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Smoking and the correlation between birth weight and placental weight. Evidence of interaction with maternal haptoglobin phenotype

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ABSTRACT

Objective: The negative effects of cigarette smoking on human reproduction are well known. In a previous paper we have reported that negative effects of smoking on fertility are observed in women carrying the Haptoglobin (Hp) 2 phenotype only. In the present note we have examined the effect of smoking on the correlation between birth weight (BW) and placental weight (PW) and the interaction with maternal Hp phenotype.
Study design: We have studied 584 consecutive newborns and their healthy mothers from the White population of the central area of Italy. Written informed consent was obtained by mothers to participate to this investigation that was approved by the Department of Pediatrics. Maternal Hp phenotype was determined by the method of Smithies as previously described. Differences between correlation coefficients were evaluated according to Snedecor and Cochran and according to Soper. Difference between means was calculated by Student's-*t* test using commercial software (SPSS).
Results: A strong decrease of correlation is seen in smoking mothers with Hp 2 phenotype only ($p < 0.0001$). No statistically significant effect of smoking is present in mothers with Hp1 or Hp2-1 phenotype. A statistically significant decrease of BW in smoking mothers is observed in both Hp 2 mothers and in mothers carrying the Hp*1 allele. On the contrary a decrease of PW is observed only in mothers carrying Hp*1 allele but not in Hp 2 mothers. This indicates a concordant effect of smoking on BW and PW in mothers carrying Hp*1 allele but a discordant effect of BW and PW in Hp 2 mothers. This could explain the lack of correlation between BW and PW in smoking mothers carrying the Hp 2 phenotype.
Conclusion: The combined phenotype smoking-Hp 2 shows different effects on BW and PW. Hp 2 has no effect on the decrease of BW determined by smoking but shows important effect in neutralizing the decrease of PW due to smoking: Hp polymorphism may be a factor with protective effects prevalent on placental growth as compared to fetal growth.

Introduction

Harmonic growth of the two portions of feto-placental unit would be an optimal situation for fetal development. Indeed the ratio birth weight/placental weight has been correlated with perinatal morbidity and mortality and with cardiovascular diseases in adulthood suggesting that this index is an important clinical parameter [1,2]. We have proposed the correlation between birth weight (BW) and placental weight (PW) as an index of a balanced intrauterine development: this parameter allows also the calculation of the proportion of birth weight variance that can be explained by placental weight. Such correlation is lower than 0.60: therefore less than 40% of BW variance can be explained by PW suggesting that there are factors that influence in a concordant manner BW and PW and many others that influence in an independent manner the two parameters.

The negative effects of cigarette smoking on human reproduction are well known: disturbance of maternal cycle, anticipation of menopause, increased risk of abortion, ectopic pregnancy and reduction of fetal growth have been well documented [3–5] (Fig. 1).

In a previous paper we have reported that negative effects of smoking on fertility are observed in women carrying the Hp 2

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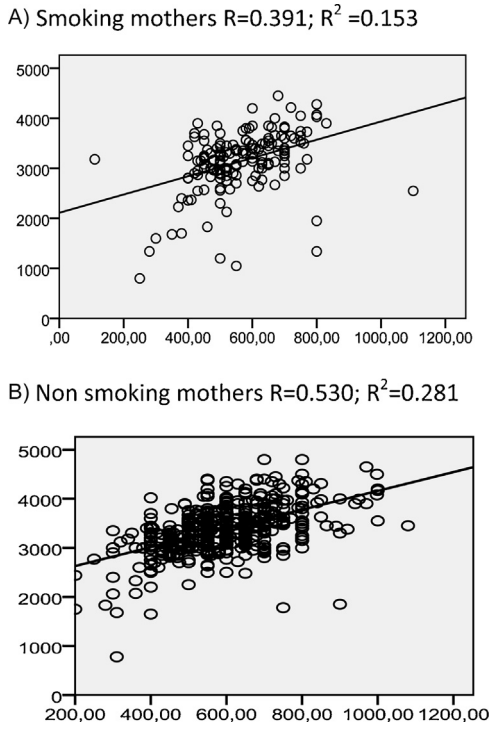

Fig. 1. Correlation between birth weight and placental weight. *X* axis = Placental weight, *y* axis = Birth weight.

phenotype only [6]. In the present note we have examined the effect of smoking on the correlation between BW and PW and the interaction with maternal Hp phenotype.

