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The Impact of Prenatal Glucocorticoid Exposure on Offspring Cardiac Development

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Abstract: ***Glucocorticoids are the main part of the treatment of preterm birth, which can promote fetal lung maturation and reduce neonatal respiratory distress syndrome. NRDS), neonatal intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and perinatal mortality. However, many studies in recent years have shown that antenatal corticosteroid (ACS) exposure has adverse effects on cardiac myocytes in offspring, resulting in long-term cardiac damage in offspring. This article reviews the recent studies on the regulation of cardiac maturation, cardiac hypertrophy, hemodynamic effects, energy metabolism regulation, and susceptibility to heart disease in offspring treated with glucocorticoids, in order to provide clinical evidence on the harm of ACS to the heart health of offspring, so that clinical attention should be paid to the risk of ACS and the reasonable indications for the use of ACS.***

Keywords: ACS, GR, Fatty acid oxidation, PGC-1α, DNA methylation.

1. Introduction

Glucocorticoids, as classic therapeutic agents, are extensively employed in clinical practice and are indispensable when treating pregnant women with preterm birth (delivery of a live fetus before 37 weeks of gestation). To lower the incidence and mortality rates of preterm infants in the clinical setting, Liggins & Howie initiated antenatal corticosteroid therapy (ACS) several decades ago. This therapy has significantly decreased the incidence of neonatal respiratory distress syndrome (NRDS) in preterm infants and is also associated with a reduced risk of neonatal intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and hyperbilirubinemia (HB) [1]. At present, numerous national guidelines commonly recommend the application of antenatal corticosteroids (ACS) to pregnant women within 24 - 34 weeks of gestation who have a risk of preterm birth within 7 days, considering it beneficial for reducing neonatal morbidity and mortality [2]. The administration methods of ACS that are unanimously recognized in the clinical setting are intramuscular injection of 12 mg of betamethasone once every 24 hours, for a total of two times; or intramuscular injection of 6 mg of dexamethasone once every 12 hours, for a total of four times. Dexamethasone and betamethasone, as synthetic glucocorticoids, are capable of crossing the placental barrier [3], and it is employed in the clinical setting to simulate the effect of endogenous glucocorticoids in the fetus. A considerable number of studies have been conducted on the benefits of antenatal corticosteroids (ACS) for the pulmonary function of preterm infants; however, its influence on fetal cardiac function has been controversial in recent years. On the one hand, it is believed that fetal exposure to maternal glucocorticoids can accelerate cardiovascular maturation, improve basic cardiovascular function, and enhance the cardiovascular defense ability of premature infants against physiological stress after life outside the womb [4]; On the other hand, there is a view that prenatal exposure to glucocorticoids is associated with alterations in myocardial cell glucose metabolism and limited changes in aortic function, and it increases the risk of cardiovascular failure in adulthood [5]. Furthermore, at present, there remains significant uncertainty regarding the timing of ACS application in the clinical setting (within 7 days of the risk of preterm labor). Research statistics have revealed that due to the poor predictability of preterm birth, the proportion of pregnant women who deliver more than 7 days after the administration of ACS is as high as 60% [6]. Whether such inaccuracy in grasping the timing of ACS utilization will impact the programming effect of glucocorticoids on the fetal heart is likewise deserving of further investigation.

2. Endogenous Glucocorticoid Production and Fetal Heart Development

It is generally believed that the development and maturation of the fetal heart is a highly dynamic process, mice at embryonic day 14.5 [7], humans around the 7th week of gestation, The anatomical structure of the fetal heart is basically formed, followed by the functional maturation of cardiac cells and tissues. It is generally believed that in the late pregnancy, cardiomyocytes gradually turn to terminal differentiation. Myofibrils in cardiomyocytes begin to expand and assemble, M lines form, transverse tubules (T-tubules) form, and the sarcoplasmic reticulum (SR) expands [8], the electrophysiological function of cardiomyocytes tends to mature. In addition, the energy metabolism of cardiomyocytes began to shift from glycolysis to fatty acid oxidation [9], mitochondria in cells increase in number and become larger [10], the expression of genes associated with the cell cycle was suppressed, while the expression of genes related to cardiomyocyte hypertrophy was upregulated, additionally, cardiomyocytes exhibited a tendency towards polyploidy and binucleation [11]. The exit of cardiomyocytes from the cell proliferation cycle indicates a significant reduction in the proliferative potential of mature cardiomyocytes. However, this does not equate to a complete loss of proliferative capacity in healthy mature cardiac cells. Research has indicated that the proliferation rate of human cardiomyocytes declines to a low level approximately two decades post-birth [12], the maintenance of this proliferative potential of cardiomyocytes is important for the further development of the fetal heart after birth and the maintenance of cardiac tolerance to damage.

