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Occipitofrontal circumference in newborns of betamethasone treated mothers

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1 Introduction

The observation by LIGGINS and HOWIE [12] that antenatal administration of corticoids reduces the risk of respiratory distress syndrome (RDS) in newborns had been confirmed by several investigators, resulting in an increased use of this prophylactic treatment.

Treatment with corticoids accelerate the synthesis of the surface-active dipalmitoyl lecithin in the lungs by stimulating the cholin phosphotransferase activity [7]. In animal studies, however, corticoid administered antenatally has been found to cause several side effects by partly unclarified mechanisms demonstrated by a reduced weight of thymus, suprarenal glands, liver, pancreas, lungs, heart and placenta [2, 9, 10].

In humans no permanent side effects after antenatal corticoid treatment had been demonstrated. Similarly it is uncertain whether acute side effects occurs. It is still under discussion whether the risk of infection in mothers and infants is increased after treatment with corticoids in pregnancies complicated by prolonged rupture of the membranes [6, 11]. Already LIGGINS and HOWIE (1972) [12] suggested that there may be an increased risk of fetal death in pregnancies complicated by preeclampsia and treated with corticoid, but this likewise wait for a clarification. Maternal blood pressure in hypertensive women is not affected by corticoid therapy [15]. However, development of pulmonary edema in women after treatment with betamimetics and corticoids is described in a few cases [13, 14].

Administration of corticoids in high doses to newborn mice and rats reduces the DNA-incorporation in the brain [4, 8]. Betamethasone given in high doses every other day for a total of three doses to pregnant rhesus monkeys likewise causes a reduction of both size and DNA-concentration of the brains in the offspring [5]. Betamethasone given to rhesus monkeys for 13 days prior to delivery in doses equivalent to those given to humans results in reduced head circumference of their offspring compared to saline-treated control animals. How-

Curriculum vitae

HENRIK VERDER, *born in Copenhagen in 1942. Graduated in Medicine by the University of Copenhagen 1968. Specialist in pediatric 1978. Senior registrar, Department of Pediatrics, University of Copenhagen, Glostrup Hospital 1977–1981. Senior registrar, Department of Pediatrics, Rigshospitalet, Copenhagen University, 1981–1982. Senior registrar, Department of Neonatology, Rigshospitalet, from June 1982. Doctoral thesis 1980 (perinatology). Secretary in Danish Pediatric Society 1979–1982. Lecturer in pediatric at the University of Copenhagen from 1978.*

ever, no reduction of the head circumference was seen after treatment with betamethasone in same doses for only 3 days [10].

Therefore, it was found important to realize if reduction of brain size was found after corticoid treatment in humans. This paper reports on occipitofrontal circumference in newborns of betamethasone-treated women as compared with the circumference at time of birth according to reference curves.

2 Material and methods

The material is comprised of two groups treated with different corticoids. The first group comprises 46 newborns whose mothers during the period January 1977–March 1978 were treated antenatally with Celeston® (3 mg betamethasone-acetate + 3 mg betamethasone-disodiumphosphate per ml)*. A dose of two ml was given daily intramuscularly for three consecutive days. The gestational age at birth was 34–41 weeks. The second group comprises 52 infants of mothers treated with Celestona® (4 mg betamethasone-disodiumphosphate per ml)*. Two ml were given intramuscularly daily for three consecutive days. The gestational age at birth was 35–40 weeks. This part of the study took place in the period March 1978–March 1979.

The indication for corticoid treatment was imminent preterm delivery. Twins, cases of uncertain gestational age and cases of intrauterine death were excluded before the calculations. There were no cases of diabetes mellitus in the two groups treated with corticoids.

Gestational age was estimated from the first day of the last menstrual period.

The occipitofrontal circumference was rounded off to half or whole centimers. Same type of fiberglas tape was used in all the measurements. It is a common experience that varying length of the occipitofrontal circumference are obtained due to different measuring technique. Three sets of measurements done blindly in five different infants gave a maximal variation of 0.3 cm for each infant.

* Celeston® and Celestona® (Schering Corp.).

