)	10 (38.5)	13 (44.8)	$\chi^2 = 0.34$	0.843
Gestational length (weeks) ^b	36.7 ± 1.4	35.3 ± 3.1	37.4 ± 1.8	$F = 6.53$	0.002
Birthweight (g) ^b	2929 ± 457	2620 ± 659	3056 ± 502	$F = 4.74$	0.011

Values are *n* (%) unless otherwise stated.

^aBorn <37 weeks of gestation.

^bMean ± SD.

NC = natural conception.

infants ($P = 0.002$). Regarding birthweight, the significance of difference was mainly due to the IVF infants who had lower birthweight compared to controls ($P = 0.01$). Mothers in all three groups reported that most infants suffered from colic pains (ICSI 63.6%, IVF 50%, NC 44.8%). ICSI infants and those in the NC group were more often breastfed (86.2 and 91.2% respectively) than IVF infants (53.8%). The difference between the groups was significant ($P < 0.001$). There were no significant differences between infants in the three groups regarding sleeping difficulties (ICSI 38.2%, IVF 38.5%, NC 44.8%), or feeding difficulties (ICSI 20.6%, IVF 23.1%, NC 34.5%).

Psychological effects of the method of conception

Participants in both the ICSI (63%) and the IVF (47.4%) groups considered the method of conception that they employed as psychologically demanding. Furthermore, the waiting period after the embryo transfer was considered to be the most stressful phase of the treatment by mothers in both groups (ICSI 44.4%, IVF 55%). Once pregnancy occurred, 26.9% of mothers in the ICSI group and 36.8% of IVF mothers reported that they stayed in bed for the first month, while only 4% of the control mothers reported doing so. The difference between the groups was significant ($P = 0.01$). Also 70% of mothers in the ICSI group and 65% of mothers in the IVF group reported that they abstained from sex during the whole pregnancy period, compared to only 19.2% of mothers in the NC group. Again the difference between the groups was significant ($P = 0.001$).

Infants' cognitive development

The main research question concerned the cognitive development of infants in the ICSI group. Two-way multivariate ANOVA of Developmental Indices gave non-significant results for group differences (Wilk's $L = 0.96$, $F = 0.77$, 4 and 168 df, $P = 0.54$) or sex differences (Wilk's $L = 0.97$, $F = 1.16$, 2 and 84 df, $P = 0.32$). Both the group effect size ($\eta^2 = 0.02$) and the gender effect size ($\eta^2 = 0.03$) were very low. Univariately, between-group differences were not significant regarding either MDI or Psychomotor Developmental Index

Table IV. Infants' cognitive development

	Bayley scores	
	MDI	PDI
ICSI	101.4 ± 16.0	94.1 ± 22.9
Boys (<i>n</i> = 15)	97.6 ± 15.7	85.7 ± 21.3
Girls (<i>n</i> = 19)	104.4 ± 16.0	100.7 ± 22.4
IVF	95.7 ± 16.4	85 ± 13.6
Boys (<i>n</i> = 14)	97.1 ± 17.5	86.5 ± 13.6
Girls (<i>n</i> = 12)	94 ± 15.6	83.3 ± 13.8
NC	98.9 ± 17.5	90.7 ± 19.4
Boys (<i>n</i> = 10)	100.6 ± 9.3	88.2 ± 18.6
Girls (<i>n</i> = 19)	98 ± 20.7	92 ± 20.1
Significance of group effect ^a	$F = 0.83$	$F = 1.41$
	df = 2 and 85	df = 2 and 85
	$P = 0.44$	$P = 0.25$
Group effect size ^a	$\eta^2 = 0.02$	$\eta^2 = 0.03$

Values are mean ± SD.

^aAfter adjustment for gender effect.

MDI = Mental Development Index; PDI = Psychomotor Development Index; NC = natural conception.

(PDI) (Table IV). Analysis of covariance also showed no significance between group differences in Bayley scores, after adjustment for differences in maternal age and infant birthweight ($F = 0.55$, df = 2 and 84, $P = 0.58$ for MDI and $F = 1.09$, df = 2 and 84, $P = 0.34$ for PDI) or maternal age and gestational length ($F = 0.63$, df = 2 and 80, $P = 0.53$ for MDI and $F = 0.96$, df = 2 and 80, $P = 0.39$ for PDI).

