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Cognitive and socio-emotional development and manifestation of learning disabilities of 8- to 10-year-old children born after intracytoplasmatic sperm injection compared to naturally conceived children

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Summary

Objective: The purpose of the present study was to investigate the cognitive and socio-emotional development, as well as the manifestation of learning disabilities of eight- to ten-year-old children born after intracytoplasmatic sperm injection (ICSI). *Materials and Methods:* Developmental outcomes of 40 children born after ICSI were compared with those of 40 children born after spontaneous conception (SC). Outcome measures included the Raven's Progressive Matrices Test, Child Behavior Checklist (CBCL), and Athina Test of Learning Difficulties. *Results:* Regarding cognitive development, ICSI children tend to obtain a similar intelligence score with SC children on Raven's Test. No significant differences were noted on CBCL's syndrome and abilities' profiles, and on Athina Test. *Conclusions:* ICSI and SC children show a comparable cognitive and socio-emotional development and have the same chances of manifesting learning disabilities. None of the demographic factors taken into consideration (age, sex of the child, and educational level of the parents) nor the mode of conception seem to affect their well-being.

Key words: Cognitive development; Socio-emotional development; Learning difficulties; ICSI.

Introduction

Intracytoplasmatic sperm injection (ICSI) was developed in 1992 at the Centre for Reproductive Medicine, Vrije University in Brussels, Belgium [1]. Certain forms of subfertility, largely those derived from male problems, cannot be treated by conventional IVF, and the development of ICSI has allowed some of these couples to conceive [2]. At present 2-4% of children born in developed countries are conceived through assisted reproductive techniques (ART), with ICSI being the most effective means of treating these cases [3].

The ICSI procedure involves fertilization by injection of a single sperm directly into an oocyte, often with spermatozoa with impaired mobility and morphology. By selecting a single sperm for injection, the ICSI technique bypasses the usual process of natural selection which occurs both during natural conception and in conventional IVF, resulting in a greater chance of fertilization with abnormal sperm [4]. An ongoing discussion about the potential genetic and developmental risks to ICSI offspring has resulted, due to this high degree of human intervention [5]. The concerns that have arisen concern the transmission of genetic abnormalities, as well as of foreign genetic material and the potential for chemical and mechanical damage [2].

To date a series of studies on cognitive development have been conducted in which children conceived by ICSI were compared with naturally conceived (NC) control subjects. The majority of these studies show no delayed development regarding their intelligence functioning [6-10, 11]. In this context, no significant differences were found on WPPSI-R verbal and performance scales between five-year-old ICSI and spontaneously conceived (SC) children from Belgium, Sweden, and the USA [5]. However, some differences were noted on the visual-spatial subtests of the Performance Scale (object assembly, block design, and mazes) where ICSI children obtained a lower score. Also, regarding their socio-emotional development, significant differences by site were found on subtests related to child behavior problems. These results were not attributed to the mode of conception.

A European collaborative follow-up study compared five-year-old ICSI conceived children with IVF and NC controls [12] who were recruited in five countries (Belgium, Denmark, Greece, Sweden, and United Kingdom). Although no significant differences were found when ICSI, IVF, and NC scores on WPPSI-R were compared, the findings indicate that demographic factors such as maternal educational level and maternal age at the time of the birth

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might play different roles in the cognitive development of ICSI and IVF children.

As a continuation of the two previous large-scale studies, a proportion of the Belgian populations assessed at age five was reassessed at the age of eight by means of WISC-R [13]. Regarding intellectual functioning, ICSI children obtained significantly higher total, verbal, and performance intelligence scores than SC children, nevertheless remaining in similar ranges. Moreover, higher maternal educational level was found to be responsible for the slightly higher intelligence scores in the ICSI group and it was hypothesized that its association with older maternal age, possibly led to a higher degree of child stimulation.

A follow-up study was conducted and the second-wave results on the cognitive development of ten-year-old ICSI children were compared with the outcome at eight years [14]. The results showed that the ten-year-old ICSI children obtained total, verbal, and performance intelligence scores comparable to those of SC children. With regards to long-term follow-up, the IQ results of ICSI and SC children at age ten appear to have converged (from slightly higher scores in the ICSI children at age eight), probably indicating a decreased effect of maternal educational level or stimulating home environment in the ICSI group over time.