The control group consisted of 1012 infants born at Herlev Hospital in 1978. Excluded were non-caucasian infants, twins, stillborns, cases of uncertain gestational age and infants of mothers treated with corticoid. For each gestational week a curve was traced, for boys as well as for girls, using the occipitofrontal circumference in centimeters as abscissa and the number of children as ordinate. Curves were traced both in cases including placental insufficiency and without.

Placental insufficiency was defined as low or decreasing estriol and/or human placental lactogen. These parameters were measured routinely in all patients from the 30th week. Thus, the cases with placental insufficiency include severe cases (small for gestational age) and light cases (appropriate for gestational age).

3 Results

Tab. I shows the number of normal infants in different gestational age, as well as average occipitofrontal circumference.

Tab. I. Occipitofrontal circumference in non-treated newborns at different gestational ages.

Gestational age (weeks)	Occipitofrontal circumference			
	♂		♀	
	Mean value (cm)	(n)	Mean value (cm)	(n)
34	31.3	(4)	31.5	(2)
35	31.2	(5)	31.6	(9)
36	33.2	(17)	32.8	(11)
37	33.2	(22)	32.3	(32)
38	33.5	(71)	33.3	(55)
39	34.1	(103)	33.5	(76)
40	34.6	(187)	33.8	(188)
41	34.8	(72)	33.9	(78)
42	35.0	(40)	34.4	(40)

Fig. 1 shows the reference curve for the occipitofrontal circumference at the time of delivery in different gestational ages for boys and girls. The 90, 50 and 10 percentiles are indicated. The curve for girls is found to be approximately one half centimeter below that of the boys. The weekly increase is above one half centimeter. The average

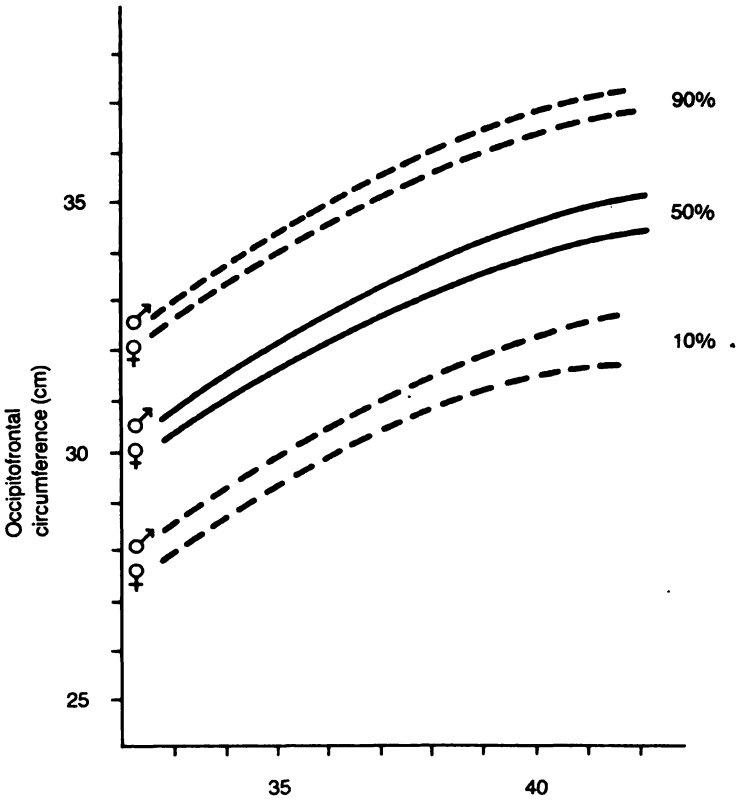

Fig. 1. Percentiles of occipitofrontal circumference in non-treated newborns.

Tab. II. Occipitofrontal circumference at time of birth in infants treated with Celeston® compared with the circumference in non-treated infants. Cases with placental insufficiency excluded. Celeston® administered more than 7 days before birth.

