Influence of the mother's preceding pregnancy on the gestation length of the current pregnancy. An immunological explanation?

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Abstract

Introduction. A number of epidemiological studies on various diseases have drawn attention to relationships between fetal life events, as measured by health indicators and pathological events later in life. This accounts for the renewed interest in fetal health indicators.The objective of this retrospective study is to investigate the relationship between the sex of conceptuses of the mother's preceding pregnancies and the gestation length of the current pregnancy.

Methods. A population of 7773 neonates were divided into cohorts, according to the sex of the current neonate and number and sex of the mother's preceding pregnancies. Average gestation lengths for each cohort were measured and compared between different configurations of preceding pregnancies.

Results. There a positive association between the length of gestation of the neonate and its mother's preceding pregnancies of same sex as its own. Gestation length increases with the number of conceptuses of same sex among the preceding pregnancies. Likewise, there is a negative association between the length of gestation of the neonate and its mother's preceding pregnancies of opposite sex to its own. Gestation length decreases with the number of conceptuses of opposite sex among the preceding pregnancies.

Discussion. The results of our study are compatible with the immunological hypothesis, based on the sex-linked concepto-gravidic antigenic dissimilarity, proposed to explain the association between preceding pregnancy and fetal development.

Conclusion. The influence of the preceding pregnancy is significant enough to be taken into account for effective management of current pregnancies as well as for efficient clinical trial analysis.

Introduction

A number of epidemiological studies dealing with various diseases have drawn attention to relationships between fetal life events, as measured by health indicators, and pathological events later in life (Aihie Sayer et al., 1997; Barker, 1997, 2004; Elo and Preston, 1992; Harding, 2001; Kajantie et al., 2005; Mittwoch, 1993; Thompson et al., 2001). This accounts for the renewed interest in fetal health indicators. A recent analysis of 27,243 neonates has shown a significant association between the mother's preceding pregnancies and fetal development and neonatal survival (Vernier et al., 2010). A positive association was found when current conceptus and conceptuses of preceding pregnancies were of the same sex, and a negative association when they were of opposite sex. An immunological hypothesis was put forward to explain the phenomenon. It is based on the sex-linked concepto-gravidic antigenic dissimilarity, due to paternal antigens of the conceptus, and capable of affecting fetal development and neonatal survival through a selective implantation process (Vernier et al., 2010).

Early in gestation, the implantation of the blastocyst is a critical stage that almost half of the conceptuses fail to achieve (Bjercke, 1999; Clark, 2003; Norwitz et al., 2001; Tyler, 1961; Vatten and Skjaerven, 2004). Implantation seems to be immunologically controlled (Kirby et al., 1967; Simmons and Russel, 1966; Tyler, 1961). Both male and female conceptuses can induce an immune reaction from the gravida. The concepto-gravidic dissimilarity, due to paternal antigens of the conceptus, favors the implantation of the blastocyst (Ackerman et al., 1988; Billington, 1964; James, 1965; Novitski and Sandler, 1956; Tyler, 1961; Vatten and Skjaerven, 2004), provides a selective advantage to the latter (Bruckner and Catalano, 2007; Vatten and Skjaerven, 2004; Warburton and Naylor, 1971), and primes the gravida vis-à-vis some paternal antigens. Then, on the occasion of a subsequent pregnancy, the previous sensitization of the gravida reduces both the concepto-gravidic dissimilarity effect and the implantation advantage (Niswander and Gordon, 1972; Novitski and Sandler, 1956; Vernier, 1975; Warburton and Naylor, 1971). Thus, the blastocyst carrying a given set of sex-linked paternal antigens, against which the mother has been previously sensitized, would implant less easily than the blastocyst whose mother has not been so exposed. However, if the former survives the implantation it will be stronger than the latter to pursue the gestation. This translates, in population terms, to survival of the strong and culling of the weak (Bruckner and Catalano, 2007; Wells, 2000; Trivers and Willard, 1973), as expressed in fetal development and neonatal survival differentials (Vernier et al., 2010). The objective of the present retrospective study is to investigate the relationship between the sex of conceptuses of the mother's preceding pregnancies and the gestation length of the current pregnancy.