Studies have demonstrated that endogenous glucocorticoids play a crucial role in regulating fetal heart maturation. Endogenous glucocorticoids originate from two primary sources. The first source is the synthesis by the fetal adrenal gland (which reaches functional maturity around 30 weeks of gestation in humans and embryonic day 14.5 in mice [13]), The adrenal structure of human and other primate fetuses is rather distinctive before 30 weeks of gestation, mainly composed of the definitive zone (DZ), the fetal zone (FZ), and the transitional zone (TZ) in the middle. The DZ is accountable for the synthesis of glucocorticoids during the mid-trimester of pregnancy. The DZ can employ 17-α hydroxylase to convert progesterone, a metabolite of the FZ, into 17-α hydroxyprogesterone, which is subsequently transformed into 11-deoxycortisol and eventually into cortisol [14]; The other is the passage of maternal glucocorticoids across the placenta into the fetal circulation which are synthesized by the maternal zona fasciculata, which develops from the fetal DZ, by the same process as in the fetus. However, due to the placental barrier effect: P-glycoprotein in the placenta mediates active reverse transport of glucocorticoids from fetus to mother to maintain the maternal-fetal glucocorticoid gradient [15]; The placenta of humans and animals contains 11β-hydroxysteroid deoxy-2 (11β-HSD-2), which converts cortisol to an inactive 11-ketone metabolite and prevents the transport of maternal glucocorticoids into the fetal circulation, resulting in fetal overexposure to maternal glucocorticoids [16]. Consequently, low concentrations of glucocorticoids are maintained in the circulation during most of fetal growth and development. However, about a week before birth, the endogenous glucocorticoids in the fetal circulation increase exponentially due to the interaction between the fetus and the placenta. In order to initiate labor, promote the further maturation of fetal lung, heart and other tissues and organs, and make the fetus adapt to the extrauterine environment, the following mechanisms may be mainly involved: The secretion of corticotropin-releasing hormone (CRH) by the placenta increases dramatically during the third trimester, although placental CRH mainly enters the maternal circulation [17]. However, a small fraction of CRH signals entering the fetal circulation can activate the fetal hypothalamic-pituitary-adrenal-placental (HPAP) axis, forming a positive feedback to promote the increase of fetal adrenal glucocorticoid synthesis [18]; Placental 11β-HSD-2 activity decreased [19], the passage of maternal glucocorticoids into the fetal circulation is increased. ACS simulates exactly this process [20], However, premature cardiac myocytes are exposed to exogenous glucocorticoids without an adequate reserve, leading to premature exit from the cell proliferation cycle and diminished potential for fetal cardiac cell proliferation and repair postnatally. Consequently, it is crucial to consider the potential for prenatal glucocorticoid exposure, whether premature or excessive, to alter the normal glucocorticoid-regulated cardiac maturation trajectory, which may result in lifelong consequences [21]. This highlights the necessity of accurately assessing the risk of preterm birth, potential preterm complications, and long-term cardiac effects on offspring when utilizing ACS for pregnant women at risk of preterm birth. It also underscores the importance of carefully evaluating the indications for ACS use, which will facilitate more precise clinical application in the future.

