Long-term follow-up of children born after inadvertent administration of a gonadotrophin-releasing hormone agonist in early pregnancy

E.Lahat, A.Raziel, S.Friedler, M.Schieber-Kazir and R.Ron-El

Departments of Obstetrics and Gynecology, and Pediatric Neurology, Assaf Harofeh Medical Center, affiliated to Sackler Faculty of Medicine, Tel Aviv University, Israel

Our objective was to evaluate long-term outcome of children born after inadvertent administration of a gonadotrophin-releasing hormone agonist (GnRHa) in early pregnancy, compared to a control group of children born to matched women undergoing in-vitro fertilization and children born after spontaneous pregnancies. Six children from six pregnancies, exposed to a long-acting gonadotrophin agonist, comprised the study group and 20 children were included in the control groups. Pre-, peri- and post-natal data were collected and the children were followed and examined at a mean age of 7.8 ± 2.0 years. All children underwent physical and neurological examination, and psychological tests. In the study group, one child was born with a major congenital malformation (cleft palate), and four children subsequently demonstrated neurodevelopmental abnormalities, including epileptic disorder (n = 1), attention deficit hyperactivity disorder (n = 3), motor difficulties (n = 3) and speech difficulties (n = 1). In the control groups, one child had attention deficit hyperactivity disorder. This observation of neurodevelopmental abnormalities in four of six children in the study group justifies the need for long-term follow-up of more children previously exposed to gonadotrophin-releasing hormone agonist.

Key words: GnRHa/pregnancy

Introduction

Pituitary down-regulation with gonadotrophin-releasing hormone agonist (GnRHa) was introduced for controlled ovarian stimulation in in-vitro fertilization (IVF) treatment in an attempt to reduce the likelihood of cancellation due to premature luteinization and escaped ovulation (Porter et al., 1984). Since then, it has become almost the standard treatment for ovarian stimulation.

GnRHa can be given as a long protocol in either the early follicular phase or in the mid-late luteal phase. Both timings of GnRHa administration are widely used. Many IVF centres prefer luteal phase GnRHa commencement, since it seems that cyst formation is less frequent in this case (Herman et al., 1990). This mode of treatment may sometimes take place immediately after an inadvertent spontaneous conception has been established, since most of the couples referred to assisted reproductive technologies (ART) are not absolutely infertile. The incidence of such inadvertent pregnancies is 0.8% (Cahill, 1998).

The risk to the fetus as a result of the presence of GnRHa, and the likelihood of this event occurring, are discussed in several studies. However, all were based only on early postnatal examination of the infants (Sopelak and Hodgmen, 1987; Martinez et al., 1988; Dicker et al., 1989; Forman et al., 1990; Golan et al., 1990; Lejeune et al., 1990; Isherwood et al., 1990; Ghazi et al., 1991; Smitz et al., 1991; Herman et al., 1992; Jackson et al., 1992; Lockwood et al., 1992; Gonen et al., 1993; Shulman et al., 1993; Balasch et al., 1993; Har-Toov et al., 1993; Wilshire et al., 1993; Young et al., 1993; Cahill et al., 1994; Abu-Heijia et al., 1995; Chang and Soong, 1995; Elefant et al., 1995).

The purpose of our study was to evaluate the long-term physical and neurodevelopmental outcome of children born following inadvertent administration of GnRHa during early pregnancy.

Materials and methods

All pregnancies established at our IVF unit from January, 1987 to December, 1995 comprised the data base for this retrospective study. During this time, all patients with early pregnancies who were inadvertently exposed to a long-acting GnRHa planned for the mid-luteal period were studied. Couples were not advised to take contraceptive precautions but were informed about the possible chance of inadvertent pregnancy. Therefore all the patients were instructed to have their blood tests for oestradiol and progesterone during the preceding menstruation period, or 10 days after GnRHa treatment if menses did not occur. In all cases in which serum progesterone was >1.0 ng/ml, serum β human chorionic gonadotrophin (βHCG) was also requested. When a positive test (>20 IU βHCG) was recorded, treatment with GnRHa was immediately discontinued and the woman was followed up for progesterone concentrations and pregnancy development. In cases where progesterone levels were low (<10 ng/ml), especially when Depo GnRHa was used (Decaptyl 3.2 mg microcapsules, Ferring, Malmo, Sweden), progesterone in oil was given up to the eighth gestational week.