Fewer large-scale studies have been carried out on the socio-emotional development of preschool to school-aged children. Apart from the study conducted by Ponjaert-Kristoffersen *et al.*, (2004) that was mentioned above, three other important studies have taken place [15-17]. Their results are reassuring and lead to the conclusion that ICSI children do not have a higher risk of behavioral and emotional problems when compared with children born after SC.

Materials and Methods

Participants

The present sample consisted of a total of 80 children divided into two groups: a) 40 ICSI children and b) 40 NC children (control group). There was an even distribution in terms of: 1) the age which ranged from eight to ten years (mean value 8.85), 2) gender as 43 girls (19 NC and 21 ICSI) and 37 boys (21 NC and 19 ICSI) participated, 3) the parents' educational level, and 4) the parents' economical status.

Procedure

The ICSI conceived children were collected from a private clinic in Athens which specializes in this technique. Initially informing parents was by telephone and if they accepted their children to participate in the research, then a second telephone conversation followed during which the date and time for a home meeting and session were established.

NC children came from a public hospital's maternity clinic in Athens. For this group only a single telephone conversation was needed during which parents were informed and replied immediately regarding their child's participation in the research. The sessions were conducted in a neutral space (private office).

The administration of the two psychometric tools (Raven's test and Athina test) was conducted individually and lasted an average of one hour and ten minutes, during which time the completion of the CBCL questionnaire was completed by one of the parents (usually the mother) after the necessary clarifications were given. Before each session, parents were requested to sign a formal statement in which they gave their consent for their child's participation in this research.

Outcome measures

The performance tests, intelligence tests, as well as most behavior evaluation scales are standardized tests that allow users to compare the grades of a student or a group of students with the grades of the group-norm. Thus, most standardized tests are considered norm reference tests [18]. Cognitive and socio-emotional development, as well as learning disabilities were respectively measured with Raven's Progressive Matrices Test, Child Behavior Checklist (CBCL), and Athina Test. All outcome measures consisted of standardized tests with satisfactory psychometric properties regarding reliability and validity.

Intelligence test - Raven's Test

The homogeneous or single phase tests are those criteria which refer to one of the general intelligence's basic functions. One such test is the Raven's Progressive Matrices (Progressive Types Scale) for children [19]. The questions of the Matrix are two-dimensional analogy problems and control for perceptual capacity. Their solution requires audiovisual processes, but not visual-motor perception abilities. In order to answer the Raven progressive types correctly, the child must discover the axiom that applies each time, moving from left to right or from top to bottom of the page. More specifically it consists of tests that comprise various types of drawings-formulations with a missing fragment and the examinee must choose the correct one. Gradually the tests' degree of difficulty increases and logical correlation and deductive reasoning abilities are required of the children [20].

Athina Test

The Athina Test is an individually administered, clinical instrument for assessing learning difficulties. It provides standardized measures of a variety of abilities reflecting different aspects of learning difficulties. Its assessments are in the form of psychometric scales and evaluate the developmental level and rate of the child, in the following five areas of development which include various scales: cognitive ability (linguistic analogies, vocabulary), sequence direct memory (numerical memory), completion of incomplete expressions (sentence completion), the graph-phonemic awareness (graphs distinction, phoneme composition), as well as neuro-psychological maturity (right-left perception), [21]. The Athina Test was created in 1999 in the psychometric laboratory of the Psychology Department at the School of Philosophy of the National and Kapodistrian University of Athens based on and using as models two widely used assessment tests: the 'Aston Index: a classroom test for screening and diagnosing of language difficulties' and the 'ITPA: Illinois Test of Phycholinguistic Abilities'.

The main purpose of the differential-analytical evaluation provided by the Athina Test is: first, the detection of deficient areas in the child's development that are associated with learning difficulties and second, the planning and implementation of appropriate teaching - corrective intervention. This test corresponds to the developmental level of children from the beginning of the fifth year of age until the end of the ninth year, namely children attending kindergarten, and the A, B, C and D grades of primary school.