Materials and Methods

The basic data are derived from the Child Health and Development Studies (CHDS). Between August 1959 and September 1966, ~ 20000 pregnant women, members of the Kaiser Foundation Health Plan residing in the San Francisco – East Bay area, reported for prenatal care in some Kaiser clinics. They constituted the CHDS study population. Data on parents and children were obtained from interviews and medical records. The study population represented a broad range of economic, social and educational characteristics, and was not atypical of an employed population (Van den Berg et al., 1988). The current Length of Gestation Study is based on a sample of the CHDS population which included 7773 neonates who were alive at the time of hospital discharge, and whose mothers had been interviewed about their reproductive history. Multiple births and newborns from diabetic mothers were excluded from the study. The neonates were divided into cohorts according to the sex of the current neonate and the number and sex of the mother's preceding pregnancies. Comparisons were made between pairs of cohorts of the same sex and parity but with different configurations of preceding pregnancies. The analysis included parity one, two, three, and four or more, and the 'dose effect' of preceding pregnancies.

Results

Characteristics of the participants in the Length of Gestation Study.

TABLE 1

Gestation length of male and female neonate and mother's parity.

The gestation length of the male neonate is shorter than the gestation length of the female neonate, for each parity of the mother (Table 2). The difference between the gestation length of male and female neonates increases with the mother's parity. The average difference, for all parities is 0.56 day. The gestation length of a male neonate born from a primiparous mother is slightly longer than the gestation length of a male neonate born from a multiparous mother (280.75 vs. 280.36 days). The gestation length of a female neonate born from a primiparous mother is slightly shorter than the gestation length of a female born from a multiparous mother (280.96 vs. 281.07days). In general, the gestation length of a male or female neonate increases for the first three parities of the mother (Table 2).

TABLE 2

Gestation length of male and female neonate and mother's preceding pregnancies.

The gestation length of a male neonate born after a male preceding pregnancy of its mother lasts 0.58 day longer than the gestation length of a male neonate born after a female preceding pregnancy of its mother (Table 3). The gestation length of a male neonate born after 2 male preceding pregnancies of its mother lasts 3.76 days longer ($P < 0.05$) than the gestation length of a male neonate born after 2 female preceding pregnancies of its mother. The gestation length of a male neonate born after 3 or more male preceding pregnancies of its mother lasts 3.72 days longer ($0.05 < P < 0.10$) than the gestation length of a male neonate born after 3 or more female preceding pregnancies of its mother (Table 3).

TABLE 3

The gestation length of a female neonate born after a female preceding pregnancy of its mother lasts 1.44 day longer ($0.05 < P < 0.10$) than the gestation length of a female neonate born after a male preceding pregnancy of its mother (Table 4). The gestation length of a female neonate born after 2 female preceding pregnancies of its mother lasts 2.49 days longer than the gestation length of a female neonate born after 2 male preceding pregnancies of its mother. The gestation length of a female neonate born after 3 or more female preceding pregnancies of its mother lasts 0.14 day longer than the gestation length of a female neonate born after 3 or more male preceding pregnancies of its mother (Table 4).

TABLE 4

The value of the gestation length of the neonate, born after mixed (male and female) preceding pregnancies of its mother, stands between "after all female" and "after all male" preceding pregnancies (Tables 3 and 4).

Discussion

Influence of the conceptus' sex and mother's parity on gestation length.

The gestation length of neonates increases slightly for the first three parities of the mother and decreases at higher parities. The gestation length of a female neonate is longer than the gestation length of a male neonate for each parity. The mean difference between male and female neonate is about half (.56) a day, in favor of the female neonate. The difference between female and male neonates increases with the mother's parity for the first four parities, and levels off at higher parities. Inversely, the gestation length ratio decreases with the mother's parity (Table 2).

Influence of the sex of the conceptuses of the mother's preceding pregnancies on gestation length of the current pregnancy.

The gestation length of the neonate, born after same sex preceding pregnancies as its own, is longer than the gestation length of the neonate born after opposite sex preceding pregnancies. This difference increases with the number of same sex preceding pregnancies, and decreases with the number of opposite sex preceding pregnancies (Table 5).

TABLE 5

There is a positive association between the length of gestation of the neonate and its mother's preceding pregnancies of the same sex as its own (Table 5). Thus, the value of the gestation length of the male neonate increases with the number (dose effect) of male conceptuses (zero, one, two …) among the mother's preceding pregnancies (Table 3). Similarly, the value of the gestation length of the female neonate increases with the number (dose effect) of female conceptuses (zero, one, two …) among the mother's preceding pregnancies (Table 4).