There were two control groups: one group of children born to matched women undergoing IVF using a GnRHa and another group of children born on the same delivery day after spontaneous pregnancies. Data regarding the delivery and postnatal course of all groups were collected from their hospital charts.

Medical history, body measurements, physical and neurological examinations of all children were performed by the same examiner (E.L., a paediatric neurologist).
Long-term follow-up after exposure to GnRH agonist

Table I. Clinical data of women exposed to inadvertent administration of GnRHa soon after conception

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Infertility aetiology</th>
<th>Duration of GnRHa exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>Tubal factor</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>DES/PCOD</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>Unexplained</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Male</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>Unexplained</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>Male</td>
<td>5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>35.8 ± 5</td>
<td></td>
<td>5.5 ± 1.4</td>
</tr>
</tbody>
</table>

DES = diethylstilboestrol syndrome; PCOD = polycystic ovarian disease.

Table II. Natal and post-natal characteristics of the newborn infants born following exposure to GnRHa

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex (M/F)</th>
<th>Mode of delivery</th>
<th>Gestational age (weeks)</th>
<th>Apgar score (1/5 min)</th>
<th>Birthweight (g)</th>
<th>Birth head circumference (cm)</th>
<th>Postnatal complications</th>
<th>Congenital malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Vaginal</td>
<td>35</td>
<td>10/10</td>
<td>2700</td>
<td>32.5</td>
<td>-</td>
<td>Sacral dimple</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Vaginal</td>
<td>34</td>
<td>9/10</td>
<td>2020</td>
<td>30.4</td>
<td>Transient tachypnoea pneumothorax</td>
<td>Cleft palate</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Vaginal</td>
<td>39</td>
<td>10/10</td>
<td>2500</td>
<td>35.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Vaginal</td>
<td>39</td>
<td>9/10</td>
<td>2130*</td>
<td>33.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Caesarian section</td>
<td>37</td>
<td>9/10</td>
<td>3000</td>
<td>34.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Vaginal</td>
<td>38</td>
<td>9/10</td>
<td>3780</td>
<td>35.0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Small for gestational age.

A widely accepted definition of major and minor malformations was used: malformations that generally caused functional impairment or required surgical correction, were defined as major, and the remainder as minor (Holmes, 1976). Psychological evaluation of the children was performed by a child psychologist, using the WISC-R (Wechsler Intelligence Scale for Children – Revised) for all the children, except for the youngest child (3 years and 11 months) who was tested with the WISPI test (Wechsler Pre-School and Primary Scale for Intelligence). The diagnosis of attention deficit hyperactivity disorder (ADHD) was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised (DSM IVR; American Psychiatric Association, 1994). The psychological evaluations of all the children were performed by the same person (M.S.-K.).

Results

Six children from six pregnancies/deliveries, comprised the study group. The parents were asked to participate in the study and all agreed except for one family who refused to perform the psychological section of the evaluation. The mean ± SD age of the women was 35.8 ± 5 years (range 29–41 years) and median age was 33 years. The clinical data of the women exposed to the inadvertent administration of GnRHa soon after their conception is summarized in Table I. The mean infertility duration was 5.5 ± 1.4 years. GnRHa exposure ranged from 4 to 14 days with a mean exposure time of 9.3 ± 3.4 days.

Five pregnancies culminated in vaginal delivery and one by Caesarean section. Table II summarizes the postnatal characteristics of the newborn infants. There were three males and three females; all except one (case no. 2) were term infants. Birth weights were appropriate for gestational age in all infants except for one (case no. 4) whose weight was small for his gestational age. Apgar scores were normal in all infants. The postnatal course was unremarkable in all except for the premature infant (case no. 2) who developed transient tachypnoea a few hours following delivery, requiring oxygen therapy for 24 h. Small right pneumothorax seen on chest X-ray resolved spontaneously.

