

Perinatal Treatment of Some Respiratory Disorders with Glucocorticoids in Relation to Prematurity

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Abstract

Presented work evaluated the benefits and risks of antenatal and neonatal treatment with glucocorticoids, as related to prematurity in humans. Major attention was devoted to the aspects of DOHaD area and to experimental models of laboratory animals, aiming at clarifying the possible contribution of exogenous glucocorticoids to the phenomena of programming/imprinting. It is suggested that the practice of multiple cycles of antenatal treatment with glucocorticoids should be reduced to the minimum, whereas neonatal treatment with glucocorticoids could be limited only to exceptional clinical cases.

Keywords: *Glucocorticoids; Perinatal Programming/Imprinting; Experimental Models*

Abbreviations

BW: Body Weight; DOHaD: Developmental Origins of Health and Disease; GC: Glucocorticoid

Introduction

At present the procedures of clinical management of pregnant women with the threat of preterm parturition and premature infant birth are among the most important problems of obstetrics and neonatology. It is estimated that in the whole world approximately 13 million of premature infants are born each year. The situation is more complicated in developing countries: for example, in Mexico the rate of prematurity is about 20%, but in developed countries the importance of this problem is also quite significant: in United States of America and in European countries this rate is between 5 and 10% [1]. Therefore, when at the end of sixties of the last century a researcher from New Zealand, Graham Liggins began to discover, first in the ewes and thereafter in humans, that administration of exogenous glucocorticoids (GC) to the pregnant females helps a premature newborn to survive, these studies resulted during the next decades in the elaboration and approval of simple clinical protocol of low cost for antenatal therapy with GC, being applied to pregnant women with a threat of preterm parturition.

Moreover, this protocol had a quite logical and strong reasoning: in fact, the peak of endogenous GC in fetal circulation, during the period close to the end of pregnancy, occurs in premature infants in a much less significant mode [2], therefore these infants present a certain insufficiency of adrenal glands that could be corrected by administration of exogenous GC to pregnant mother. It is quite important also that the peak of endogenous GC in the fetus helps prepare fetal tissues, and first of all the lungs, to postnatal life [3] and as a consequence of it, the main attention was attracted to the capacity of antenatal GC therapy to induce pulmonary maturation. Finally, during the years 1994 and 1995 the NIH Consensus was presented and published [4] about the benefits of antenatal GC therapy, what resulted in rapid augment of the use of this protocol in the whole world, including Latin America and Brazil, approaching almost 80% of all the cases in the recent years [5].

During the decades of 80s and 90s of the last century another clinical protocol began to be used for neonatal GC therapy, applied to premature infants for improving their pulmonary function [6]. Unfortunately, in this case pediatric authorities of USA and Canada had to try limiting the use of this protocol [7].

Antenatal Glucocorticoid Therapy: Benefits and Risks

Already the Consensus of NIH mentioned above [4] reasonably underlined the capacity of this protocol to diminish neonatal mortality, as well as the risk of respiratory distress syndrome and intraventricular hemorrhage in premature infants. The approved protocol, mostly used till the present time, consists of intramuscular administration of two doses of betamethasone 12 mg, with the interval of 24h between them, in pregnant women on 24 - 34 weeks of gestation. Less frequently another option is employed, with the use of dexamethasone administered 4 times at a dose of 6 mg, with the interval of 6 h between the injections. The advantage of these fluorinated GC is lower metabolism in placenta, as compared to non-fluorinated GC: prednisolone, methylprednisolone and hydrocortisone [8].

However, already during the first years of the use of antenatal GC therapy it became clear that the main problem of this protocol is in the intention of many obstetricians to repeat each week the cycle of GC therapy in situations when preterm parturition does not occur during a week soon after GC administration. One of reviews has shown that almost 60% of American obstetricians employ more than 6 cycles of antenatal GC therapy, and a number of such applications came to 16 in United Kingdom! [9]. One of reviews performed in Brazil has demonstrated that the use of multiple cycles of antenatal GC therapy occurs in almost 25% of the cases [10].

Exactly in this point it is pertinent to underline that already in a publication about biomedical foundations of antenatal GC therapy that accompanied the above mentioned NIH Consensus [4] the alert was made expressively against the use of multiple cycles of betamethasone or dexamethasone antenatally [11], stressing the capacity of these, highly potent GC to interfere strongly in the development of various fetal organs and tissues, including the brain. Therefore, it is not a surprise that rapidly the data began to emerge about adverse effects of multiple cycles of antenatal GC therapy.

Among these adverse effects the most prominent are retardation of somatic and cephalic growth and in relation to the latter also the higher risk of some neurobehavioral disorders in the offspring [12]. Although NIH reaffirmed in 2000 the alert against the use of multiple cycles of antenatal GC therapy, nevertheless, various authors observed that unfortunately, such practice continues in various places of the world [13].

Let's underline also that the approved protocol of antenatal GC therapy is also not completely free of problems. In fact, the studies of last years presented undesirable effects of such protocol in long term, such as alterations in the arch of aorta and higher reactions of salivary cortisol to stress in the offspring [14,15].