Discussion

One of the main research questions of the present study concerned the cognitive development of infants conceived by ICSI. The results indicated that the ICSI group did not differ from the IVF or NC group in the MDI or the PDI. This finding is in accordance with those of other studies (Sutcliffe *et al.*, 2001; Bonduelle *et al.*, 2003) that reported no significant differences in psychomotor development between ICSI, IVF or NC infants. All scores of infants in the three groups, both for boys and for girls, were within the normal range and the

differences between the groups were not statistically significant. It appears that the scores in the three groups were somewhat lower than those usually found in other countries. However, the distribution itself of the Bayley Scales in Greece has not yet been studied.

As far as birthweight was concerned, this was lower in the IVF infants than the ICSI and the naturally conceived infants. However, there were more twins and more prematurely born infants in the IVF group and this may explain the lower birthweight of these infants.

A second aim of the study was to understand the psychological effect of ICSI on Greek mothers and to compare this to the effects of IVF. It seems that both methods are perceived as psychologically demanding and that the most stressful phase of both treatments is the period extending from the completion of the treatment to the day the outcome is announced (Leiblum *et al.*, 1987; Papaligoura, 1992, 1998). Most participants stated that they had discussed the method of conception with their family, a strikingly different finding from a previous study in Greece (Papaligoura, 1992) in which most couples stated that they had discussed IVF with no one. This difference in attitude may very well reflect the limited public awareness in Greece that existed a few years ago, regarding the IVF procedure. In the earlier study, when discussing the reason for not disclosing the method of conception, couples mentioned their concern that people would not understand what IVF was about, thereby assuming that the infant born after the application of IVF may have been the outcome of gamete donation.

It is evident that mothers in the IVF and ICSI groups experienced anxiety during pregnancy. This finding is in accordance with previous research concerning the effects of IVF (McMahon *et al.*, 1997; Papaligoura, 1998). The anxiety of the mothers was evident from their responses to two interview topics. First, most mothers in both the ICSI and IVF groups did not have sexual relations during pregnancy, whereas this was only true for a small number of mothers in the NC group. The reason which these mothers gave for not having sexual relations was that they were afraid something bad might happen to the baby. Second, their anxiety was evident from the fact that a high percentage of them, compared with the mothers in the control group, stayed in bed for the first month of pregnancy with no apparent medical reason (i.e. no bleeding or pains) but simply because they considered it safer to rest. In respect to the mode of delivery, the higher rate of Caesarean sections in the IVF and ICSI groups is in accordance with some studies (Beral *et al.*, 1990; Friedler *et al.*, 1992; Reubinoff *et al.*, 1997; Papaligoura, 1998) but in contrast to others (Leslie *et al.*, 1998; Koivurova *et al.*, 2002; Sydsjö *et al.*, 2002) where no difference was found in mode of delivery between IVF and control groups. The higher rates of Caesarean deliveries, in the present study, could be attributed to a number of factors. First, to the higher rates of multiple births; second, to the older age of mothers; and third, to the anxiety of the Greek medical teams who still view these pregnancies as more 'precious' and do not want to take any 'risks' (Delaisi de Parseval, 1981). However, a finding of the present study which raises some concern is the high percentage of Caesarean sections in the NC group. This finding has also been reported in other countries (Koivurova

et al., 2002) and needs to be further studied so that the underlying causes for this practice can be identified.

After birth, mothers in all three groups reported that infants suffered from colic pains but had no sleeping or feeding problems. However, the fact that fewer mothers in the IVF group (60%) breastfed their infants compared to mothers in the other two groups (90% of mothers in the ICSI group and 85% of mothers in the NC group) is surprising and needs to be further examined. One possible explanation could be the larger number of twins and premature infants found in the IVF group. Another possible explanation could be that IVF mothers had a higher percentage of infertility problems attributed to a female factor as opposed to ICSI mothers who had an infertility problem mainly due to sperm abnormalities. This difference could be a factor which affected the body image of IVF mothers, making them feel less competent and, therefore, more likely to abandon breastfeeding than mothers in the ICSI group.

In conclusion, it seems that the psychological effects of IVF and ICSI on mothers are similar. Both procedures increase the anxiety of participants during pregnancy but the cognitive development of infants is not affected.