There is a negative association between the length of gestation of the neonate and its mother's preceding pregnancies of opposite sex to its own (Table 5). Thus, the value of the gestation length of the male neonate decreases with the number (dose effect) of female conceptuses (zero, one, two, three …) among the mother's preceding pregnancies (Table 3). Likewise, the value of the gestation length of the female neonate decreases with the number (dose effect) of male conceptuses (zero, one, two …) among the mother's preceding pregnancies (Table 4).

Factors of variation of the gestation length.

There are many factors purporting to influence gestation length in the literature. They can be classified into three groups that relate to the conceptus, its parents (mostly the mother), and the reproductive environment (Adams et al., 1997; Conney et al., 2006; Chan and Lao, 2009; DeFranco et al., 2007; Kajantie and Raikkonen, 2010; Lunde et al., 2007; McLean et al., 1995; Mittendorf et al., 1999; Smith et al., 2003; Svensson et al., 2009). They are often associated with gestation length through the conceptus'sex and/or the mother's parity. Our analysis rests on comparisons of cohorts of neonates of same sex and mother's parity which controls, in part, for the potential confounding effect of these factors. Moreover, we are not aware of any factors having revealed similar patterns of variation in gestation length with preceding pregnancies, as observed here. However, three early health indicators, birth weight, placenta weight and neonatal survival, have recently been shown to have the same pattern of association with the preceding pregnancies as the one shown by gestation length in our study (Vernier et al. 2010). The same pattern for the four indicators suggests a common operating mechanism which could explain the results of the present study.

The sex-linked concepto-gravidic dissimilarity and the length of gestation.

The results of our study are compatible with the immunological hypothesis proposed to explain the association between the mother's preceding pregnancies and fetal development, where gestation length is one of the indicators (Vernier et al., 2010). The hypothesis is based on the sex-linked concepto-gravidic antigenic dissimilarity, due to the paternal antigens of the conceptus and capable of affecting the gestation length through the implantation-selection process. During a first pregnancy, the sex-linked antigenic dissimilarity between the conceptus and the gravida favors the implantation of the blastocyst (Ackerman et al., 1988; Billington, 1964; James, 1965; Novitski and Chandler, 1956; Tyler, 1961; Vatten and Skjaerven, 2004), provides a selective advantage to the latter (Bruckner and Catalano, 2007; Vatten and Skjaerven, 2004; Warburton and Naylor, 1971) and primes the gravida vis-à-vis sex-linked antigens. On the occasion of a subsequent pregnancy, the sensitized gravida will tend to "attack" the blastocyst carrier of the same antigens against which she has been sensitized previously. This would reduce its chances of succeeding the implantation, but if it does succeed it would come out stronger to complete the rest of gestation (Niswander and Gordon, 1972; Novitski and Sandler, 1956; Vernier, 1975; Warburton and Naylor, 1971). This translates in population terms to survival of the strong and culling of the weak (Bruckner and Catalano, 2007; Wells, 2000; Trivers and Willard, 1973). Differences in the value of the indicators of fetal development, including gestation length, would then occur in relation to the presence or absence of sex specific antigens in the conceptus, as indicated by the neonate's sex. The phenomenon persists at parity three, even more rigorously, and sometimes at parity four. Subsequently, since only a few paternal antigens remain which have not been exposed to the gravida, the implantation selection increase levels off or even reverses. Conversely, this could be due to the fact that some types of maternal antibodies will only develop, if at all, at parity one, two or three (Gualtieri and Hicks, 1985).

Conclusions

Length of gestation, like three other early life indicators – birth weight, placenta weight and neonatal survival rate – follows the same distribution pattern regarding the sex of the conceptus, the mother's parity, and the mother's anterior reproductive history. The immunological mechanism, proposed to explain the association between the mother's preceding pregnancies and selection, development and survival of the conceptus, could contribute to elucidate the mechanism linking fetal life and adult disease or health. To test the consistency of our results, a prospective study using a larger sample size would address two of the limitations of our study.

