DIOXIN EXPOSURE IN UTERO AND LATER PREMATURITY. A ROLE FOR EPIGENETIC CHANGES? A REVIEW.

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Introduction

Worldwide 15 million babies are born preterm and both mortality and morbidity in this group are high. Approximately 12 % of all infants in the USA are born preterm. This figure is lower in Europe, about 6% in developed countries in Europe. Multiple gestation, maternal chronic diseases, fetal malformations, and infections are among the factors known to increase the risk of preterm birth. After a premature delivery the risk of a repeat is 25 %. In the USA a rise from 10.6 to 12.5 % took place in the last decade. And 1 % of the 1.9 % rise is unexplained[1].

Genes involved in Human Birth Timing

Approximately 70 % of Spontaneous Preterm Birth (SPTB) are spontaneous and no environmental factor can be identified and it is likely that several of these births are explained by (epi)-genetic factors.

In Finnish families with recurring premature birth a first linkage analysis of SPTB demonstrates a role for the gene encoding insulin-like growth factor 1 (**IGF-1R**)[2]. Other genes mentioned before to play a role are: maternal FSHR and TIMP2 genes encoding follicle-stimulating hormone receptor and tissue inhibitor of metalloproteinase 2 and the fetal IL6R and COL5A2 genes, encoding interleukin 6 receptor and collagen type V, alpha 2. And recently a potential novel SPTB gene, encoding the fetal AR (androgen receptor) and the interleukin-2 receptor gamma subunit IL2RG , is identified by linkage and association analysis of X chromosomal markers. Long **AR CAG repeats (≥26),** so less activity, are overrepresented and short repeats (≤ 19) are underrepresented in individuals born preterm compared to those born at term. IGF1R is a downstream target for AR. AR is involved in activation of IGF1R. Both genes are identified as fetal susceptibility factors for SPTB and interactions might play a role. The role of motherly genes are considered to be more important for the timing of birth then paternal genes, however in this last Finnish study by Karjalainen the fetal AR gene is related to SPTB not the maternal gene[3]. Studies with successful induction of parturition by local prostaglandin treatment leads to a decreased AR and progesterone receptor level in the human uterine cervix. And hyper-methylation of the AR promoter downregulates expression of IGF1R. In this study Karjalainen comes to the conclusion that both AR and IGF1R are important genes in the onset of preterm birth[3].The androgen receptor, estrogen receptor and progesterone receptor are members of the steroid hormone receptor family. In literature maternal factors are said to be more crucial but it now becomes clear that also fetal genes (being partly of paternal origin) are important. So fathers can play a role in premature deliveries.

There are two known examples of pollutants/medications that are related to premature delivery: DES and anti-epileptic drugs.

DES and prematurity.

In pregnancies with the use of DES (Di-Ethyl-Stilboestrol) there is an increase in miscarriages, ectopic pregnancies and *premature deliveries* in DES-daughters especially with structural abnormalities of the uterus and cervix (25%). There are indications of a transgenerational effect as is shown in the sons of these daughters that have an increased incidence in hypospadias [4]. It is not known if these sons have more premature deliveries

in their offspring. However a transgenerational effect is also seen in the offspring , both daughters and sons of mothers using anti-epileptic drugs[7] .

Anti-epileptic drugs and prematurity.

Studies to effects of anti-epileptic drugs demonstrates irregular menstrual periods in the daughters and more obstetrical complications in their pregnancies 5[5,6]. The mothers using the drugs all deliver at term, but both the daughters and sons, exposed in utero, show an increase in premature delivery in relation to their mothers (resp. 3.9% versus 13.9 %)[7]. Anti-epileptic drugs are known to be teratogenic , have enzyme inducing capacities, and in animal studies the hormone progesterone is negatively influenced in the offspring[8]. The nuclear receptors CAR (constitutive androstane receptor) and PXR (pregnane X receptor) mediate the effects of phenobarbital and other anti-epileptic drugs on gene transcription. DDE the metabolite of DDT as well as some PCBs congeners works like phenobarbital and are a known inhibitor of the Androgen receptor and might play a role in premature deliveries [9].

Dioxins/PCBs and prematurity.

Direct effects on reproductive outcome like prematurity is described for both dioxins and PCBs. In Yusho cases with dermatological findings and high levels of PCB/PCDF exposure an adverse effect on pregnancy outcome like SPTB (Spontaneous Preterm Birth) in women is found [10]. In Taiwan a same disaster took place ten years later (Yucheng) and premature delivery is described together with intra-uterine growth retardation [11]. In the paper of "Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies " no relation with preterm deliveries is mentioned in the F0 generation with POPs , PCB-153, DDE. Only exposure to the outdoor air pollutant 2.5 was found to be related to preterm delivery [12]. But in another paper a direct negative influence on gestational age of PCBs and DDE in pregnancies is described of about 1-3 days in children born in 1960-1963[13].Irregular menstrual periods are described in Taiwanese mothers in relation to levels of dioxins and PCBs in the placenta of their babies [14].

Besides these direct effects transgenerational effects can be expected and these effects can take place via the mother " to be", but also via the father "to be". So semen and its quality is important.

Semen and dioxins.

Problems with semen and later a lower male sex ratio is described after the Seveso incidence, and the Yucheng disaster in women and man exposed in infancy until the age of 20 years [15,16,17]. The lower sex ratio is related to both mothers and fathers. In the Yusho cohort study in the sons and daughters of the exposed parents at any age the sex ratio was lower. And especially in the parents exposed under 20 years the sex ratio was lower; in the second generation the sons and daughters of the exposed mother have a lower sex ratio, but not in the sons and daughters of the exposed fathers. The sex ratio was lowest in daughters of early-exposed Yusho mothers. So it seems that a transmission to the second generation is along the female line. It is not yet clear why the sex ratio is lower after exposure to dioxins and that it is seen especially when exposed below the age of 19 years [18]. The transgenerational effect can be explained by an epigenetic mechanism in the oocyte of the daughter. The effects might be mediated by steroid hormone receptors and both dioxins and PCBs can be anti-estrogenic and anti-androgenic[18] .

Animal studies in mice support the orientation to paternal genes in the F1 generation. Developmental dioxin exposure of both the father and/ or the mother " to be" is associated with an increased risk of preterm birth in adult mice[19]. Authors blame less progesterone responsiveness at the maternal-fetal interface.

Interesting and opening up possibilities for therapy is the finding that preconception omega-3 acid supplementation of adult male mice with a history of developmental 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure prevents preterm birth when they mate with unexposed female partners. Placenta's show a normalization of placental progesterone receptor activity and of toll-like receptor 4 mRNA expression and a marked increase in PGDH expression (15-hydroxyprostaglandin dehydrogenase). This enzyme catabolizes the inflammatory PGE2 (prostaglandin2) in an inactive form. These animal studies suggest that a paternal preconception diet that includes omega-3 fatty acids prevents the toxic response resulting in preterm birth and

restore progesterone activity[20]. A positive effect in general of these fatty acids supplementation is found in a group of infertile men with idiopathic oligoasthenoteratospermia [21].

In conclusion

Recent studies to the (epi)-genetic cause of preterm birth has demonstrated that also paternal genes besides maternal genes can be important like the genes encoding for **AR and IGF1R** in relation with preterm birth. Dioxins can interfere with the androgen receptor. As is shown already in mice studies, a preconceptional (at least 3 months) diet with omega-3-fatty acids as present in nuts and fishoil together with a healthy lifestyle might help to prevent premature birth in the offspring .

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