

Rh system and intrauterine growth. Interaction with season of birth

F. Gloria-Bottini^a, G.F. Meloni^b, A. Finocchi^a,
S. Porcu^b, A. Amante^a and E. Bottini^{a,*}

^a*Chair of Preventive and Social Pediatrics, University of Rome Tor Vergata, School of Medicine, Rome, Italy*

^b*Department of Pediatrics, University of Sassari, School of Medicine, Sassari, Italy*

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Based on the hypothesis that maternal-fetal genetic differences in membrane transport and signal transduction may influence intrauterine development, the recent acquisition on transport function of Rh protein prompted us to study the relationship between joint maternal-fetal Rh phenotype and birth weight. Considering that metabolic effect of maternal-fetal competition could be amplified by environmental conditions, we have investigated possible seasonal effects on such relationship.

We have studied 5291 infants born in Sardinia in the period January 1993–December 1996 and 984 infants born in Rome during 1996.

In Rh(–) mothers there is a significant association between season of birth and birth weight that shows the highest mean value in infants born in autumn (i.e. conceived in winter). The association is much more evident in male than in female infants. In male infants from Rh(–) mothers, the association between birth weight and season is significant in Rh(+) male newborns only.

Recent observations by our group in NIDDM suggest that glucose transport in RBC may be related to D protein, thus we propose an interpretation of the present observation in terms of transport function. When the density of D protein in the infant is greater than in the mother, the balance is in favour of the infant who may attain a significant developmental advantage when conceived in the cold season.

Keywords: Rhesus system, intra-uterine growth, seasonality

*Correspondence to: Prof. Egidio Bottini, Dipartimento di Biopatologia e Diagnostica per Immagini, Facoltà di Medicina, Via della ricerca scientifica, snc, 00133 Roma, Italy. Tel.: +39 6 72596030; Fax: +39 6 72596028; E-mail: bottini@med.uniroma2.it.

1. Introduction

Recent studies have shown that Rh locus is composed of two genes: RhD, which encodes the major D antigen and is present only in Rh-positive genomes, and RhCE, which encodes both Cc and Ee polypeptides, most likely by alternative splicing events. Several membrane components including the Rh proteins and other glycoproteins recently characterized are probably different subunits of an oligomeric complex with transport function in the erythrocyte [3,9,13]. Rh may play an important role in the organization of membrane phospholipids and/or membrane expression of various glycoproteins [1]. Variations of lipid bilayer, on the other hand, could influence the function of various proteins involved in substrate transport and signal transduction [5]. Indeed recent observations by our group suggest that genetic variability of Rh proteins may influence glucose transport in the erythrocyte [6].

Maternal-fetal genetic differences within the normal variability in membrane transport and signal transduction could contribute significantly to the normal variability of intrauterine developmental parameters [2]. Moreover, effects of maternal-fetal competition connected with differences in relative efficiency of substrate transport and/or signal transduction could be amplified by environmental conditions including seasonal variation [7,8].

In the present note we have searched for possible effects of joint mother-newborn Rh phenotype on intrauterine growth in two samples of consecutive infants from healthy puerperae.

2. Subjects and methods

A consecutive sample of 5291 infants including all newborns delivered in the period January 1993–December 1996 in the Maternity Department of the University of Sassari and a consecutive sample of 984 infants including all newborns delivered during 1996 in the Maternity Department of the University of Rome Tor Vergata have been studied along with their mothers.

Table 1
Birth weight, season of birth and maternal Rh phenotype. Values marked with asterisk refer to analysis on \log_{10} of birth weight

	Males						Females					
	Mother Rh(-)			Mother Rh(+)			Mother Rh(-)			Mother Rh(+)		
	mean(g)	S.E.	n°	mean(g)	S.E.	n°	mean(g)	S.E.	n°	mean(g)	S.E.	n°
Sassari												
winter	3203	74	39	3310	21	622	3212	58	46	3173	19	616
spring	3352	93	32	3304	21	633	3201	97	35	3170	20	559
summer	3319	65	35	3285	19	677	3274	56	45	3181	20	624
autumn	3449	86	32	3304	20	652	3331	67	36	3139	19	608
Rome												
winter	2868	219	12	3249	63	93	3155	93	10	3218	53	103
spring	3252	108	17	3310	49	120	3026	178	14	3162	46	103
summer	3164	119	14	3296	48	135	3102	130	15	3126	45	99
autumn	3456	131	14	3307	42	122	3254	155	14	3228	46	99
Variance analysis												
Main effect	0.007	0.006*		N.S.			N.S.			N.S.		
Season	0.009	0.009*		N.S.			N.S.			N.S.		
Population		N.S.		N.S.			N.S.			N.S.		
Interaction		N.S.		N.S.			N.S.			N.S.		

Rh(D) blood group was determined according to standard laboratory method. Variance analysis was performed by SPSS programs [12]. The procedure was carried out on both \log_{10} of birth weight and on raw data.

Among Rh(-) mothers a direct Coombs test was present in 6 newborns in Sassari (Sardinia) and in 2 newborns in Rome. Excluding these subjects from analyses, the results in Table 1 and in Table 2 remain practically unchanged.

In few infants Rh determination has not been performed: this explains the fact that the number of male newborns from Rh(-) mothers is greater in Table 1 than in Table 2.

3. Results

Table 1 shows the weight of newborns in relation to season of birth and to Rh phenotype of the mother. In male infants from Rh(-) mothers there is a significant association between birth weight and season of birth. The association is significant after Bonferroni correction for multiple comparison. Variance analysis evaluates the effects of the two independent variables: season of birth (four categories) and population (two categories: Sassari and Rome) on birth weight (dependent variable). Overall (main effect) there is a significant effect on birth weight in males from Rh(-) mothers. This effect is due to season while the variable population has no significant effect and there is no significant interaction between the two independent variables, sea-

son and population. In brief, the analysis shows that the effect of season on birth weight in male newborns from Rh(-) mothers is the same in Rome and Sassari.