Regarding its structural and functional characteristics, the

Athina test is [21] multithematic - qualifying test: it seeks to cover as many aspects of child development as possible, which are associated with school learning and adaptation. It can also be used as a preliminary test for an initial evaluation of the child and to determine whether or not further examination with the assistance of more specific psychological scales will be required; intra-individual assessment diagnostic test: the diagnostic desideratum is not just to determine whether the child's developmental level is cognate with their chronological age by comparing the child's performance with that of coeval children (inter-individual differences), but also and more importantly to determine whether there are differences between the various individual abilities and performances within the child under evaluation (intra-individual differences).

CBCL (Child Behavior Checklist-Achenbach System of Empirically Based Assessment-ASEBA)

The Achenbach questionnaires are universally acknowledged and widely used to assess adaptive behavior and psychopathology of children and adolescents. The CBCL / 6-18 questionnaire for parents is completed by parents, guardians or those who live with the children in an environment similar to family and includes the competence profile (activities scale, social, and school scale) and the syndromes profile (internalized and externalized problems). The first page contains questions on demographic information and socioeconomic status of the parents, as well as data on the child's abilities. The second page contains open-descriptive questions about the child's different characteristics and in the last two pages (3 and 4) the evaluator rates each problem (emotional-social-behavior) with a scale of 0, 1 or 2 (0 = does not fit the child, 1 = fits somewhat or sometimes, 2 = very fit or very often).

Each scale consists of data, the values of which are summed up to provide the scale's score. This indicates the extent to which the child demonstrates the ability which is represented by the scale. The data and scales' scores, namely the child's profile, are recorded in special ASEBA diagrams which determine the areas where the abilities and the problems of the child are within normal, marginal or clinical spectrum [22, 23].

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for quantitative variables and as percentages for qualitative variables. The Kolmogorov-Smirnov test was utilized for normality analysis of the parameters. The comparison of quantitative and qualitative variables were performed using the Independent samples *t*-test or the Mann-Whitney test in case of violation of normality and the Fisher's exact test, respectively. The multiple linear and logistic regression models were used for comparison of the questionnaires' subscales, between the two conception groups adjusting the demographic variables, so we can control the above comparison for the effect of differences that may exist among these groups in demographics characteristics. All assumptions of linear and logistic regression analysis were also examined. All tests are two-sided, statistical significance was set at $p < 0.05$. All analyses were carried out using the statistical package SPSS vr 17.00.

Results

Table 1 shows the demographics of the population of the present study. The sample consisted of 46.3% boys and 53.8% girls, with an average age of 8.85 years, with a minimum age of eight years, and with a maximum of 9.8 years.

The majority of parents had high educational level. More specifically the father's level of education was 21.3% medium and 78.8% high, while the mother's level was 32.5% medium and 67.5% high.

Table 1. — *Demographic population data.*

Gender n (%)	Boy	37 (46.3%)
	Girl	43 (53.8%)
Father's educational level n (%)	High school	17 (21.3%)
	University	63 (78.8%)
Mother's educational level n (%)	High school	26 (32.5%)
	University	54 (67.5%)
Age (mean ± SD)	---	8.85 ± 0.48

Table 2. — *Homogeneity between the compared groups.*

		Natural conception	ICSI	*p*-value
Gender n (%)	Boy	18 (45.0%)	19 (47.5%)	1.000
	Girl	22 (55.0%)	21 (52.5%)	
Father's educational level n (%)	High School	7 (17.5%)	10 (25.0%)	0.586
	University	33 (82.5%)	30 (75.0%)	
Mother's educational level n (%)	High School	10 (25.0%)	16 (40.0%)	0.232
	University	30 (75.0%)	24 (60.0%)	
Age (mean ± SD)		8.87 ± 0.47	8.82 ± 0.48	0.657

Table 2 presents the control of homogeneity between the two populations. The authors observed that both populations were homogeneous in relation to the demographic characteristics. They also observed that there was no statistically significant difference between the two groups for all subscales of Athina Test except for the 'graphs distinction' where children with natural conception have statistically significant higher value compared to children with ICSI (Table 3).

There was no statistically significant difference between the two populations for all subscales of the Achenbach questionnaire in connection with the Syndromes Scale. However there was a statistically significant difference for the subscales 'activities', 'school', and 'Competence Scale Total' where naturally conceived children presented statistically significant lower value compared to children with ICSI (Table 4).