Gestational age (weeks)	Sex	Occipitofrontal circumference (cm)	
		Treated	Non-treated (mean values, Tab. I)
35	♀	30.5	31.6
36	♀	31.0	32.8
36	♀	31.0	32.8
37	♂	30.0	33.2
37	♀	33.0	32.3
37	♀	34.0	32.3
39	♂	34.0	34.1
39	♀	33.0	33.5
39	♀	34.0	33.5

occipitofrontal circumference for infants treated with Celeston® and Celestona® are shown in Fig. 2 A–B. The average occipitofrontal circumference were found to be normal except in the Celeston®-treated boys (Fig. 2 A). Focusing only

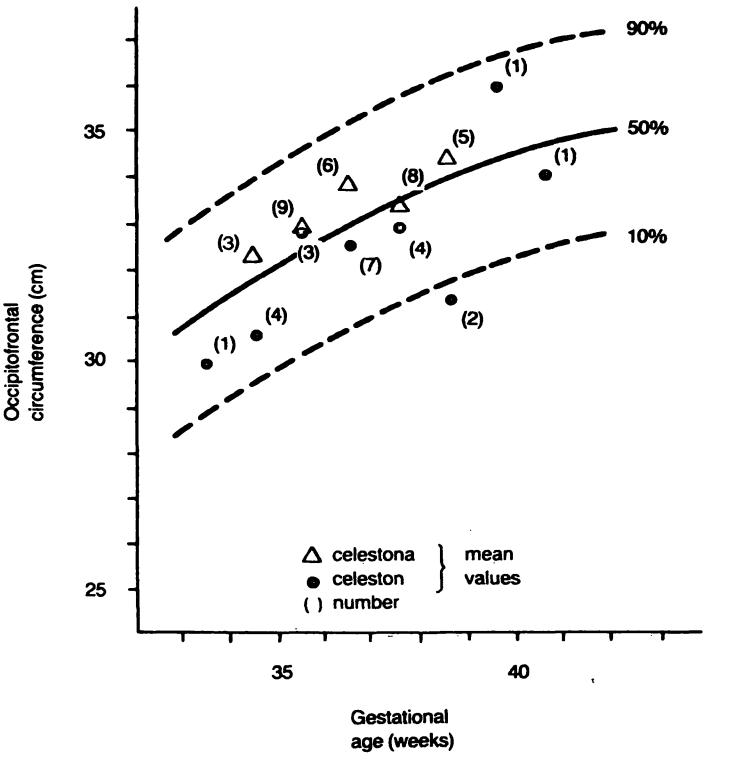

Fig. 2 A. Occipitofrontal circumference at birth in all boys of mothers treated with celeston and celestona compared to normal occipitofrontal circumference outlined as percentiles.

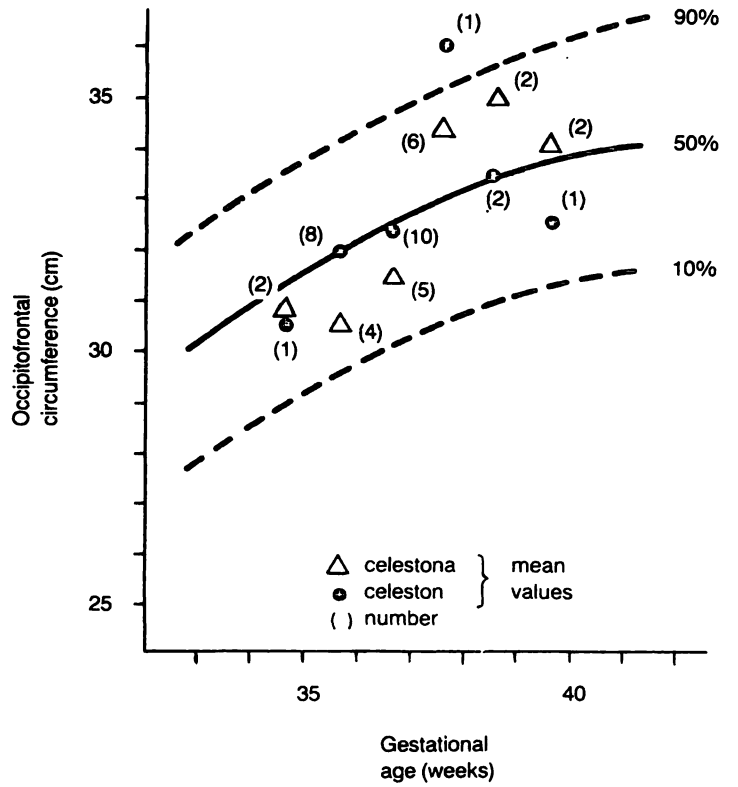

Fig. 2 B. Occipitofrontal circumference at birth in all girls of mothers treated with celeston and celestona compared to normal occipitofrontal circumference outlined as percentiles.

