Development of children born after ovarian superovulation induced by long-acting gonadotropin-releasing hormone agonist and menotropins, and by in vitro fertilization

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The use of a gonodotropin-releasing hormone (Gn-RH) agonist in an in vitro fertilization (IVF) program raises the question of any influence on the physical, neurologic, and mental development of the children. We compared the development of children born after long-acting Gn-RH agonist treatment with that of children born after spontaneous pregnancies. Children from singleton pregnancies and ≥28 months of age were examined by a pediatric neurologist and a psychologist who did not know to which group the children belonged. The General Cognitive Index test was used. Each group included 30 children. Five children cooperated only partly. Physical and neurologic findings were normal in all children, except that one in the group born after in vitro fertilization had diffuse hypotonia, attention-deficit hyperactivity disorder, and hyperactivity. The General Cognitive Index for the 26 children in the study group and the 29 children in the control group who fully cooperated were 102 ± 13.3 and 106 ± 13.5, respectively ($p = 0.37$). The verbal perception, motor, and memory indexes were not significantly different. We conclude that the long-acting Gn-RH agonist had no clinically identifiable influence on the development of these children. (J PEDIATR 1994;125:734-7)

Although registries of different nations include data for more than 40,000 babies born as the result of in vitro fertilization,[1] only a few studies have summarized the obstetric and perinatal outcome of pregnancies after IVF[2-4] and compared the outcome of IVF infants with that of those born after natural conception.[5-7] Several studies have shown that the overall risk of malformation in IVF infants is not increased.[5-9] Three studies have dealt with late development of children born after IVF. The first two[10, 11] did not examine the children in a systematic or blinded manner and included small numbers; the third,[12] although a matched comparison between the IVF children and those born after spontaneous pregnancies, did not consider the medications used to induce ovarian superovulation.

GCI	General Cognitive Index
Gn-RH	Gonadotropin-releasing hormone
hMG	Human menopausal gonadotropin
IVF	In vitro fertilization

Studies have indirectly shown that gonadotropin-releasing hormone agonist is not associated with an increased risk of congenital malformations.[1, 10] However, the wide use of

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Gn-RH agonist, especially the long-acting Gn-RH agonist drugs,[13] to induce superovulation[14] raises the question of whether the medication has any influence on the late physical, neurologic, and mental development of these infants.

The purpose of our study was to compare the development of children born after superovulation induced by a long-acting Gn-RH agonist in an in vitro fertilization and embryo transfer procedure with that of children born after spontaneous pregnancies.

METHODS

The study included two groups of infants older than 28 months of age, all born in the same medical center after a singleton pregnancy. The study group consisted of children born after superovulation induced by a long-acting Gn-RH agonist, human menopausal gonadotropin, and by IVF and embryo transfer; the control group consisted of children born after spontaneous pregnancy. The mothers of the children in the study group had received a long-acting Gn-RH agonist, triptorelin (Decapeptyl microcapsules, 3.2 mg; Ferring, Malmö, Sweden), either in the early menstrual or mid-luteal phase, as described previously.[13] Every child in the study group was matched to another child born on the same day with a gestational age difference of less than 2 weeks.

The evaluation included socioeconomic, medical, and pregnancy history data obtained from the hospital charts of the mothers. Perinatal data, including mode of delivery, gestational age, birth weight, and Apgar scores, also were analyzed. A general pediatric examination searching for more than 130 major and minor malformations was performed. Height, weight, and head circumference were measured. The neurologic examination included evaluation of cranial nerve functions, muscle tone, muscle strength, and presence of normal deep tendon reflexes and any abnormal reflexes. Cerebellar function was assessed by observing the gait, posture, and coordination of the children.

The psychometric examination used the General Cognitive Index test,[15] which is equivalent to the "Q" test evaluating verbal, perceptual, quantitative, motor, and memory qualities. The GCI is a scaled score that underwent standardization and fits the age of the children in the study group. All children were examined by the same pediatrician, pediatric neurologist, and child psychologist in a "masked" manner. The study was approved by the institutional review board in our medical center. The Student *t* test was used to test for differences in the obstetric variables and in neurologic and psychologic development. The chi-square test was used to compare proportions of the groups, and the socioeconomic details were analyzed by analysis of covariance.

Table I. Socioeconomic characteristics of study and control groups (mean ± SD)

	IVF study group	Control group	*p*
Education of parents (yr)			
Father	13.5 ± 3.8	13.8 ± 2.9	NS
Mother	13.5 ± 2.9	13.2 ± 2.6	NS
Children in family (No.)	2.0 ± 0.7	2.7 ± 1.6	<0.05
Category of income (1 to 5)	3.3 ± 0.6	2.9 ± 0.7	<0.05
Frequency of first-born status of examined child (%)	58.6	41.4	<0.05*

Values (except *p* values) are mean ± SD. *NS*, Not significant.
*The last variable was examined by chi-square test, and all others by *t* test.

RESULTS

Each group included 32 children. Two children in the IVF group refused to cooperate in the psycologic tests; they and their matched control subjects were excluded. However, their physical and neurologic findings were normal. The income of the families were classified into five groups; group 1 was considered to have the lowest income and group 5 the highest. Significant differences were noted between the IVF group and the control group in the number of children in the family, the frequency with which the examined child was the first born in the family, and the family's socioeconomic level (Table I).

