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A long term evaluation of infants who received a beta-mimetic drug while in utero

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Statistical Analysis: A. Heyting

1 Introduction

During the past few years, many pregnant women have received prolonged administration of beta-mimetic drugs.

This therapy does not seem to cause changes in the glycemic balance or in hepatic function of the newborn [3].

In the fetus some side effects due to betamimetic drugs have been described [4, 5, 6, 7].

RENAUD [6, 7] noticed that sometimes the fetal heart beats faster. However NOCHIMSON [5] could not observe such effects. Elevated blood levels of glucose and insulin have been described [4, 7] and it has been suggested that increased glycogenolysis is involved [7].

According to RENAUD [7] this is accompanied by increased lipolysis and a falling of pH and base excess.

Before asserting the safety of such treatment, it is important to confirm that **there are no long-term effects upon live-born infants who may have been exposed to beta-mimetics in utero.** This was our aim in studying those infants whose mothers had been treated with ritodrine hydrochloride (Prepar®): a beta-mimetic commonly used by our obstetric colleagues.

2 Materials and methods

Two groups were studied: one of infants born to mothers treated with ritodrine and the other of matched controls from untreated mothers. The mean duration of maternal treatment with ritodrine hydrochloride was 24 days, the range being 3 to 93 days, with a daily dose of 60–80 mg.

Each infant in the ritodrine group was matched with a control according to the following criteria:

1. Birthplace: (Clinique Gynécologique et Obstétricale I de Strasbourg)
2. Duration of gestation at birth: within one week if born before 33 weeks, and two weeks if born after that.
3. Sex.
4. Birthweight: within 200 grams if born before 33 weeks and 400 grams if born after.

To comply with the strict matching criteria, we finally had 42 pairs: 21 of each sex.

Curriculum vitae

HUBERT FREYSZ *was born in Strasbourg in 1944, on the 17th of February. He Studied Medicine in Strasbourg. "Interne" in 1967 and "Chef de Clinique-Assistant" in 1973, he worked in the department of néonatology of the "Clinique Pédiatrique" of Strasbourg. Main research interests: Beta mimetics, Pediatric cardiology.*

Tab. I. Data on mothers treated with ritodrine hydrochloride whose infants were included in our study (42 cases).

Previous obstetric history	History of the pregnancy	Other diseases	Type of delivery
Threatened premature delivery: 14 cases	Threatened premature delivery: all the 42 cases	Urinary infection: 8 cases	Spontaneous vaginal: 33 cases
Abortion: 11 cases	Toxemia: 6 cases	Anemia: 4 cases	Caesarian section: 5 cases
Sterility: 2 cases	Placenta praevia: 2 cases	Pulmonary tuberculosis: 1 case	Vaccuum extraction: 2 cases
Toxemia: 1 case	Cholestatic jaundice: 1 case		Breech delivery: 2 cases

The clinical evaluation was always performed by the same physician. It consisted of:

1. A detailed questionnaire covering pregnancy, delivery; any problem during the neonatal period; the infant's medical history and the date when the major milestones in psychomotor development appeared.
2. A complete medical examination.
3. Urine analysis: for proteinuria, glycosuria and microscopy of any sediments.
4. An electrocardiogram.
5. The Denver test [1, 2].

Statistical analysis comparing, pair by pair, the children of treated and untreated mothers was performed by applying the appropriate statistical tests on the basis of the Tab. II.

3 Results

The two groups of infants were comparable with the exception of duration of gestation at delivery and birth weight (Tab. III).

The possible reason for this is discussed below. The mean age of the two groups at the time of examination was 24.8 months (Tab. IV). The distribution of the pairs was:

1. 12–17 months: 16%
2. 18–23 months: 34%
3. 24–29 months: 28%
4. 30–36 months: 22%

Increase in height and weight was not affected by ritodrine, as is shown in Tab. IV.

Tab. II. Pair by pair statistical analysis.

a = the number of pairs for which the child of the treated mother and the control are both normal as far as the examination in question is concerned.
b = the number of pairs for which the child of the treated mother is considered to be abnormal and the control child is judged to be normal.
c = the number of pairs for which the child of the treated mother is considered to be normal and control child is judged to be abnormal.
d = the number of pairs for which both children are considered to be abnormal.