The polymorphism of haptoglobin

Haptoglobin (Hp) is a polymorphic α2-sialoglycoprotein that in blood plasma binds free hemoglobin released from erythrocytes inhibiting the formation of reactive species. Hp presents three common genotypes (phenotypes) Hp*1/*1 (Hp 1), Hp*2/*1(Hp 2/1) and Hp*2/*2 (Hp 2). It is composed of a α-chain and a β-chain and its polymorphism is due to an intragenic duplication in the α-chain. Hp*1/*1 polypeptides form tetrameric small molecules $(Hp1\alpha\text{-}Hp\beta)_2$ that at electrophoresis migrate as a single band, Hp*2/*1 polypeptides form heteropolymer linear molecules $(Hp1\alpha\text{-}Hp\beta)_m$ $(Hp2\alpha\text{-}Hp\beta)_m$, and Hp*2/*2 polypeptides form cyclic homopolymer molecules$(Hp2\alpha\text{-}Hp\beta)_m$ that migrate as a series of slowest bands. Compared with other genotypes Hp*1/*1 produces more protein and smaller polymers that may diffuse more readily in the tissues. The molecular mass of the phenotypes is as follows: Hp1 86 kDa, Hp2/1 86–300 kDa, Hp2 170–900 kDa [7]. There is evidence of functional differences between polymers of Hp2-1 and polymers of Hp2 phenotypes [8].

This protein protects against hemoglobin peroxidation and its phenotypes have been linked to several diseases such as coronary artery disease, type 1 diabetes, Crohn's disease, inflammatory diseases, Parkinson, malaria, moreover it may be an indicator of neonatal jaundice, a predictor of nephropathy in type 2 diabetes and shows a protective role in the brain after intra-cerebral hemorrhage [9–17].

The antioxidant property of Hp may have a role of preeminent importance at implantation and during the first stages of development, protecting the embryo from oxidative damage. Previous studies by our group suggest that women with Hp 1 phenotype reproduce at earlier age and have a higher reproductive potential as compared to women with other Hp phenotypes [18]. The Hp*1 allele produces more protein that is associated with an increased production of the antioxidant cytokine and smaller polymers that diffuse more readily at the site of implantation. Conversely, the Hp*2 allele produces less protein and large molecules that may diffuse less readily at the site of implantation [7].

Material and Methods

We have studied 584 consecutive newborns and their healthy mothers from the White population of the central area of Italy.

Written informed consent was obtained by mothers to participate to this investigation that was approved by the I.R.B.

Maternal Hp phenotype was determined by the method of Smithies [19] as previously described [18].

Differences between correlation coefficients were evaluated according to Snedecor and Cochran [20] and according to Soper [21]. Difference between means was calculated by Student's-*t* test using commercial software (SPSS).

Results

Table 1 shows the demographics of the study population.

Table 2 shows the BW–PW correlation in relation to maternal smoking. Smoking decreases the correlation coefficient.

Table 3 shows the BW–PW correlation in relation to maternal smoking and Hp phenotype. A strong decrease of correlation is seen in smoking mothers with Hp 2 phenotype only ($p < 0.0001$). No statistically significant effect of smoking is present in mothers with Hp1 or Hp2-1 phenotype.

We have examined the possible effect of maternal age and gestational age on the pattern of relationship reported in Table 3. No appreciable effect has been observed concerning gestational age (≤38 weeks vs. >38 weeks). Maternal age has shown a significant effect: while in very young mothers (<24 years) no significant difference is observed between Hp 2 and other Hp phenotypes, such difference is very marked in mothers aging more than 24 years.

Table 4 reports the distribution of BW and PW in the relation to smoking and Hp phenotypes. A statistically significant decrease of BW in smoking mothers is observed in both Hp 2 mothers and in mothers carrying the Hp*1 allele. On the contrary a decrease of PW is observed only in mothers carrying Hp*1 allele but not in Hp 2 mothers. This indicates a concordant effect of smoking on BW and PW in mothers carrying Hp*1 allele but a discordant effect of BW and PW in Hp 2 mothers. This could explain the lack of correlation between BW and PW in smoking mothers carrying the Hp 2 phenotype.

Comment

The present data suggest that the effects of smoking on the correlation between BW and PW are dependent on maternal Hp phenotype. In presence of Hp 1 and Hp 2-1 phenotypes there is practically no effect of smoking on BW/PW correlation while this effect is very marked in mothers with Hp 2 phenotype. Similar differences have been previously observed for fertility parameters [6]. The low correlation between BW and PW observed in smoking mothers carrying the Hp 2 phenotype could be explain by the fact that while in presence of Hp 1 or Hp 2-1 phenotype smoking is associated with both low BW and low PW, in presence of Hp 2 phenotype smoking is associated with low BW but not with a significant decrease of PW.

Both HP2-1 and Hp 2 are formed by polymers with a higher molecular weight compared to Hp 1. The molecular conformation of Hp 2-1 polymers however, is different from that of Hp 2