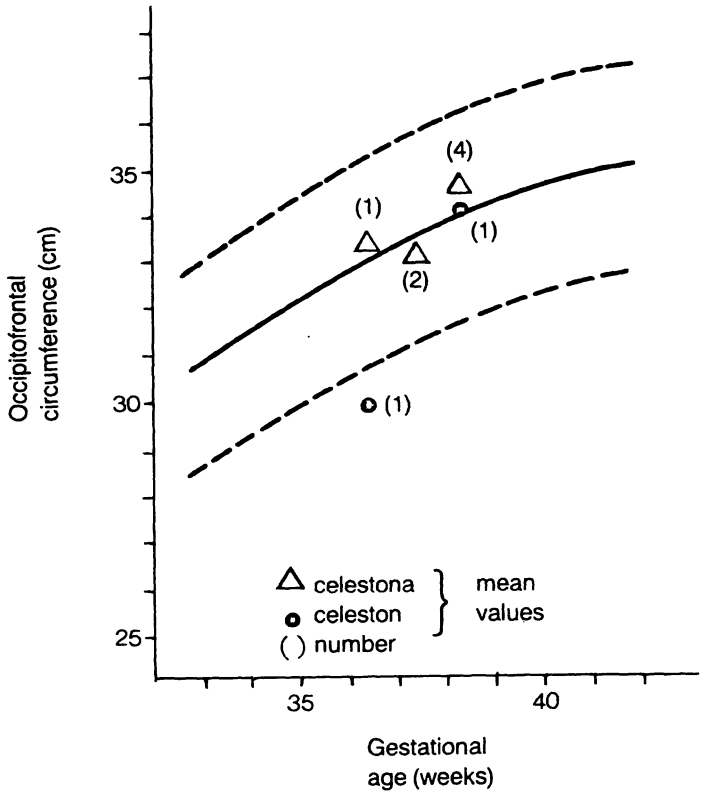

Fig. 3 A. Occipitofrontal circumference in boys of mothers treated with celeston and celestona. Cases with placental insufficiency are excluded. Corticoid administratered more than 7 days before birth.

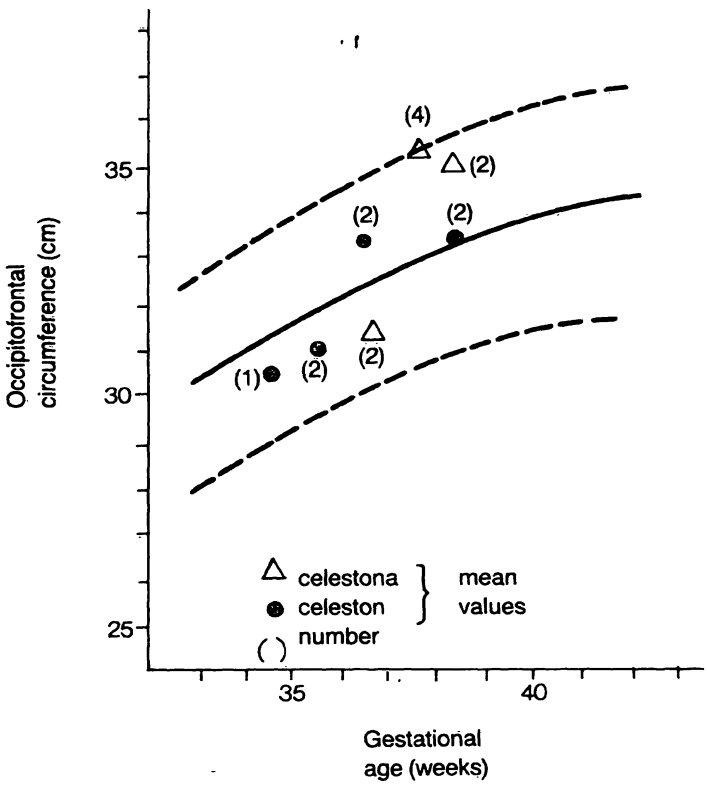

Fig. 3 B. Occipitofrontal circumference in girls of mothers treated with celeston and celestona. Cases with placental insufficiency are excluded. Corticoid administratered more than 7 days before birth.