		Matched	Controls	
		normal	abnormal	total
Infants born to	normal	a	c	a + c
Treated mothers	abnormal	b	d	b + d
	total	a + b	c + d	a + b + c + d

Tab. III. Duration of gestation and weight, at birth, for infants from treated mothers and matched controls.

	Infants of treated mothers	Matched controls	P-value (2-sided)
Duration of gestation (Weeks)	37.9 ± 1.9	38.3 ± 2.1	0.047 Rank's test
Birth weight (Grams)	2847 ± 559	2965 ± 568	0.009 Student's test

Tab. IV. The ages, heights, head circumferences and weights of the two groups of infants at the time of examination.

	Infants of treated mothers	Matched controls	P-value (one-sided) Student's test
Age (Months)	24.8 ± 5.2	24.8 ± 5.1	0.83
Height (Cms)	86 ± 5	86 ± 6	0.79
Head circumference (Cms)	48 ± 2	48 ± 2	0.53
Weight (Kgs)	12.4 ± 1.8	12.7 ± 1.8	0.67

There was also no difference in the distribution of physical abnormalities between the two groups (Tab. V).

The incidence of infections was almost identical for the two groups. There were no marked differences in the incidence of diseases of the respiratory, digestive, cardiovascular, urino-genital and skeletal systems as shown in Tab. VI.

Similarly, there was no difference in the incidence of diseases of the central nervous system, or psychiatric disorders between the two groups.

Examination of the children's environment and upbringing, both of which may have serious repercussions on the psychomotor development of a child, revealed no significant differences between the groups.

When the actual psychomotor development of the groups was compared, there were no differences in the ages at which the main milestones were attained (Tab. VII).

Analysis of the Denver tests confirmed this: there were no pathological results although three were doubtful in each group. There was no significant difference (P = 0.69, one-sided Sign test).

No child had proteinuria or glycosuria, and the urinary sediment was normal in every case.

The electrocardiograms (E.C.G.) showed no change in 36 of the infants from treated mothers, and 34 of the matched controls (P = 0.81, one-sided Sign test).

Among the E.C.G. changes noted in the group of infants from treated mothers were:

1. One case of shortening of the P-R interval.
2. 2 cases of inverted T waves in lead V4.
3. One case of left ventricular hypertrophy.

This last patient was re-examined more than a year after the first examination. At this time there were no functional signs, but chest X-ray was reported as showing moderate left ventricular hypertrophy.

Tab. V. Distribution of abnormalities for the two groups of infants.

Abnormalities system	Infants of treated mothers	Matched controls	P-value (one-sided) sign Test
Skeletal system:			
skull	3	0	0.25
palate	0	0	–
teeth	2	3	1.00
cervico-thoracic spinal column	0	1	1.00
thoraco-lumbar spinal column	0	1	1.00
arms	0	0	–
legs	3	2	1.00
thoracic cage	5	3	0.69
eyes	0	4	0.13
ears	3	2	1.00
abdomen	2	1	1.00
genital organs	8	7	1.00
others	18	15	0.66

Blood pressure was 120/80 mmHg when taken on all four limbs. This child will be followed up, since the interpretation is difficult. The patient has also had a cystic lymphangioma excised from the neck.

4 Discussion

The difference in duration of gestation at birth, and birth weight, are to be expected. The infants from ritodrine-treated mothers represent a threatened group, otherwise the mothers would not have been given therapy, whereas the controls are not. It is interesting, in this context, to note that this difference in weight had disappeared by the time of examination.

If beta-mimetics induced an increase in pre-natal mortality this would introduce a grave error in our study which only concerns live-born children. Our obstetric colleagues state that, according to their experience, this is certainly not so [6].

There was no statistically significant difference in the incidence of pathologies, the psychomotor development, the clinical examination and other investigations, between the two groups of infants.

If any discrepancy had been found it could have been due either to the direct action of ritrodrine hydrochloride or the factors which initiate premature labour. To separate and weigh these possible aetiologies, would have been extremely difficult: fortunately it was not necessary.

4.1 Conclusion

The administration of ritodrine hydrochloride to pregnant women is not associated with any harmful effects to the live-born child. We would like to see this work confirmed in other centres.

Tab. VI. The incidence of infection and diseases in the two groups of infants.