Relationship between Antenatal Glucocorticoid Therapy and DOHaD Concept

Historically, the first studies of English epidemiologist David Barker appeared at the end of 80s in the last century, i.e. somewhat earlier than presentation and publication of NIH Consensus [4], however it took approximately 20 years for international scientific community to "absorb" and discuss the so called "Barker's hypothesis" that finally transformed into one of the main concepts of DOHaD paradigm [16]. During the elaboration of this paradigm it became clear that both endogenous and exogenous GC can be among the most important mediators of the phenomena of programming/imprinting [17]. As a result of such discussion, the question has emerged, if prenatal GC therapy represents one more source or the origin of disorders in adults [18]. This preoccupation was shared by other authors [19]. It is not accidental that presenting the results of follow-up till the age of 30 years in the group of individuals exposed to antenatal GC therapy, registered insulin resistance was interpreted as an example of programming/imprinting, according to "Barker's hypothesis" [20].

Neonatal Glucocorticoid Therapy: the Adversity Confirmed

The reaction of scientific community in medicine to neonatal use of exogenous GC was somewhat more rapid: already at the beginning of current century the publications appeared with strong alert against such type of GC therapy. In fact, it was clearly demonstrated that

systemic use of dexamethasone at doses between 0.5 and 1.0 mg/kg BW per day, at the beginning of postnatal life in premature infants can augment the risk of cerebral palsy and of some other neurologic dysfunctions thereafter [21]. However, major preoccupation was generated by confirmation of long-term consequences, as referred to neurobehavior of children at school age, that were treated with dexamethasone already in neonatal period [22]. One of recent studies has shown that at the end of adolescence the individuals treated with GC neonatally, had lower brain volume [23].

So it is not a surprise that various authors concluded firmly about the necessity to abandon completely the protocol of neonatal GC therapy or, at least, to promote its use in a quite limited mode [21,24]. Therefore, it is not easy to understand, how and why neonatal GC use continues in many neonatal clinical units, in spite of the reaffirmed position of American Academy of Pediatrics in 2006 against the neonatal GC therapy [25]. One of the explanations of such situation is the necessity to try performing the extubation of preterm infant in more rapid mode, and it appears that dexamethasone serves for this aim relatively well. Therefore it is a good news that in the last years a tendency was registered for diminution of the use of neonatal GC therapy and of GC dose utilized [23].

Experimental Models for Evaluation of Perinatal Glucocorticoid Therapy

Our experimental studies *in vivo* were performed at first in Federal University of Santa Maria (UFSM) and thereafter in the University of Ijuí (Unijui) in parallel with epidemiologic research of David Barker and his colleagues [16] and together with publications of alerts by researchers [21] and pediatric authorities [7]. In these our works a course of three dexamethasone injections at a dose of 1 or 2 mg/kg BW in neonatal period caused irreversible or partially reversible retardation of body and some organ growth in rats [26,27]. Although the doses applied were at least two times higher than the doses used in neonatal clinics (0.5 to 1.0 mg/kg), total cumulative doses used by us (3 or 6 mg/kg) corresponded to cumulative doses in real clinical situations: 10 to 20 mg/kg [23]. It is important to underline that a model of neonatal rats utilized in our studies corresponds exactly to premature human infants born during the 3rd trimester of gestation, because of the difference in the extent of maturation of rats and humans at the moment of birth.

However, it is pertinent to note that already during the 60s of the last century, the dramatic negative impact of cortisol at high dose was shown, when administered in neonatal period, for somatic growth in rats [28]. Similar data, as related to growth of offspring, were obtained in the 70s of the last century, utilizing prednisone during a gestation in mice [29]. In addition, at the beginning of the current century it was shown that tapering regimen (reproducing neonatal GC therapy with stepwise diminution of a dose, in order to facilitate the removal of dexamethasone) is also capable to provoke the retardation of somatic and brain growth in rats [30].

Concluding Remarks

Resuming the data described above, the main doubts and uncertainties about perinatal GC therapy, as referred to prematurity, can lead to formulation of the following recommendations:

1. Antenatal GC therapy in approved mode of unique cycle of betamethasone presents obvious benefits, however, the use of multiple cycles should be reduced to the minimum.
2. Neonatal GC therapy can be applied only in exceptional situations, trying to consult preferably the parents of premature infants.
3. In all the cases the planning should be performed beforehand for epidemiologic studies of long-term follow-up of individuals exposed to perinatal GC therapy.
4. The research on experimental models should be performed, in order to discover the modes of diminishing adverse impact of perinatal GC therapy, especially in long term.

As referred to the 3rd recommendation above, the role of health professionals is very significant in the area of Public Health. However, one of the most difficult problems to be resolved is the gathering of information during many years and even decades. On our opinion, this could be possible via organization of Regional DOHaD Centers, but the support of various entities and authorities should be very important for realizing this goal.

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