Pregnancy-induced diseases were more frequent in the women who underwent IVF. Hypertensive disorders were present in seven and three women in the study and control groups, respectively, and urinary tract infection in three and one. Gestational diabetes class A occurred in three mothers in each group. One case of placenta previa and two of premature contractions were recorded in the study group; the two mothers with premature contractions gave birth in gestational weeks 37 and 38. No significant differences in maternal age, duration of gestation, birth weight, and the 1- and 5-minute Apgar scores of the IVF and control groups were noted (Table II). Measurements of growth were also not significantly different and were all within normal limits.

Physical examination revealed no significant minor or major malformations except that one child in the control group had a hemangioma 2.5 cm in diameter. One child in the IVF group had diffuse hypotonia and attention-deficit hyperactivity disorder. The diagnosis of attention-deficit hyperactivity disorder was established in a clinical interview with the parent(s) and after examination by a pediatric

Table II. Obstetric, neonatal, and growth data of IVF study and control groups (mean ± SD)

	IVF-study group (n = 30)	Control group (n = 30)	p*
Maternal age (yr)	32.8 ± 3.4	31.0 ± 4.9	NS
Gestational age (wk)	38.0 ± 1.8	39.2 ± 1.4	NS
Apgar score			
At 1 min	9.3 ± 1.0	9.5 ± 0.9	NS
At 5 min	9.8 ± 0.4	9.9 ± 0.3	NS
Neonatal weight	3100 ± 480	3339 ± 436	NS
Age (mo)	36.6 ± 8.0	38.6 ± 8.7	NS
Weight (kg)	14.4 ± 1.1	14.6 ± 1.7	NS
Height (cm)	94.5 ± 3.1	95.2 ± 4.3	NS
Head circumference (cm)	49.8 ± 0.9	49.6 ± 0.92	NS
Male/female ratio	17/13	15/15	NS

NS, Not significant.
*All variables were examined by *t* test except for the male/female ratio, which was analyzed by chi-square test.

neurologist (according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*[16]); it was confirmed with the Revised Conners Parent and Teacher Behavior Rating Scales.[17] All other children in both the study and the control groups had normal neurologic findings. No complaints of problems in learning, attention, or emotional functioning of the children were expressed by the parents.

Five children in the IVF group and one in the control group cooperated only partly; thus 81% of the children in the IVF study group and 97% in the control group completed the test. Therefore, to avoid distorting the results, we analyzed the data with and without the five partly cooperating children.

The GCI test results were not significantly different, whether the data from all children or from only the fully cooperating ones were analyzed (Table III). Because some of the socioeconomic variables were significantly different between the study and the control groups, series of analyses of covariance were performed. The analysis revealed no significant differences between the groups after the covariation of these socioeconomic variables was evaluated. As shown in Table III, the chance for a β error in this comparison was low.

DISCUSSION

Fertilization and early embryonic development outside the body were thought to increase the potential risk of birth defects. The suggested mechanisms were chromosomal aberrations, induction of point mutations,[18] and nondisjunction resulting in nullisomy, monosomy, and trisomy, as well as structural abnormalities such as haploidy and diploidy.[19]

Table III. General Cognitive Index of the fully cooperating children in the study and control groups

	IVF study group (n = 26)	Control group (n = 29)	p	β error*
GCI	102 ± 13.3	106 ± 13.5	0.37	0.04
Verbal	52 ± 9.2	55 ± 9.7	0.28	0.02
Perception	54 ± 8.7	55 ± 8.2	0.63	0.13
Quantitative	45 ± 8.3	49 ± 9.6	0.10	0.07
Motor	55 ± 8.0	56 ± 10.1	0.68	0.18
Memory	49 ± 6.7	51 ± 8.9	0.51	0.07

All variables were examined by *t* test. Values (except *p* values and β error) are
*One-tailed test.

However, in a large series recently reported, no specific malformations were significantly increased in children born after the IVF procedure.[9]

Previous studies[10, 12] examined children whose mothers had been treated with either clomiphene citrate or hMG to induce superovulation. Since the introduction of Gn-RH agonist, the combination of Gn-RH agonist and hMG has become the most widely used protocol in IVF.[20] However, this drug, despite its advantages, has introduced some problems. The luteolytic effect of the Gn-RH agonist (e.g., suppression of steroid production in the corpus luteum) had been established in 1979,[21] and its unfavorable effect on corpus luteum function after IVF was shown in 1988.[22] Luteal supplementation in the form of progestational agents or human chorionic gonadotropin[23, 24] was associated with a higher pregnancy rate. This influence of the Gn-RH agonist on the corpus luteum confirms the activity of the medication during the luteal phase and probably in the early embryonal stage. Therefore we carried out our study to examine the late physical, neurologic, and mental development of the children born to mothers who had received Gn-RH agonist.

The careful matching of the groups, the lack of knowledge of the children's grouping by the examiners, and the strict inclusion criteria in both the study and the control groups seem to give sufficient reliability to these results. In contrast to previous studies,[10, 11] the GCI showed no differences between groups. We conclude that up to the age of 36 months, these children, whose mothers were treated with long-acting Gn-RH agonist, had no physical, neurologic, or mental impairment compared with matched control subjects from spontaneous pregnancies.

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