3. Mechanism of ACS Promoting Fetal Cardiomyocyte Hypertrophy

3.1 Glucocorticoid Receptor Mediated

Cardiomyocytes are generally known to express both glucocorticoid receptors (GR) and mineralocorticoid receptors (MR). Endogenous glucocorticoids can exert their effects through either GR or MR. Notably, MR exhibits a high affinity for endogenous glucocorticoids [22]. Activation of MR can promote cardiomyocyte proliferation, whereas activation of GR inhibits cardiomyocyte proliferation but promotes cardiomyocyte hypertrophy, thereby increasing the heart-to-body weight ratio. Typically, exogenous glucocorticoids such as dexamethasone and betamethasone exhibit limited efficacy in activating MR [23], which mainly by activating GR and triggering a cascade of effects [24]. Fetal hearts of GR deficient mice were found to have both macroscopic and microstructural disruption, a reduced heart to body weight ratio, and short and disorganized myofibrils [25]. This suggests that glucocorticoids promote the elongation and orderly arrangement of myofibrils of cardiomyocytes through GR, which plays an important role in promoting cardiac maturation. Besides the direct effect of glucocorticoids on the heart through GR, glucocorticoids also have an indirect regulatory effect on the heart, which is closely related to the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoid exposure may inhibit the HPA axis, deprive cardiac MR Of physiological glucocorticoid ligands in a short period of time, and then seriously change the balance of cardiac MR/GR, thereby enhancing the pro-cardiomyocyte hypertrophy effect activated by GR and reducing the pro-cardiomyocyte proliferation effect activated by MR [22]. This also means that the number of cardiomyocytes in preterm infants is lower than that in term infants, and the overall potential of their hearts is also reduced. Whether this affects the heart development in youth and the heart susceptibility in adulthood needs to be further studied.

3.2 Pathways That Promote Cardiac Hypertrophy

The PI3K/Akt/p-GSK-3β pathway was activated by dexamethasone injection from the 17th day of pregnancy in rats. Phosphorylated GSK-3β directly regulated the downstream transcription factor β-catenin and the zinc finger transcription factor GATA-4. β-catenin activation can enhance the proliferation of early cardiomyocytes, while GATA-4 promoting cardiomyocyte hypertrophy [26] and increasing cardiac contractility related protein troponin T [9]. It also increases markedly protein levels of VEGF which regulates coronary angiogenesis and left ventricular hypertrophy in physiological cardiac hypertrophy [27]. This series of changes can promote the rapid adaptation of the fetal heart to the extrauterine environment after birth. This animal experiment shows that ACS has a more obvious positive effect on promoting heart maturation. However, Tessa AC Garrud et al. respectively administered dexamethasone and betamethasone on day 14 of chick embryo and found that they had different pathways of action on cardiomyocytes. Dexamethasone activated caspase-3 through JNK/pERK-p38 pathway, promoted cardiomyocyte hypertrophy, and may cause ventricular diastolic dysfunction. Betamethasone inhibits CDK2 through JNK/pERK-p53 pathway and

decreases cardiomyocyte number, leading to dilated cardiomyopathy and ventricular systolic and diastolic dysfunction [28]. Previous studies have shown that betamethasone is superior in promoting fetal lung maturation [29]. However, the above experiments suggest that it may have more adverse effects on cardiac maturation. Of course, the above experiments are different in the administration time, 17 days of gestation in rats is equivalent to about 34 weeks of human pregnancy, 14 days of chicken embryo is equivalent to about 28 weeks of human pregnancy, and this different administration time seems to have different effects on the heart. ACS during late pregnancy seems to have a positive effect on short-term cardiac maturation, but may lead to ventricular hypertrophy later in the rat model. However, rats are rodents, and the results cannot be fully supported by human primates. At present, the World Health Organization (WHO) suggests that ACS is generally not recommended for late preterm birth (live birth at 34-37 weeks of gestation), and its overall impact on preterm infants is more harmful than beneficial [30]. A systematic review of clinical studies examining the impact of prenatal ACS on human offspring's blood pressure and cardiac function revealed that ACS has minimal influence on offspring's blood pressure. However, the effects of ACS on cardiac structure and function remain inconclusive due to limitations in echocardiography and cardiac MRI availability in many clinical studies [31]. This underscores the importance of utilizing echocardiography and other diagnostic methods in future studies examining the impact of ACS on cardiac function in human offspring. This approach will provide more robust clinical data and evidence to support the precise application of ACS management strategies.