Tables 5 and 6 show the multiple linear regression analysis for Raven's Test, Athina test, and for Achenbach's CBCL questionnaire. Using the above model, the authors attempted to examine the difference between the conception groups (normal *vs* ICSI) in the aforementioned psychometric tools, adjusting the effect of differences that may exist among these groups in demographics characteristics. The above models present no violations of the conditions for its correct implementation as the control for collinearity of variables, the constant variance, and the normal distribution of the residuals.

For the Raven's Test score index, no difference was observed between the two groups ($p = 0.32$) and none of the

Table 3. — *Comparison of Raven's and Athina Test subscales between the two groups.*

	Natural Conception	ICSI	*p*-value
Raven score	115.95±6.15	113.33±8.77	0.126
Linguistic analogies	9.85±1.96	10.05±1.68	0.625
Vocabulary	10.30±2.34	10.55±2.50	0.646
Numerical memory	10.40±2.69	10.75±2.73	0.565
Sentence completion	10.13±1.81	10.13±1.84	1.000
Graphs discernment	13.78±2.02	12.65±2.66	0.036
Phoneme composition	10.30±2.19	9.65±2.15	0.284
Right-left perception n (%) adequate	29 (72.5%)	33 (82.5%)	0.422
Numerical memory (days-m`onths) n (%) adequate	32(80.0%)	31 (77.5%)	1.000
Numerical memory (counting) n (%) adequate	39 (97.5%)	38 (95%)	1.000

All quantitative data are presented as mean±SD.

Table 4. — *Comparison of Achenbach questionnaire's subscales between the two groups.*

	Natural conception	ICSI	*p*-value
Activities	10.19±1.74	11.14±2.04	0.027
Social	7.97±1.85	8.72±2.45	0.129
School	5.37±0.72	5.66±0.38	0.026
Competence scale total	23.54±2.81	25.67±3.48	0.004
Stress-depression	4.04±2.71	3.45±3.15	0.369
Withdrawal-depression	1.38±1.10	1.20±1.71	0.572
Physical complaints	0.87±1.04	0.83±1.13	0.842
Social problems	2.84±2.41	2.75±2.62	0.878
Thinking problems	1.97±2.29	1.48±1.78	0.284
Attention problems	3.12±2.59	2.23±2.44	0.116
Rules transgression	1.66±1.44	1.55±1.47	0.733
Aggressive behavior	4.39±4.74	3.73±3.78	0.487
Other problems	2.86±2.49	2.88±2.56	0.982
Syndromes scale total	23.04±15.98	20.05±15.87	0.403

demographic factors affected the specific variable significantly. Regarding the Athina Test scales, there was no statistically significant difference between the two groups except for the index 'graph distinction' ($p = 0.050$) where there was a marginal difference seemingly affected by the child's gender.

With regards the Achenbach's CBCL questionnaire's Competence Profile Scales, differences were observed between the two groups in the variables 'activities' ($p = 0.028$), 'School Scale' ($p = 0.025$), and 'Competence Scale Total' ($p = 0.003$). No demographic factor affected the first two variables, while the last was affected by the parents' educational level. With regards to the 'Social Scale' in the Competence Profile and all Scales in the Syndromes Profile, there were no differences observed between the two groups.

Table 5. — *Linear and logistic regression model for Raven's Test and Athina Test subscales as dependent variables.*

Dependent variable	$Beta_{adjusted}$ Group Coefficient	SE	*p*-value
Raven score	-1.827	1.823	0.320
Linguistic analogies	0.192	0.402	0.634
Vocabulary	0.494	0.529	0.354
Numerical memory	0.442	0.623	0.480
Sentence completion	0.136	0.394	0.732
Graphs distinction	-1.056	0.529	0.050
Phoneme composition	-0.553	0.498	0.271
	Adjusted OR Group Coefficient	95% CI	*p*-value
Right-left perception	2.070	0.67-6.40	0.205
Numerical memory (days-months)	0.901	0.29-2.38	0.862

All models are adjusted for age, gender, mother's educational level, and father's educational level.

