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REVIEW

The significance of genetics in pathophysiologic models of premature birth

Jose UBEROS *

Neonatal Unit, Hospital Clínico San Cecilio, Granada, Spain

*Corresponding author: Jose Uberos, Neonatal Unit, Hospital Clínico San Cecilio, Granada, Spain. E-mail: juberos@ugr.es

ABSTRACT

INTRODUCTION: Prematurity is a major health problem in all countries, especially in certain ethnic groups and increasing recurrence imply the influence of genetic factors. Published genetic polymorphisms are identified in relation to the 4 pathophysiological models of prematurity described: chorioamniotic-decidual inflammation, premature contraction pathway, decidual hemorrhage and susceptibility to environmental toxins.
EVIDENCE ACQUISITION: The research identified 240 articles, 52 articles are excluded because they are not original, not written in English or duplicated. From them 125 articles were included in qualitative analysis This review aims to update recent knowledge about genes associated with premature birth.
EVIDENCE SYNTHESIS: Polymorphisms in specific genes are responsible, in varying degrees, for prematurity and the different pathogenetic mechanisms are involved.
CONCLUSIONS: The fetus is genetically different from its mother and is recognized as such by the immune system. Generality has shown that maternal physiology adapts to tolerate and nourish the fetus and that both mother and fetus play an active role in the birth process.

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Key words: Infant, premature - Genetics - Epidemiology - Review.

Introduction

Premature birth is one of the most prevalent health problems affecting the pediatric population in developed countries. It represents 8-10% of all births and is associated with 75% of perinatal mortality and 50% of childhood disability. Despite the efforts of clinicians and researchers, the rate of preterm births in developed countries continues to increase. In the USA, it rose from 9.5% in 1981 to 12.7% in 2005. In Denmark, which enjoys universal health coverage and optimal standards of prenatal care, the rate of premature births increased by 22% from 1995 to 2004. Among the risk factors for prematurity, maternal age and ethnicity have been cited.[1] In Spain, the age of mothers of preterm infants with very low birthweight has increased progressively, from an average of 30.3 (SD 5.6) years in 2008 to 34.4 (SD 3.9) years in 2014 (unpublished data).

Regarding ethnicity, the prevalence of prematurity in the black population (16%) is double that in the white population (8.4%).[1] Other factors involved in prematurity and multiple gestations account for 12-27% of all premature births. Other possible predisposing factors that have been considered include infection, stress, poor diet, drug abuse, metabolic imbalance and inherited factors.[1]

The single most significant predictor of pre-

term birth is the existence of a previous preterm birth. Studies of twins and recurrence in families confirm that the recurrence of preterm birth in subsequent pregnancies is 3-7 times higher in medically-induced preterm births and in extremely premature births. Moreover, the risk of recurrent preterm birth at the same gestational age is also increased in the next pregnancy.[2] Therefore, according to some authors,[1] genetics could explain about 40% of the risk of prematurity.

Pathophysiologic models of prematurity

There are three primary categories of prematurity: 1) preterm delivery by medical indication, due to specific situations such as preeclampsia or intrauterine growth restriction, which affect both the mother and the fetus; this category accounts for 30-35% of all premature births; 2) Premature rupture of the membranes, which accounts for 25-30% of preterm births and is intrinsically related to infection, placental abruption or anatomical defects; 3) Spontaneous prematurity, with no clear identifying cause, which accounts for 35-45% of preterm births.[3] Thus, the most numerous of these groups is that of spontaneous preterm birth. From the pathophysiologic standpoint, at least three situations should be considered: increased uterine contractility, cervical dilation and rupture of the membranes.[2]

Romero *et al.*[4] defined four pathophysiologic models of prematurity:

— activation of the maternal-fetal hypothalamic-pituitary-adrenal axis. Factors related to the maternal environment, and/or the genetic susceptibility of the mother, may activate the hypothalamic-pituitary-adrenal axis, thus increasing estrogen production, which interacts with the myometrium to raise the number of gap receptors, oxytocin receptor mRNA levels and prostaglandin F2c activity;[5]

