PRENATAL MATERNAL STRESS AND ITS CONSEQUENCES FOR THE FETUS

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INTRODUCTION

Maternal HPA axis is involved in the early neuroendocrine programming of the brain fetus. The stressor stimuli action, leads to the activation of this axis which releases to the blood large amounts of the following hormones: CRH, ACTH, cortisol and noradrenaline. If these hormones reaches the fetus during pregnancy, this will cause negative effects at short and long term. If the stressor stimuli persists in a cronic way, the negative feedback over the HPA axis will be altered and so it will be the release of all these hormones.

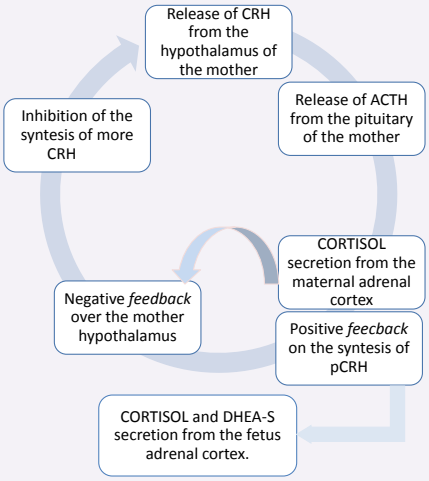
AIMS

- ❖ Determine the role of the cortisol released for the mother and it's neuroendocrine effects for the fetus.
- ❖ Clarify if the prenatal maternal stress can cause consequences in the fetus in the future.

METHODOLOGY

- ❖ Literature research on online databases (PubMed and Isi Web of Knowledge).
- ❖ Literature research using the references of other articles previously readed.

REGULATION OF HPA AXIS



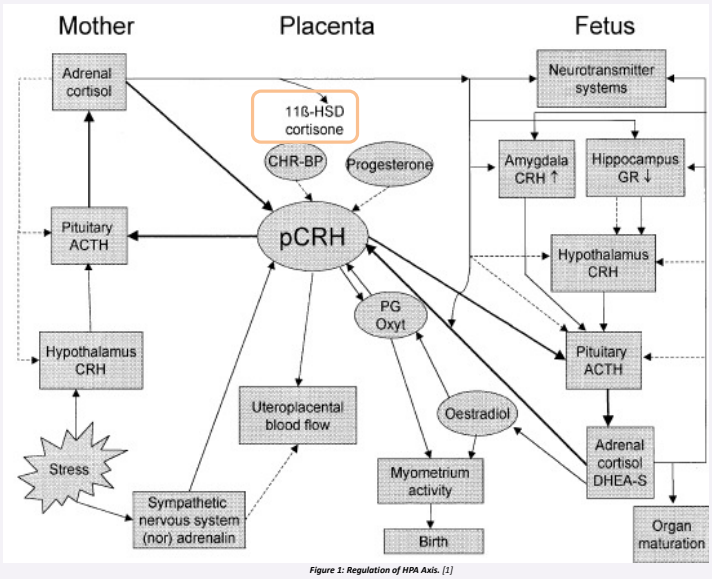


Figure 1: Regulation of HPA Axis. [1]

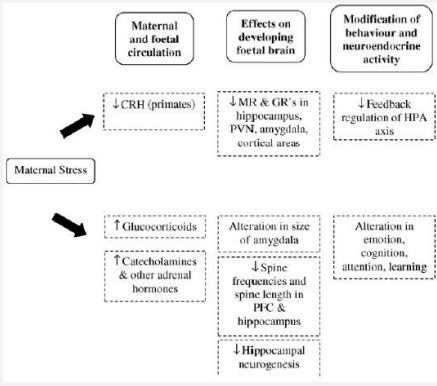


Figure 2: Routes through which maternal stress hormones can induce changes in fetal brain development and in the programming of the behavior. [2]

THE CORTISOL ROLE

- ❖ Between the pregnant mother and the fetus there are not neural connections → stressor stimuli needs to be transmited to the fetus somehow:
  1. Stress hormones.
  2. Changes in utero-placental blood flow.
  3. Transitory hipoxia periods.

- ❖ **Cortisol** has been porposed as the first hormone to play an important role in the **early fetal programming**.

- ❖ **Cortisol** plays a major role in the **proper regulation** of the **HPA axis.**

- ❖ **Cortisol** in **normal concentrations**, allows the **maturation of fetal organs**. When cortisol exceeds **critical levels**, this causes a broad range of **negative effects** on the fetus.