Table 6. — *Linear regression model for Achenbach questionnaire's subscales as dependent variables.*

Dependent variable	$Beta_{adjusted}$ Group Coefficient	SE	*p*-value
Activities	1.005	0.448	0.028
Social	0.777	0.482	0.112
School	0.318	0.139	0.025
Competence scale total	2.250	0.729	0.003
Stress-depression	-0.223	0.710	0.754
Withdrawal-depression	0.006	0.361	0.987
Physical complaints	-0.109	0.266	0.683
Social problems	0.255	0.568	0.655
Thinking problems	-0.496	0.483	0.308
Attention problems	-0.777	0.574	0.180
Rules transgression	0.011	0.334	0.973
Aggressive behavior	-0.264	0.934	0.778
Other problems	0.227	0.572	0.693
Syndromes scale total	-1.329	3.614	0.714

All models are adjusted for age, gender, mother's educational level, and father's educational level.

Discussion

This study aimed to explore the cognitive and socio-emotional development of eight- to ten-year-old ICSI children compared with NC age-matched controls. Overall, the results regarding ICSI children's cognitive and socio-emotional development appear to be reassuring for parents and clinicians.

Regarding the cognitive development, no differences were identified between ICSI and NC children on the IQ score of the Raven's Test. The mean IQ score on the Raven's Test for both groups was approximately the same (114) and neither demographic factor (of those taken into consideration) nor the mode of conception seemed to in-

fluence it. The present results are in line with previous large scale studies concerning the cognitive development of ICSI children.

Regarding the ICSI children's socio-emotional development, this research showed that the two groups presented no differences in the CBCL profile of syndromes, in internalized and externalized syndromes, and their scores range within normal spectrum. The Competence Profile indicated a statistically small but essentially insignificant difference in the 'Activities' scale, 'School' scale and 'Competence Total' scale in favor of the ICSI children. It should be noted that the scores of both groups were within normal spectrum for each of the above scales, but those of ICSI children were slightly higher. These scales were not affected by demographic factors. The most likely explanation for the 'activities' scale may be the parents' desire to provide their children with as many stimuli as possible or encourage them to broaden their interests, even if these activities are performed at home. It is emphasized that the majority of these activities do not depend on the parents' economical status, as they are provided (often for free) by the municipality in which the family resides. In the 'School' scale, the score was based on the subjective assessment and judgment of the parents for their child's performance in the various courses, which may not be true to reality. Thus, the highest score in the 'Competence Scale Total' emerges as a direct consequence, since it is the sum of the two previous scales' scores and the 'Social' scale, which in this case showed no difference between the two groups. A frequently voiced concern regarding "high tech" families (IVF and ICSI) is that, due to the experience of infertility and its treatment, parents may be overprotective of their longed-for children when they eventually arrive. It has also been suggested that these mothers and fathers may set themselves unattainably high standards of parenting and may have unrealistically higher expectations of their children [24].

The results indicated that infertility treatment by ICSI does not appear to affect the emotional-behavioral development of this specific group of children. Furthermore, no significant effects due to gender, educational level of the mother, and age of the mother at birth were noticed.

Regarding the manifestation of learning difficulties, the results of the present research, after the Athina Test administration, presented homogeneity in the various diagnostic scales between the two teams. The only difference was observed in the Scale 'Graph Distinction' where while both groups' scores belong to the same diagnostic category ("marginally high"), yet the average value for ICSI children was 12.65 and for naturally conceived children 13.78. This difference was marginal and cannot be attributed to a difference in visual perception or to a more developed graph-phonemic awareness of NC children. Therefore the present study findings conclude that ICSI children do not present learning difficulties at either a higher frequence or a more pronounced degree compared to NC children, since their developmental quotients range within normal spectrum. Also, there were no indications of ADHD manifestation in this specific population, based on the analysis of the Achenbach's CBCL questionnaire diagnostic profile.

Conclusion

In conclusion, the results of the present study are reassuring regarding ICSI children's cognitive and socio-emotional development, as well as the manifestation of learning difficulties from the age of eight- to ten years. The findings so far suggest that ICSI children do not suffer any significant developmental delay as compared with NC children. Further follow-up research is needed in order to evaluate both the cognitive and psychological well being of ICSI children at puberty and adolescence. Also, the possible role of other personal, family, and contextual variables in the development of children born after ICSI should be explored.

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