4. ACS Affects Fetal Hemodynamics

The mechanism by which glucocorticoids promote fetal cardiac maturation is complex. As mentioned above, it can activate GR in the heart to directly regulate cardiomyocytes, but GR is also distributed in other tissues and organs. It is interesting to ponder whether glucocorticoids have any effect on regulating cardiac maturation when acting on GR in other parts. Mice with a gene deletion seem to have the answer. It was found that SMGRKO mice (in which only the GR gene in cardiomyocytes and vascular smooth muscle cells was knocked out) had no difference in heart size and maturity compared with normal mice [25]. This suggests that GR activation at other locations is quite important for cardiac maturation. Glucocorticoids can activate these GRs to maintain normal pressor effect and keep fetal hemodynamics stable, suggesting that hemodynamics plays a non-negligible role in promoting cardiac development and maturation. Of course, hemodynamics is not only important for fetal heart development, but also plays a decisive role in the growth and development of the whole fetus. Insufficient placental blood flow is an important cause of fetal intrauterine growth restriction (IUGR). However, such placental vascular inhibition may be related to excessive or premature glucocorticoid exposure [32]. Animal studies have shown that the deletion of 11β-HSD2 gene leads to the premature release of maternal glucocorticoids into the fetal circulation, and the mouse fetus shows a series of abnormalities such as placental vascular morphology, umbilical blood flow velocity, fetal weight, fetal heart function, and IUGR [33]. This study confirmed the adverse effects of glucocorticoids on placental angiogenesis and umbilical cord blood flow in mice at inappropriate time or dose. Among the factors contributing to preterm birth, IUGR is responsible for approximately 20% [34], preterm infants with IUGR may need ACS, and some scholars believe that ACS will aggravate the cardiovascular side effects of IUGR fetus [35], for example, overexposure to endogenous glucocorticoids is one of the causes of IUGR [33], if ACS is used again in this situation, the cardiovascular risk to the fetus will be even greater; However, some scholars hold a different view and believe that the fetal cardiovascular risk of ACS is still inconclusive [36]. Some clinical studies have found that prenatal betamethasone treatment can lead to an increase in the variation of fetal heart rate at the baseline of fetal monitoring, but has no effect on fetal Doppler flow index [37]. Currently, guidelines from multiple countries concur that the dosage and indications for ACS in preterm pregnant women with IUGR remain unchanged. However, exogenous glucocorticoids may exert varying effects and pose different risks to preterm fetuses depending on their underlying etiologies, which has contributed to the ongoing controversy surrounding ACS use in recent years. Existing research lacks sufficient specificity and depth, and many experimental studies have yielded conflicting results.

5. Effects of ACS on Energy Metabolism in Fetal Cardiomyocytes

In addition to structural changes, heart maturation also includes transformation of energy metabolism in cardiomyocytes. Normally, the fetal heart generates most ATP from acetyl-coa produced by glycolysis. However, after birth, due to the increased ATP demand of the mature heart, the energy requirement is mainly met by mitochondrial fatty acid β-oxidation [9]. The process of energy metabolism transition in cardiomyocytes is complex, involving mitochondrial maturation and upregulated expression of genes associated with fatty acid β-oxidation [27]. Dexamethasone has shown that glucocorticoids can rapidly induce peroxisome proliferators-activated receptor γ coactivator-1α in vivo and in vitro. PGC-1αand Peroxisome Proliferator Activated Receptorα (PPARα), PGC-1α is a key regulator of cardiac mitochondrial function, normally expressed in the fetal heart during late gestation and significantly increased after birth, PPAR is a regulator of fatty acid beta oxidation and cardiomyocyte mitochondrial respiration, promoting cardiomyocyte energy production, which is essential for the functional and metabolic maturation of the fetal heart [38-39]. However, it is noteworthy that administration of dexamethasone during the third trimester of pregnancy led to a decrease in the expression of PGC-1α and GR 40, this provides evidence for prudent use of ACS in the late pregnancy. The above experiments also demonstrated the important role of PGC-1α in regulating the maturation of energy metabolism in cardiomyocytes. PGC-1α is known to increase the level of reactive oxygen species (ROS), which in turn activates Parkin (an E3 ubiquitin ligase) pathway and induces mitochondrial autophagy in cardiomyocytes, leading to mitochondrial remodeling, an essential step in mitochondrial energy metabolism transformation [40]. However, increased ROS means increased levels of oxidative stress in cardiomyocytes, damaging DNA and causing cell cycle arrest [41], accelerating cellular senescence. Therefore,

it is hypothesized that the administration of exogenous glucocorticoids may diminish the potential for cardiomyocyte proliferation and repair in premature infants. Furthermore, the combination of glucocorticoids and antioxidants could enhance treatment safety. This approach not only leverages the beneficial effects of glucocorticoids to regulate cardiomyocyte mitochondrial function and promote energy metabolism transformation but also mitigates the adverse effects of glucocorticoids by reducing oxidative stress levels [42].