— chorioamniotic-decidual inflammation. In this model, a uterine infection, even if subclinical, can provoke an inflammatory response and the production of inflammatory mediators such as IL-1, IL-8, prostaglandins and proteases. According to some authors,[6] one in three preterm births occur after a subclinical intraamniotic infection. The microorganisms in amniotic fluid culture are the same as are isolated in the genital tract, the most common route of infection being that of ascending colonization. Since 30% of cases of chorioamnionitis are associated with the development of systemic inflammatory response syndrome in the fetus, from an evolutionary standpoint, premature birth in the context of an infection may provide added survival value by allowing the expulsion of infected tissues and thus preserving the future reproductive capacity of the mother.

The vaginal microbiome is more stable during pregnancy than otherwise. The increased presence of steroids is known to increase the quantity of glycogen in the vaginal epithelium and modifies glycosylation, which in turn affects bacterial adherence. Some epithelial cell surface carbohydrates are essential for bacterial adhesion, for example the glycan of the Lewis b blood group with respect to the adhesion of *Helicobacter pylori*. These features of the carbohydrate structure in the epithelia promote bacterial adhesion and may be genetically regulated.

Hyman *et al.*[7] showed that the diversity of the vaginal microbiome during pregnancy is associated with preterm birth, and that race and ethnicity are very significant variables in this process. Furthermore, it has been shown that the placental microbiome is more heterogeneous in preterm than in term infants.[8]

Bleeding from the decidua and the subsequent generation of thrombin provoke a pleiotropic cascade that can damage the fetal membranes and lead to their premature rupture.[5]

Susceptibility to environmental toxins and pathologic uterine contraction/dilatation: the mechanical stretching of the myometrium and the fetal membranes promotes the synthesis of prostaglandins, IL8 and collagenases, which strongly influence cervical ripening, membrane rupture and uterine contractions.[9]

Evidence acquisition

In this study, we analyze articles published in English and recorded in PubMed. The fol-

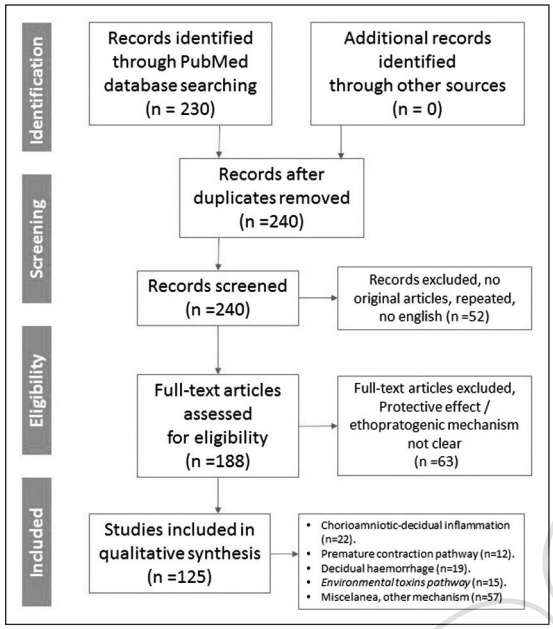

Figure 1.—PRISMA flow diagram.

lowing sequence was used as the search strategy: "Premature birth/genetics" [Majr]. 240 articles were recovered. PRISMA flow diagram is shown in Figure 1. 188 publications significantly associated with genetics and premature birth were reviewed. From them 63 articles were excluded by describing an unclear effect on prematurity. Table I shows the genetic polymorphisms commonly reported to be associated with prematurity grouped by common etiologic groups.[10-32]

Evidence synthesis

Identifying genes in prematurity

A study of twinning, carried out in Sweden,[32] has shown that both low birth weight and prematurity are heritable. These authors recorded a coefficient of genetic relatedness that was 50 times higher among relatives with a history of premature births than in the general population. It has been suggested that polymorphisms in specific genes are responsible, in varying degrees, for prematurity and the different pathogenetic mechanisms are involved.[5]