Tab. III. Occipitofrontal circumference at time of birth in infants treated with Celestona® compared with the circumference in non-treated infants. Cases with placental insufficiency excluded. Celestona® administered more than 7 days before birth.

Gestational age (weeks)	Sex	Occipitofrontal circumferences (cm)	
		Treated	Non-treated (mean values, Tab. I)
37	♂	33.5	33.2
37	♀	31.0	32.3
37	♀	32.0	32.3
38	♀	35.0	33.3
38	♀	37.0	33.3
38	♂	33.0	33.5
38	♀	35.0	33.3
38	♂	33.5	33.5
38	♀	35.0	33.3
39	♀	33.0	33.5
39	♂	32.0	34.1
39	♂	34.0	34.1
39	♂	37.0	34.1
39	♀	37.0	33.5
39	♂	35.0	34.1

on cases in which corticoids were given more than 7 days before delivery and in which no placental dysfunction was diagnosed, no deviation from the normal were found (Tab. II and III, and Fig. 3 A–B).

4 Comment

As mentioned, corticoids exert an impeding effect on the evolution of the brain. This effect is seen after large doses of corticoids or long-term treatment. In their experiments with rhesus monkeys JOHNSON et al. [10] were not able to show a significant reduction of the occipitofrontal circumference at birth after short term betamethasone treatment with doses equivalent to those used in human treatment. Likewise no reduction of the occipitofrontal circumference at birth was found in the present investigation when cases with placental dysfunction are excluded.

However, it is still possible that Celeston® may have an impeding effect on brain growth in boys.

But the group treated with Celeston® contains only two boys without placental dysfunction.

In the present study no correction was done in the last trimester on the gestational age on the basis of biparietal diameter or estimated fetal weight. So, small or large fetal measurements could be due to inhibition or acceleration of the fetal growth. The estimation of the gestational age has a range of ± 2–3 weeks due to the biological variation in the time-span between the first day of the menstrual period and the ovulation and between the ovulation and birth [3]. Measurement of biparietal diameter in early pregnancy opens up the possibility of a more precise dating of the gestational age in pregnancies with uncertain last menstrual period. However, babies with uncertain gestational age was excluded in the present investigation.

LIGGINS and HOWIE [12] found no intellectual reduction in 4-year-old children whose mothers were treated with betamethasone in pregnancy. However, these findings do not disprove a retardation in the examined childrens brain evolution. The corticoid effect on the brain is complex and different brain parts are affected in different ways [4]. It is probable that corticoids in some cases can delay development of the brain without causing permanent damage on the nerve cells. DE LEMOS et al. [5] found a significant reduction of the brain weight, head circumference and the DNA-content in the brain of rhesus fetuses after administration of large doses of dexamethasone every other day for a total of three doses. Six months after delivery the difference in DNA-content of the brain, brain weight and head circumference had narrowed between the control group and the group which had received steroid. In agreement with this, COTTERRELL et al. [4] found an inhibition of thymidin incorporation in cerebral cells of rats after treatment with cortisol during the first 4 days after birth. At the age of 13–20 days an accelerated mitotic activity in the brain was found in the treated rats. BARRADA et al. [2] like other investigators found a reduction in the weight of the fetal rabbit brain after treatment with betamethasone. The DNA-concentration in the brain and total number of brain cells, however, was not affected and the concentrations of brain phospholipids and protein were higher in the treated fetuses.

BALLARD et al. [1] have shown that betamethasone used in humans results in a corticoid concentration in the cord blood, corresponding to that seen in untreated preterm infants developing RDS. Thus, the effect of corticoid administered antenatally is comparable to a physiological stress in the fetus. Possible for this reason antenatal corticoid treatment in humans in usual doses is not so dangerous as compared with high dose treatment in animal studies. The data found in the actual study are in agreement with this theory.

Summary

Celestona® (betamethasone-disodiumphosphate) and Celeston® (betamethasone-acetat + betamethasone-disodiumphosphate) given intramuscularly to pregnant women in order to reduce the frequency of respiratory distress syndrome does not reduce the occipitofrontal circumference of the newborn infants. Before the results from the actual work were available an impeding effect of the evolution of the brain was found in the light of animal experiments.