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References

- Bayley N (1993) Bayley Scales of Infant Development. 2nd edn, The Psychological Corporation London: Harcourt Brace & Company.
- Beral V, Doyle P, Tan L, Bason B and Campbell S (1990) Outcome of pregnancies resulting from assisted conception. *Br Med Bull* 46,753–768.
- Boivin J, Shooq-Svanberg A, Anderson L, Hjelmstedt A, Berg T and Collins A (1998) Distress level in men undergoing intracytoplasmic sperm injection versus in-vitro fertilization. *Hum Reprod* 13,1403–1406.
- Bonduelle M, Legein J, Buysse A, Van Assche E, Wisanto A, Devroy P, Van Steirteghem AC and Liebaers I (1996) Prospective follow-up study of 423 children born after intracytoplasmic sperm injection. *Hum Reprod* 11,1558–1564.
- Bonduelle M, Joris H, Hofmans K, Liebaers IV and Van Steirteghem A (1998) Mental development of 201 ICSI children at 2 years of age. *Lancet* 351,1553.
- Bonduelle M, Liebaers I, Deketelaere V, Derde M, Camus M, Devroy P and Van Steirteghem A (2002) Neonatal data on a cohort of 2889 infants born after ICSI (1991–1999) and of 2995 infants born after IVF (1983–1999). *Hum Reprod* 17,671–694.
- Bonduelle M, Ponjaert I, Van Steirteghem A, Derde M, Devroy P and Liebaers I (2003) Developmental outcome at 2 years of age for children born after ICSI compared with children born after IVF. *Hum Reprod* 18,342–350.
- Bowen J, Gibson F, Leslie G and Saunders D (1998) Medical and developmental outcome at 1 year for children conceived by intracytoplasmic sperm injection. *Lancet* 351,1529–1534.
- Delaisi G and Verdier P (1994) *Enfant de personne*. Editions Odile Jacob, Paris.
- DelaisiDeParseval G (1981) *La part du père*. Seuil, Paris.
- Friedler S, Mashiah S and Laufer N (1992) Births in Israel resulting from in-vitro fertilization/embryo transfer, 1982–1989: National Registry of the Israeli Association for Fertility Research. *Hum Reprod* 7,1159–1163.
- Koivurova S, Hartikainen A, Karinen L, Gissler M, Hemminki E, Martikainen H, Tuomivaara L and Järvelin M (2002) The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in Northern Finland 1990–1995. *Hum Reprod* 17,2897–2903.
- Leiblum S, Kemmannn E and Lane M (1987) The psychological concomitants of in vitro fertilization. *J Psychos Obstet Gynecol* 6,165–178.
- Leslie G, Gibson F, McMahon C, Tennant C and Saunders D (1998) Infants

- conceived using in-vitro fertilization do not over-utilize health care resources after the neonatal period. *Hum Reprod* 13,2055–2059.
- McMahon C, Ungerer J, Beaurepaire J, Tennant C and Saunders D (1997) Anxiety during pregnancy and fetal attachment after in-vitro fertilization conception. *Hum Reprod* 12,176–182.
- Palermo GJ, Devroy P and Van Steirteghem A (1992) Pregnancies after intracytoplasmic sperm injection of single spermatozoon into an oocyte. *Lancet* 340,17–18.
- Papaligoura Z (1992) The effects of in-vitro-fertilization. Paper Presented at the 4th Congress of the Greek Psychological Society, Athens, 16–19 April.
- Papaligoura Z (1998) The Effects of In-Vitro Fertilization on Parent–Infant Communication. PhD thesis, University of Edinburgh.
- Reubinoff B, Samueloff A, Ben-Haim M, Friedler S, Schenker J and Lewin A (1997) Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. *Fertil Steril* 67,1077–1083.
- Sydsjö G, Wadsby M, Kjellberg S and Sydsjö A (2002) Relationships and parenthood in couples after assisted reproduction and in spontaneous primiparous couples: a prospective long-term follow-up study. *Hum Reprod* 17,3242–3250.
- Sutcliffe A, Taylor B, Li J, Thornton S, Grudzinskas J and Lieberman B (1999) Children born after intracytoplasmic sperm injection: population control study. *Br Med J* 318,704–705.
- Sutcliffe A, Saunders K, Thornton S, Lieberman B and Grudzinskas J (2001) Outcome in the second year of life after in-vitro fertilization by intracytoplasmic sperm injection: population control study. *Lancet* 357,2080–2084.
- Templeton A (1995) Infertility—epidemiology, aetiology and effective management. *Health Bull. (Edinb)* 53,294–298.
- Veld, In't P, Brandenburg H, Verhoeff A, Dhont M and Loss F (1995) Sex chromosomal abnormalities and intracytoplasmic injection. *Lancet* 346,773.
- VanSteirteghem A, Nagy Z and Joris H (1993) High fertilization and implantation rates after intracytoplasmic sperm injection. *Hum Reprod* 8,1061–1066.

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