Pathology	Infants of treated mothers	Matched controls	P-value (one-sided) sign test
Infections	33	34	1.00
Respiratory system	1	2	1.00
Cardiovascular system	0	0	–
Gastro intestinal system	13	15	0.82
Urino-Genital system	0	0	–
Skeletal system	0	2	0.50
Miscellaneous	1	0	1.00

Tab. VII. Psychomotor development in the two groups of infants

Milestones in psychomotor development	Mean age that milestones were attained (months)		P-value (one-sided) Rank's test
	Infants of treated mothers	Matched controls	
Able to stand unaided for one minute	8.1 ± 1.4	7.8 ± 1.6	0.16
Able to walk ten steps unaided	14.3 ± 3.5	13.9 ± 3.1	0.24
Able to use 3 or 4 isolated words	18.3 ± 4.4	16.8 ± 3.8	0.10
Age at which a phrase of 3 or 4 words was used	26.2 ± 4.2	25.0 ± 4.8	0.16

Summary

The administration of beta-mimetic drugs to pregnant women poses the problem of possible long-term repercussions in the children born to these mothers. 42 children from women who had been treated with 60–80 mg a day of ritodrine hydrochloride (Pre-par®), during a period varying from 3 to 93 days, were closely matched with infants from untreated mothers.
Each child, (aged from one to 3 years), was fully investigated on the basis of: a detailed questionnaire to the mother; careful clinical examination; assessment of psychomotor development; the Denver test; electrocardiography and urine analysis.
There was no statistically significant difference between the two groups for any of the variables of development that were studied.
One child had left ventricular hypertrophy, which was probably incidental.
It is concluded that administration of ritodrine hydrochloride to pregnant women induces no harmful long-term effects in their offspring.

Keywords: Beta mimetic drugs, long term repercussions in children.

Zusammenfassung

Langzeitüberwachung von Kindern, die eine Beta-Mimetika-Therapie in utero erhalten haben
Die Gabe von Beta-mimetischen Substanzen an schwangere Frauen wirft das Problem von möglichen Spätfolgen bei den Kindern dieser Mütter auf. 42 Kinder von Frauen, die mit 60–80 mg pro Tag Ritodrine Hydrochlorid (Pre-par) über einen Zeitraum, der von 3–93 Tagen variierte, behandelt worden waren, wurden sorgfältig, paarweise verglichen mit Kindern von unbehandelten Müttern.
Jedes der Kinder, deren Alter von 1–3 Jahren rangierte, wurde vollständig untersucht auf der Basis von: einem eingehenden Fragebogen für die Mutter, einer sorgfältigen klinischen Untersuchung, einer Bestimmung der psychomotorischen Entwicklung, Durchführung eines Denver-Testes sowie EKG und Urinuntersuchungen.
Es fanden sich keine statistisch signifikanten Differenzen zwischen den beiden Gruppen bei irgend einer der Entwicklungsvariablen, die untersucht worden waren.
Eines der Kinder hatte eine linksventrikuläre Hypertrophie, die möglicherweise zufälliger Natur war.
Aus der Untersuchung wird der Schluß gezogen, daß die Anwendung von Ritodrine Hydrochlorid bei schwangeren Frauen keine ernsten Langzeitwirkungen bei der Nachkommenschaft hervorruft.

Schlüsselwörter: Beta-mimetische Substanzen, Spätfolgen bei den Kindern.

Résumé

Evolution à long terme des enfants soumis in utéro à un traitement bétamimétique
La prescription de bétamimétiques à des femmes gestantes soulève le problème d'une éventuelle répercussion tardive sur l'enfant soumis in utéro à cette thérapeutique.
42 enfants de mères traitées par le Pré Par (60 à 80 mg/j) pendant une période de 3 à 93 jours, sont comparés à des témoins sélectionnés sur une gamme de critères de manière à constituer 42 paires homogènes.
Nos investigations pratiquées, selon les paires entre 1 et 3 ans, comprennent un interrogatoire soigneux, un examen clinique détaillé, une appréciation du développement psychomoteur, la pratique du test de Denver, d'un électrocardiogramme et d'un examen urinaire.
L'analyse statistique n'a pas permis de mettre en évidence de différence significative entre les 2 séries concernant les différents paramètres étudiés.
On peut conclure que, mise à part la découverte chez un enfant d'une hypertrophie ventriculaire gauche électrique et radiologique peut être fortuite, le traitement bétamimétique ne nous paraît pas entraîner d'inconvénients potentiels pour l'enfant à naître.

Mots clés: Betamimétiques, évolution à long terme, héritage médicamenteux.

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