Tukey test has shown that birth weight is significantly lower in infants born in winter than in infants born in autumn. Such difference is 246 g in Sassari and 588 g in Rome. The mean value of difference (weighted for the different number of newborns in the two samples) is 327 g ($p < 0.003$; after correction for multiple comparison $p < 0.02$).

The strength of association among birth weight, Rh and season of birth seems slightly variable in different years. In the population of Sassari a higher birth weight in male infants born in autumn from Rh(-) mother has been observed in 1993, 1994 and 1995 but not in 1996 (data not shown).

An analysis of gestational duration in relation to season of birth and Rh phenotype of the mother has shown no significant association.

An analysis of variance and covariance has also been performed considering as dependent birth weight and as independent season of birth, population and gestational duration (covariate). Controlling for the effect of gestational duration, the association between birth weight and season of birth remains significant.

Table 2 shows the weight of male newborns in relation to season of birth and Rh phenotype. The association between birth weight and season is significant in Rh(+) male newborns from Rh(-) mothers only.

Rh(D) distribution in mothers and infants (all infants and males and females separately) has not shown significant association with season of birth. Possible

Table 2
Birth weight in relation to season of birth and Rh phenotype in male newborns. Values marked with asterisk refer to analysis on \log_{10} of birth weight

mother infant	Rh(-)			Rh(-) Rh(+)			Rh(+) Rh(-)			Rh(+) Rh(+)		
	mean(g)	S.E.	n°	mean(g)	S.E.	n°	mean(g)	S.E.	n°	mean(g)	S.E.	n°
Sassari												
winter	3303	200	6	3200	82	30	3248	111	27	3313	20	578
spring	3422	87	12	3343	144	19	3314	108	28	3312	21	590
summer	3223	326	3	3315	67	31	3318	76	32	3287	20	634
autumn	3204	153	9	3545	98	23	3365	147	29	3303	20	604
Rome												
winter	3165	325	2	3075	221	8	3433	179	3	3292	58	83
spring	3320	208	6	3214	129	11	2974	157	10	3389	41	107
summer	3252	252	5	3114	131	9	3228	139	13	3323	51	119
autumn	3486	177	5	3439	186	9	3201	134	16	3326	44	105
Variance analysis (effects of season of birth and locality (population) on birth weight)												
Main effect	N.S.			0.027 0.045*			N.S.			N.S.		
Season	N.S.			0.025 0.043*			N.S.			N.S.		
Population	N.S.			N.S.			N.S.			N.S.		
Interaction	N.S.			N.S.			N.S.			N.S.		

distortion of the joint mother-infant Rh distribution in relation to season of birth has been examined without significant results.

4. Discussion

Because of the clinical relevance of hemolytic disease of the newborn due to maternal-fetal incompatibility in Rh blood groups, studies on this system have been focused on immunological aspects. These studies eventually relieved the clinical burden but shadowed the biological problem of maintenance of a polymorphism showing a strong heterozygote disadvantage. It is likely that the hemolytic disease of the newborn is an accidental phenomenon largely compensated by a still unknown advantage connected with some important function of Rh system in the maternal-fetal relationship.

Recently, it has been shown that Rh is a transport protein. In addition, we have recently shown that in NIDDM the mean level of glycosylated Hb (HbA1c) is higher in Rh(+) than in Rh(-) suggesting that glucose transport in red blood cells may be related to Rh protein [6]. This prompted us to search for a possible relationship between Rh system and intrauterine development in a perspective of maternal-fetal difference in transport-function.

As pointed by Sing et al. [11], the first step in the analysis of genetic architecture of multifactorial variables including developmental parameters and common diseases is the estimate of the joint distribution

of genetic and environmental causal agents. Moreover, when studying the effect of genetic and environmental factor on intrauterine development an obvious subdivision is that between males and females [11]. In fact is well known that these two classes show differences in the pattern of intrauterine development, endocrine functions and metabolism.

The present data from two unrelated populations show that in newborns from Rh(-) mothers the birth weight is higher in those conceived in the winter (born in autumn) than in those conceived in other seasons. The phenomenon is very clear in Rh(+) newborns conceived by Rh(-) mothers, suggesting an involvement of Rh system in the maternal-fetal metabolic relationship with selective effects opposite to that of Rh hemolytic disease.

Assuming that maternal-fetal genetic differences within the normal variability of receptors, membrane transport and signal transduction could contribute significantly to the normal variability of intrauterine development [2,4], we propose a metabolic interpretation centered on maternal-fetal differences in transport rate depending on the joint Rh phenotype. If the density of D protein is greater in the infant than in the mother, the balance would be in favour of the infant who may take advantage for its development when he is conceived in the cold season (and born in autumn). Such effects are much more evident in males than in females.

At present, however, the possibility that the association is causally due to some gene near Rh and in linkage disequilibrium with it cannot be excluded. In fact, a number of genes with important metabolic functions

are clustered on the short arm of chromosome 1. Starting from telomere there are the following loci: Glucose Dehydrogenase, 6-Phosphogluconate Dehydrogenase, (Rh cluster), UDP Galactose-6-Epimerase, Glucose Transporter Protein 1, Glucose Transporter Protein 5, Phosphoglucomutase-1, Amylase loci (AMY1A – salivary; AMY1B – salivary; AMY2A – pancreatic; AMY2B – pancreatic) [10].

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