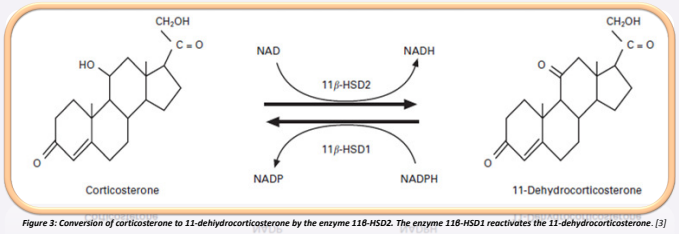


Figure 3: Conversion of corticosterone to 11-dehiydrocorticosterone by the enzyme 11ß-HSD2. The enzyme 11ß-HSD1 reactivates the 11-dehydrocorticosterone. [3]

CONSEQUENCES IN SNC DEVELOPMENT

- ❖ Release of ACTH and CRH is controlled by GR and MR → cortisol exerts an inhibitory effect over this receptors.

- ❖ GR and MR are located in: amigdala, hippocampus and pituitary. Also in endometrium, miometrium and ovaries.

Animal studies	Human studies
- *Rattus norvegicus*: last week of gestation → induction of stress. - **Increase** of mRNA levels of **CRH** at **PVN**. - **Activation** of the **piramidal neurons** in the hippocampal CA1 + CA3 regions. - **Alterations** in the **negative *feedback*** of **HPA axis**.	-**Downregulation** of the **GR** and **MR**. - **Affected neurogenesis** in the hippocampus → **Cortisol** is **highly toxic** in this region.

CORTISOL EFFECTS IN ORGAN MATURATION

- ❖ Cortisol exerts a very important programming effect in fetal development throughout pregnancy.

- ❖ This effect can change according the different [cortisol] and the stage of pregnancy.

Gestation in the short-term.	Gestation in the long-term.
- **First months** of pregnany → **levels and activity** of 11β-HSD2 are **high**. - Maternal **[cortisol]** in the **placenta** are **low**.	- Last months of pregnancy → **levels and activity** of 11β-HSD2 start to **decrease.** - Fetus exposed to **high [cortisol]** → **positive** effect in the **maturation** of fetal **systems** and **organs**.

PHYSIOLOGIC CONSEQUENCES

- ❖ Many fetuses undergoing prenatal stress suffer a decrease in weight.

Animal studies	Human studies
- **No positive correlation** between prenatal **maternal stress** and **decrease in weight** at birth of the animal. - Female rats injected with DEX* in the last week of pregnancy → **male rats born** suffered a **decrease in weight.** * 11β-HSD2 can't metabolize DEX.	- **Positive correlation** between prenatal **maternal stress** and **preterm birth**. - **Positive correlation** between prenatal **maternal stress** and **decrese in weight** at fetus birth.

COGNITIVE CONSEQUENCES

- ❖ Cognitive alterations are the result of the increase in CRH activity in the neo-cortex and amygdala.

- ❖ Both areas are related with the emocional processing and also with the alteration in the regulation of the HPA axis.

Animal studies	Human studies
- **LTP + LTD** play a major role in **space memory** and **learning**. - **Positive correlation** between prenatal **maternal stress** and **supression of LTP** in **male rats** at birth. - **Learning deficit** → **less dendrites density** in the **piramidal neurons** of CA3 hippocampal region.	- MDI → Bayley's Development Scale (Nancy Bayley, 1977). - Prenatal **maternal stress** during first or second semester of gestation is **related** to have children with **lower degree** of **intellectual** and **linguistic development**.

CONCLUSIONS

Studies with animal models allowed to demonstrate that environmental factors early in life like exposure to prenatal stress and stress hormones, can cause structural and functional changes that persist throughout the life of the animal. These studies have been the basis for many of the studies that have subsequently been carried out with human fetuses. To date, the most important part of human studies allowed to show that cortisol can influence both in the regulation and feedback of the HPA axis when the levels of this hormone exceeds a limit level.
Beyond this, the permanent activation of the HPA axis due to a chronic stressor stimuli causes a series of consequences in the fetus that can differ from alterations in the SNC to alterations at physiologic level passing through alterations in the maturation in the fetal organs and even alterations at cognitive level. Besides, some of the consequences here revised may differ according if we are talking about animal or human studies. This means that animal models are still needed in order to understand the neurological basis of prenatal maternal stress and the consequences this entails for the fetus.

REFERENCES

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[3] *Wellberg, L.A.M, Seckl, J.R. Prenatal stress, Glucocorticoids and the Programming of the Brain. (2001) Journal of Neuroendocrinology.13:113-128*