TABLE I.—*Location and polymorphism of candidate genes with preterm delivery.*

Symbol	Location/mutation - polimorphism	Gene name	References
Premature contraction pathway / maternal and foetal stress pathway			
PGR	11q22-q23 (rs660149)	Progesterone receptor	10
PTGES	9q34.3 (Chr9: 129920794–129935533)	Prostaglandin E synthase	11
CRHR1	17q21.31, (rs7225082, rs4458044, rs173365)	Corticotropin-releasing hormone receptor 1	12
PON1	7q21.3 (rs854552)	Paraoxonase 1 gene	13
KCNN3	1q21.3 (rs1218585, rs4845396, rs12058931, rs1218568, rs6426985, rs4845394)	Potassium channel, Calcium-activated, intermediate/ small conductance, subfamily N, member 3	14
Decidual hemorrhage			
F5	1q23 (1691G>A)	Coagulation factor V	15, 16
MTHFR	1p36.3 (C677T)	Methylenetetrahydrofolate reductase	17, 18
SHMT1	17p11.2 (rs1979277)	Serine Hydroxymethyltransferase, cytosolic	19
Infection/inflammation pathway			
TNFα	6p21.33 (G-308>A)	T*umor necrosis factor-alpha*	20
CSF2	5q31.1 (rs25881)	Colony stimulating factor 2	21, 22
IFNGR1	6q23-q24 (A874T)	Interferon gamma receptor 1	23
IL1A	2q14 (4845G/T)	Interleukin 1, alpha	21, 24
IL1B	2q14.1 (-511C/T)	Interleukin 1, beta	25
IL1R2	2q14.2 (allele 2 Variable number of tandem repeats in intron 2)	Interleukin 1 receptor antagonist	26-28
IL3	5q31.1 (rs7737470, rs3091307, and rs1881457)	Interleukin 3	21
IL4	5q31.1 (rs2243267, rs2243270, and rs11242123)	Interleukin 4	21
IL10	1q31-32 (C>T 819)	Interleukin 10	29, 30
IL10RA	11q23 (rs17121510)	Interleukin 10 receptor, alpha	31
IL12A	3q25.33 (rs7653097)	Interleukin 12A	21
NOS2A	17q11.2-q12	Nitric oxide synthase 2A	32
Environmental toxins pathway			
OPRM1	6q24-q25	Opioid receptor, mu 1	32
CYP2E1	10q26.3 (rs9418990, rs2070673, rs2249695, rs1536826)	Cytochrome P450, Subfamily IIE; CYP2E1	12

Chorioamniotic-decidual inflammation

Candidate genes related to inflammation have been evaluated in several studies and diverse populations.[21] Inconsistently genetic variants of tumor necrosis factor (TNF) and interleukin-1 (IL1) have been associated with risk of preterm delivery. Some of these polymorphisms of point mutations (G-308A) in TNF have shown more prevalent in African-American women and with greater frequency of vaginosis.[33] The presence of vaginosis carries an increased risk of chorioamnionitis and major prevalence of polymicrobial vaginal flora which is associated with increased risk of preterm delivery.[34] Yilmaz *et al.*[25] analyze genetic polymorphisms of TNF alpha (-238G / A, -308G / A), IL-1α (4845G / T), and IL-1β (-511C / T) and observed significant association with preterm birth.

Cui *et al.*[35] and Murtha *et al.*,[27] observed a polymorphism of interleukin-1 receptor (IL1R) associated with an increased risk of preterm labor and premature rupture of membranes (OR 2.02; 95% CI 1.44-2.85 and OR 1.42; 1.02-1.99 respectively).