The material is comprised of 52 newborn infants whose mothers were treated with Celestona® 8 mg daily for 3 days and 46 infants treated with Celeston® 12 mg daily for 3 days. The untreated population comprises 1012 newborn infants.

Excluded were non-caucasian infants, twins, stillborns and cases of uncertain gestational age. The occipitofrontal circumference in normal infants and those infants treated with betamethasone were compared in Figs. 2 and 3. Focusing only upon cases in which corticoids were given more than 7 days before delivery and in which no placental dysfunction was diagnosed, **no differences from the normal were found (Tabs. II and III, and Figs. 3 A and B).**

Keywords: Betamethasone, brain growth-intrauterine, glucocorticoids-antenatal prophylaxis, newborns, occipitofrontal circumference.

Zusammenfassung

Occipitofrontaler Umfang bei Neugeborenen von mit Betamethason behandelten Müttern

Zur Vermeidung eines RDS wurde schwangeren Frauen Celestona® (Betamethasondinatriumphosphat) bzw. Celeston® (Betamethasonacetat + Betamethasondinatriumphosphat) intramuskulär verabreicht. Danach fand sich bei den Neugeborenen keine Reduzierung des occipitofrontalen Umfangs. Bevor die Ergebnisse dieser Arbeit vorlagen, wurde aus Tierexperimenten abgeleitet, daß ein Effekt auf die Gehirnentwicklung möglich ist.

Unser Untersuchungskollektiv bestand aus 52 Neugeborenen, deren Mütter 3 Tage lang mit 8 mg Celestona® pro Tag und 46 Kindern, deren Mütter 3 Tage lang mit 12 mg Celeston pro Tag behandelt worden waren. Die Kontrollgruppe umfaßte 1012 Neugeborene. Unberücksichtigt blieben nichtkaukasische Kinder, Zwillinge, Totgeborene und Kinder mit unsicherem Gestationsalter. Die occipitofrontalen Umfänge der Untersuchungs- und der Kontrollgruppe werden in Figs. 2 und 3 einander gegenübergestellt. Betrachtet man nur Fälle, in denen die Kortikoidgabe mehr als 7 Tage vor der Geburt erfolgte und in denen keine Plazentainsuffizienz vorlag, so **ergaben sich keine Abweichungen gegenüber der Kontrollgruppe (Tabs. II und III, Figs. 3 A und B).**

Schlüsselwörter: Antenatale Glukokortikoidprophylaxe, Betamethason, intrauterines Gehirnwachstum, Neugeborene, occipitofrontaler Umfang.

Résumé

Circonférence occipito-frontale des nouveaux-nés de mères traitées par betamethasone

Le Celestona®(betamethasone-disodium phosphate) et le Celeston® (acetate de betamethasone + bethamethasone-disodiumphosphate) donnés en intra-musculaire aux femmes enceintes afin de diminuer la fréquence du syndrome de détresse respiratoire, ne diminuent pas la circonférence occipito-frontale des nouveaux-nés. Avant les résultats des travaux actuels, on avait trouvé aux vues des expérimentations animales une entrave au développement cérébral.

Le matériel consiste en 52 nouveaux-nés dont les mères avaient été traitées avec du Celestona® à la dose de 8 mg par jour pendant 3 jours et en 46 enfants dont les mères avaient été traitées avec du Celeston® à la dose de 12 mg par jour pendant 3 jours. La population non traitée comporte 1012 nouveaux-nés.

Les enfants non caucasiens, les jumeaux, les morts-nés et les cas avec un terme gestationel incertain ont été exclus.

Les circonférences occipito-frontales des enfants normaux et des enfants traités par bétaméthasone sont comparées dans les Figs. 2 et 3. Si l'on ne s'occupe que des cas ayant reçu des corticoïdes plus de 7 jours avant l'accouchement et chez lesquels on n'a pas diagnostiqué d'insuffisance placentaire, **on ne trouve pas de différence par rapport aux témoins (Tabs. II et III, et Figs. 3 A et B).**

Mots-clés: Betamethasone, circonférence occipito-frontale, croissance cérébrale intra-utérine, nouveaux-nés, prophylaxie par glucocorticoïdes anténataux.

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