Table III summarizes the long-term outcome of the children. At re-examination, their ages ranged from 3 years 11 months to 9 years 10 months, with mean and median ages of 7.8 ± 2.0 and 8.4 years respectively. One child (case no. 2), born with a soft cleft palate, was operated successfully at the age of 14 months. Another child (case no. 4), had gastrooesophageal reflux, diagnosed by radioactive milk scan and pH metric study. This child, despite conservative treatment, suffered from frequent vomiting, which twice ended in aspiration pneumonia. Surgical intervention (Nissen fundoplication) was suggested, but the parents refused.

Table III also summarizes the long term neurodevelopmental outcome. Three children (nos 4, 5 and 6) were evaluated between ages of 3–4 years, by occupational therapists because of significant difficulties in motor skill performance (gross, fine and co-ordination). All the three children required treatment for periods ranging between 6 and 18 months.

Three children (nos 1, 5 and 6) were diagnosed as having ADHD, of whom two also had motor difficulties and one had speech difficulties. One of these three children with ADHD presented at the age of 6 months with myoclonic seizures,
successfully controlled with valproic acid. There was no evidence of any prenatal complications or family history that might be associated with these abnormalities. Diagnostic workup, including neuroimaging studies and metabolic evaluation, did not reveal any underlying specific neurological illness. Physical and neurological examinations of all children were unremarkable, except for generalized, moderate hypotonia, observed in the two children with motor difficulties (nos 5 and 6). One of these children (no. 6) also had speech difficulties and was treated by a speech therapist for a period of 12 months. The WISC-R test was within normal range with mean score of 101 ± 15, in all five children. The WIPSI test was also normal in the only child in which it was performed, with a score of 93.

The control groups included 20 children (10 in each group), all of whom were term infants. The IVF group included six males and four females with mean age of 7.5 ± 1.5 years. The other group included five males and five females with mean age of 8.0 ± 1.0 years. Physical examination revealed no significant minor or major malformations in the two groups, except that one child in the spontaneous pregnancy group had a haemangioma 2.5 cm in diameter in his right thigh. One child in the IVF group had ADHD features. All other children in the two control groups had no neurological abnormalities on examination. No complaints of learning, attention or behaviour problems were expressed by the parents. The general cognitive status was within normal range in all children (mean WISC-R score of 103 ± 10 in the IVF group and 102 ± 7 in the spontaneous delivery group).

**Discussion**

Over 340 pregnancies have been reported in the literature in association with the administration of a GnRHa. The incidence of miscarriage and other pregnancy difficulties does not appear to be increased in association with GnRHa treatment (Cahill, 1998). The clinical pregnancy rate per cycle from those data (0.8%) is of the same order as that expected from natural conception per cycle in couples with tubal damage, sperm

<table>
<thead>
<tr>
<th>Case</th>
<th>M/9 y 10 m</th>
<th>F/8 y 6 m</th>
<th>M/7 y 7 m</th>
<th>M/8 y</th>
<th>M/3 y 11 m</th>
<th>F/8 y 4 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>137 (50)</td>
<td>143 (95)</td>
<td>131 (90)</td>
<td>127 (50)</td>
<td>104 (50)</td>
<td>133 (75)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>32 (50)</td>
<td>44 (97)</td>
<td>28 (75)</td>
<td>30 (60)</td>
<td>18 (50)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>52 (40)</td>
<td>54 (90)</td>
<td>53 (75)</td>
<td>52 (50)</td>
<td>50 (40)</td>
<td>51 (50)</td>
</tr>
</tbody>
</table>

Medical abnormalities:
- Gastro-oesophageal reflux
- Bronchial asthma
- Epileptic disorder
- Motor difficulties
- Speech difficulties
- ADHD

y = years; m = months; ADHD = attention deficit hyperactivity disorder.

Table III. Long-term outcome of male (M) and female (F) children born following exposure to GnRHa

<table>
<thead>
<tr>
<th>Case</th>
<th>M/9 y 10 m</th>
<th>F/8 y 6 m</th>
<th>F/7 y 7 m</th>
<th>M/8 y</th>
<th>M/3 y 11 m</th>
<th>F/8 y 4 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body measurements: (rank percentile)³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>137 (50)</td>
<td>143 (95)</td>
<td>131 (90)</td>
<td>127 (50)</td>
<td>104 (50)</td>
<td>133 (75)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>32 (50)</td>
<td>44 (97)</td>
<td>28 (75)</td>
<td>30 (60)</td>
<td>18 (50)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>52 (40)</td>
<td>54 (90)</td>
<td>53 (75)</td>
<td>52 (50)</td>
<td>50 (40)</td>
<td>51 (50)</td>
</tr>
</tbody>
</table>

³Rank percentile is the rank position of an individual in a serial assay of data, stated as a percentage of the group he/she equals or exceeds.