In a case-control study, Schmidt *et al.*[36] observed two common polymorphisms to the gene for interleukin-1 (IL1): (IL1B + 3953C> T [rs1143634], IL1B -511C> T [rs16944]), the authors note polymorphism IL1B + 3953C> T is associated with a reduced risk of premature delivery it seems equally be related to lower risk of premature birth among the Caucasian population. Murtha *et al.*[27] and Harmon *et al.*[21] observed in a study of 30 genes, association with preterm birth in 6 of them: interleukin 12A (IL12A); colony-stimulating factor-2 (CSF2); interferon γ receptor 2 (IFNGR2); killer cell immunoglobulin–like receptor, three domain, long cytoplasmic tail, 2 (KIR3DL2); interleukin 4 (IL4); and interleukin 13 (IL13). Some of these interleukins, important for the function of NK cells, change dramatically during pregnancy.[37] Wu *et al.*[38] in a meta-analysis of 33 articles analyzed polymorphism located in the interleukin 6 (IL6) promoter region, rs1800795 SNP and note that the rs1800795 CC genotype is protective for preterm birth. Hao *et al.*,[32] found a suggestive association in preterm delivery of haplotypes interleukin 1 receptor 2 (IL1R2), nitric oxide synthase 2A (NOS2A) and opioid receptor mu 1 (OPRM1) at P=0.005 level in Black, White and Hispanic groups, respectively.

Activation of the maternal-fetal hypothalamic-pituitary-adrenal axis (Premature contraction pathway / maternal and fetal stress pathway)

The *CRHR1 gene*, located on chromosome 8, is associated with activity of the corticotropin-releasing factor receptor. Brean *et al.*,[12] analyzed 99 markers for 33 genes in 257 families, using a linkage disequilibrium approach, and identified two genes with evidence of linkage with preterm birth: CRHR1 and CYP2E1 (Cytochrome *P450* gene). The *CRHR1* gene encodes one of the two receptors of CRH. Riley *et al.*,[39] showed that corticotrophin-releasing hormone (CRH) affecting paracrine/autocrine interactions within the placenta, fetal membranes, and decidual that may be involved in the maturation of the fetal hypothalamic-pituitary-adrenal axis and in the stimulus and maintenance of labor. During normal pregnancy CRH is produced by the placenta and secreted into the placental circulation, these levels increase exponentially from week 15 to 36, reaching the highest levels during labor. Women who experience preterm birth have higher levels of CRH, which suggests that the duration of pregnancy is predetermined and activated by CRH levels. Some authors have linked higher prevalence of prematurity in African American women with overexpression of *CRHR1* gene. Menon *et al.*,[40] show the absence of differences in CRH concentration between Caucasian or African American women, this after adjusting the population studied by stressors such as infection or chorioamnionitis. In this line, Klimavicius *et al.*,[41] in histopathologic studies in pregnant women show the expression of CRH receptors in the myometrium and cervix so proportionately less than in non-pregnant women.

Decidual hemorrhage

More than a decade ago that Valdes *et al.*,[42] related genetic variants related to thrombophilia with preterm birth. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that reduces 5.10-methylene tetrahydrofolate (THF) to 5-methyl THF. It is also a cofactor in the methylation pathway from homocysteine to methionine. Multiple variants of the *MTHFR* gene are known, with the most studied being polymorphism C677T, which produces a thermolabile enzyme associated with hyperhomocysteinemia. Engel *et al.*,[19] suggests a possible link between cytosolic serine hydroxymethyltransferase (encoded by SHMT1), and their interaction with folate intake and risk of spontaneous preterm birth and newborn small for gestational age. Gargano *et al.*,[15] relate some phenotypic variants of factor V and angiotensin, with placental bleeding and increased risk of prematurity.

Susceptibility to environmental toxins - Pathologic uterine contraction/dilatation

As discussed earlier, a study by Bream *et al.*,[12] where 99 markers analyzed for 33 genes in 257 families through a linkage disequilibrium approach, identifies two genes with evidence of linkage with preterm birth: *CRHR1* y *CYP2E1*. *CYP2E1,* specifically, encodes a protein that is induced by ethanol and pathologic states like fasting, diabetes, obesity, and high fat diet. Tsai *et al.*,[43] identified interactions of two genes, cytochrome P-450 1A1 (*CYP1A1*) and glutathione S-transferases Theta 1 (*GSTT1*) and their interactions with maternal smoking and prematurity.