6. Glucocorticoids Lead to Increased Cardiac Susceptibility in Adult Offspring

Whether ACS has long-term effects on the offspring's heart has been controversial. Recent studies on cardiac ischemia-reperfusion animal models in the offspring of ACS mice have found that compared with the control group, the degree of myocardial infarction in the offspring of ACS mice after cardiac hypoxia is more severe [43], This indicates that the long-term adverse effects of prenatal exposure to ACS) on offspring cardiac function cannot be overlooked. Glucocorticoids may induce hypermethylation in the promoter regions of bone morphogenetic protein 4 (BMP4) and serum/glucocorticoid-regulated kinase 1 (SGK1) genes. Consequently, hypoxia-inducible factor-1α (HIF-1α) is unable to bind to its respective site, leading to impaired cardiac protective mechanisms following hypoxic events. This results in increased myocardial cell apoptosis and heightened vulnerability and susceptibility of the offspring heart to stress [44].

It is important to highlight that the enhanced cardiac susceptibility observed in offspring exhibits a notable gender bias, with male offspring demonstrating a significantly higher incidence of myocardial infarction compared to their female counterparts. This disparity may be attributed to the protective effects of estrogen on cardiac function. Estrogen regulates cardiomyocyte energy metabolism and apoptosis, offering protection against ischemia-hypoxia-induced damage via pathways such as estrogen receptors, MAPK, PI3K-Akt, and UCNs-CRHR2 [45].

7. Summary and Outlook

ACS treatment has been widely recommended by international and domestic clinical guidelines for preterm birth occurring before 34 weeks of gestation. Consequently, ACS plays a crucial role in the management of preterm birth. However, ACS is a double-edged sword; while it can effectively reduce the incidence of NRDS, IVH, NEC, and perinatal mortality in preterm infants, it may also cause long-term cardiac damage to offspring. Therefore, it is imperative to use ACS judiciously in clinical practice, carefully weighing its benefits against potential risks. The 2024 Chinese Guidelines for the Diagnosis and Treatment of Preterm Birth recommend dexamethasone as the preferred ACS agent for preterm births between 24 -34 weeks of gestation. Research has demonstrated that dexamethasone is superior in mitigating cardiac damage compared to other ACS agents [28]. One course of dexamethasone or betamethasone is recommended for women at risk of delivery within 7 days at 24-34 weeks' gestation, a second course can be given if delivery is not achieved within a week and signs of premature Labour reappear, and third or more courses are generally not used [46], to mitigate the repeated use of ACS, minimize adverse cardiac effects, and reduce the incidence of IUGR, it is crucial to limit off-target phenomena (no delivery within 7 days post-administration). Future research should focus on accumulating more experimental and clinical data to provide a robust evidence base for the standardization, precision, and individualized application of ACS.

Currently, the most commonly utilized animal models for investigating the effects of ACS on fetal hearts include rats, mice, and sheep. The timing of myocardial cell nucleation, ploidy increase, hypertrophy, and metabolic transition to fatty acid oxidation varies among these species, with sheep being the most analogous to humans [47]. When administering the drug to animals, the dosing regimen was extrapolated based on the human pregnancy cycle without accounting for the differences in cardiac maturation timelines between species. This discrepancy may explain the inconsistencies observed between animal experimental outcomes and human clinical findings. Future studies should prioritize large mammalian models that more closely resemble human physiology to enhance the scientific validity and translatability of experimental conclusions.

Certainly, in response to the adverse effects associated with ACS, the potential of combination therapies is currently under investigation. For instance, the concurrent use of glucocorticoids along with vitamins C and E has been shown to be less detrimental to cardiac health in terms of oxidative stress compared to glucocorticoids alone. Additionally, pravastatin has demonstrated the ability to normalize placental vascular and cardiac function in mice exposed to excessive glucocorticoids [48]. Whether this combination of drugs can optimize the benefits for both mother and fetus while minimizing potential risks warrants further investigation. The role of glucocorticoids in promoting the proliferation and maturation of cardiomyocytes may also provide valuable insights for advancements in biological regenerative medicine.

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