Human studies reported on several abnormalities in the neonates including one case of talipes equino varus (Jackson et al., 1992), two cases of trisomy (13 and 18) (Wilshire et al., 1993; Young et al., 1993), one case of sacral agensis and bladder extrophy (Abu-Heija et al., 1995) and a neonate with soft cleft palate previously reported by us (Ron-El et al., 1990). The prevalence of these abnormalities is not different from that expected in the general population (Shepard, 1986). The presence of one major congenital anomaly in our series does not allow us to draw any statistical conclusion because of the small series.

The long-term follow-up in previous studies is scanty. There is one case report with a follow-up of 12 months, documenting normal development (Herman et al., 1992), and an additional recent case report (Gartner et al., 1997) describing a full-term healthy neonate sharing normal development. Another study includes 25 cases (Cahill et al., 1994), in which several parents reported on their children, all older than 3 years. All reports were of normal development, but this was not validated by either physical or neurological examination, or by appropriate psychological testing.

To our knowledge, the current study is the first one demonstrating long-term results of physical and neurological examinations, as well as psychological evaluation of children born after inadvertent exposure to GnRHa in their early pregnancy.

The long-term medical follow-up revealed one child with gastro-oesophageal reflux and bronchial asthma, and another child with epileptic disorder. These diseases are quite common during childhood: significant gastro-oesophageal reflux is diagnosed in 0.1–0.3% of infants (Herbst, 1996), bronchial asthma in 2.8–9.5% of children (Canny and Levison, 1995), and epileptic disorder in 0.9% of children (Annegers, 1993). Therefore, their presence in such a small series does not enable us to draw any statistically significant conclusions regarding a possible relationship with exposure of GnRHa during early pregnancy.

The long-term neurodevelopmental results are more intri-
Long-term follow-up after exposure to GnRH agonist


REFERENCES


The formal psychological examinations were within normal range in all children, both in the study and control groups; however, various neurodevelopmental abnormalities were observed in four of the six children in the study group, including ADHD (n = 1), motor deficits (n = 3) and speech deficits (n = 1), compared with one child with ADHD in the control groups. These abnormalities are frequently diagnosed in children whose ages are similar to those included in the study group. Prevalence rates for ADHD in previous studies range from 0.5 to 14% (Sztatmari et al., 1989). This great variation reflects differences in symptoms, methods, sources of information and diagnostic criteria used. More recent studies using sample survey methodology and the diagnostic criteria of the American Psychiatric Association (1994) reported prevalence rates of 6.7% (Anderson et al., 1987) and 9.5% (Bird et al., 1990).

Furthermore, a previous prospective follow-up study performed by us (Ron-El et al., 1994) comparing the development of 30 children born after long-acting GnRHa treatment with that of 30 children born after spontaneous pregnancies revealed only one child with hypotonia and ADHD. No significant statistical difference in the general cognitive index between the study and control groups was recorded. Similar results were obtained from another study (Morin et al., 1989), which found no association between conceptions by IVF and increased risk for congenital malformations and developmental delay. The difference between these results and the ones in the present study could be due to the different ages of the children evaluated. In our series, the children were evaluated at an older age compared with the age of the previous ones, thus enabling us to detect neurodevelopmental abnormalities that could have been missed at an earlier assessment. In any mode, the finding of neurodevelopmental abnormalities in four of six children should definitely draw our attention to close follow-up of more children previously inadvertently exposed to GnRHa.

We are not familiar with any underlying mechanism that might explain the possible relationship between the exposure to GnRHa during early pregnancy and late neurodevelopmental abnormalities. The present study describes existing cases of pregnancies inadvertently exposed in the very early stages to GnRHa. Additional long-term follow-up studies of such children are urgently needed before drawing any conclusion.
E.Lahat et al.


Received on November 13, 1998; accepted on July 5, 1998