The *PON1* gene is located on chromosome 7 and is involved in phospholipid and calcium ion binding mechanisms. Several authors, including Rykman *et al.*,[13] have identified an association between the *PON1* gene and premature birth. The *PON1* gene is a member of the paraoxonase gene family and may affect preterm birth in various ways. Mutations in this gene are associated with changes in the lipid profile (HDL, LDL), thus increasing the production of prostaglandin E_2 and provoking uterine contractions. Other courses of action affect the thrombotic pathways, activating the thrombin cascade and that of plasminogen, which in turn activates the matrix metalloproteinases. The *PON1* gene is believed to be indirectly involved in vasodilation and thrombosis. Hence, interruption of placental blood flow could form part of the pathophysiologic mechanism underlying preterm delivery.

The *KCNN3* gene, located on chromosome 1, has been linked to the activity of the calcium-activated potassium channel. Day *et al.*,[14] in a population of 600 families with preterm infants, analyzed 16 polymorphisms of the *KCNN3* gene and observed a highly significant association. Mann *et al.*,[44] identified the same association in a sample population in Argentina. One of the significant factors in preterm birth is the inactivation of the mechanisms that maintain the balance between intra-uterine contractions and relaxation. The activity of the calcium-activated potassium channel has been associated with relaxation of the myometrium, and so the overexpression of this gene, as observed in the experimental model, may compromise the birth by inducing abnormal uterine relaxation.[45]

Transgenerational epigenetics and prematurity

Preterm birth is the leading cause of infant mortality in industrialized societies. Its incidence is greatly increased among the socially disadvantaged, but the reasons for this excess are unclear and have been relatively unexplored. Several authors have proposed nutritional deficiencies or stressful social as triggers of prematurity among the most disadvantaged social classes.[46]

In some species of insects and plants, environmental phenomena such as humidity and temperature can cause phenotypic changes of epigenetic origin.[47] In humans, some authors have indicated that stress may be a source of transgenerational epigenetic changes associated with low birth weight or prematurity.[48] The possibility that environmental factors may

promote phenotypic changes that are transmitted from one generation to another is an issue that has been addressed by several authors.[49] Epigenetic changes are defined as molecular processes that regulate the activity of the genome without producing changes in the DNA sequence, which is mitotically stable. The best known epigenetic modifications involve DNA methylation, histone modifications or alterations in the structure of chromatin or non-coding RNA.

Transgenerational epigenetic inheritance is defined as the changes that are transmissible from one generation to another in the absence of the environmental exposure that initially triggered them. It requires the transmission of epigenetic information by germ cells, a situation that has been proposed in various studies and which would explain the higher prevalence of prematurity in certain families and social environments.[48] One of the best examples of transgenerational epigenetic inheritance is described by Suderman *et al.*,[50] who reported that the effects of postnatal maternal care can promote epigenetic changes in the hippocampus that facilitate appropriate maternal attitudes in the future. The contrary situation, due for example to stressful situations in the initial periods of life, would produce changes in the brain promoting unfavorable maternal attitudes in later life. Studies using an experimental mouse model have clarified some aspects of the intergenerational transmission of prematurity, showing that stress can affect gestational age over several generations.[51] Parets *et al.*,[3] examined the correlation of maternal and fetal DNA methylation patterns in a cohort of spontaneous premature births among an African-American population and provided new evidence on the role played by transgenerational epigenetic inheritance in prematurity.

Conclusions

Pregnancy involves a semi-holographic relationship between mother and fetus. The fetus is genetically different from its mother and is recognized as such by the immune system. Generality has shown that maternal physiology adapts to tolerate and nourish the fetus and that both mother and fetus play an active role in the birth process. Taking into account these considerations, we present some current findings on the genetics of prematurity, which represent novel aspects in the epidemiology of an issue that is responsible for high levels of mortality and morbidity among the pediatric population.

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