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Table 1. Characteristics of the participants in the Length of Gestation Study

Number of neonates	#	7773
Sex (%)	Male	50.9
	Female	49.1
	Sex ratio	1.07
Birth weight (oz.)	Mean	117.92
	SD	17.93
Placenta weight (g)	Mean	460.7
	SD	9.4
Mother's age (years)	Mean	26.4
	SD	5.9
Father's age (years)	Mean	29.9
	SD	6.7
Mother's race (%)	White	68.33
	Black	26.01
	Others	5.66
Mother's parities (%)	Primiparous	31.03
	Parity 2	24.16
	Parity 3	18.81
	Parity 4-7	25.99
Length of gestation (days)	Mean	280.76
	SD	15.36
	Max	381
	Min	165
Length of gestation of male neonate (days)	Mean	280.48
	SD	15.13
Length of gestation of female neonate (days)	Mean	281.04
	SD	16.24
Length of gestation distribution (%)	< 266 days	11.05
	266-279 days	32.25
	280-293 days	42.09
	> 293 days	14.58

Table 2. Gestation Length according to the sex of the neonate and the mother's parity.

	Male neonate			*Female neonate*			*GL difference*	*GL ratio*
Parity	n	mean	SD	n	mean	SD	female-male	M/F x 100
1	1235	280.75	15.28	1152	280.96	17.73	0.21	99.93
2	923	280.91	15.59	936	281.12	15.46	0.21	99.93
3	730	280.94	14.48	717	282.13	14.90	1.19	99.58
4	481	279.38	14.71	433	281.10	18.12	1.72	99.39
5-7	549	279.52	16.72	537	279.55	15.64	0.03	99.99
1-7	3918	280.48	15.13	3775	281.04	16.24	0.56	99.80

Table 3. Gestation Length (GL) of male neonates born after same-sex preceding pregnancies (SSPP) or opposite-sex preceding pregnancies (OSPP).

		n	*Mean* (in days)	*SSPP-OSPP* T-test
Male neonate at parity 1		1235	280.75	
Male neonate at parity 2		822	280.75	
Born after a male PP	M M	434	281.02	MM-FM=0.58 day
Born after a female PP	F M	388	280.44	t=0.2992 ns
Male neonate at parity 3		551	280.97	
Born after 2 male PP	MM M	167	281.93	MMM-FFM=3.76 days
Born after 2 mixed PP	mixed M	261	281.67	t =0.0137
Born after 2 female PP	FF M	123	278.17	*P* <0.05
Male neonate at parity 4+		583	278.26	
Born after 3+ male PP	MMM M	81	281.2	MMMM-FFFM=3.72 days
Born after 3+ mixed PP	mixed M	419	277.85	t=0.0797
Born after 3+ female PP	FFF M	83	277.48	0.05< *p* <0.10

Table 4. Gestation Length (GL) of female neonates born after same-sex preceding pregnancies (SSPP) or opposite-sex preceding pregnancies (OSPP).

		n	*Mean* (in days)	*SSPP-OSPP* T-test
Female neonate at parity 1		1152	280.96	
Female neonate at parity 2		851	281.05	
Born after a male PP	MF	455	280.38	FF-MF=1.44 day
Born after a female PP	FF	396	281.82	t=0.0886 $0.05 < p < 0.10$
Female neonate at parity 3		536	282.05	
Born after 2 male PP	MMF	127	280.55	FFF-MMF=2.49 days
Born after 2 mixed PP	mixed F	296	282.31	t =0.1153
Born after 2 female PP	FFF	113	283.04	ns
Female neonate at parity 4+		551	280.69	
Born after 3+ male PP	MMMF	75	280.89	FFFF- MMMF=0.14 day
Born after 3+ mixed PP	mixed F	417	280.6	t=0.4758
Born after 3+ female PP	FFFF	59	281.03	ns

Table 5. Gestation Length of neonate born after same-sex preceding pregnancies or opposite-sex preceding pregnancies.

	Parity	N	*gestation length* Mean (in days)	std dev
Neonate born after same-sex preceding pregnancies				
Male neonate				
Primiparous	1	1235	280.75	15.28
Born after 1 male preg	2	434	281.02	15.52
Born after 2 male preg	3	167	281.93	13.77
Born after 3 male preg	4+	81	281.20	18.72
Female neonate				
Primiparous	1	1152	280.96	17.73
Born after 1 female preg	2	396	281.82	15.18
Born after 2 female preg	3	113	283.04	16.15
Born after 3 female preg	4+	59	281.03	12.09
Neonate born after opposite-sex preceding pregnancies				
Male neonate				
Primiparous	1	1235	280.75	15.28
Born after 1 female preg	2	388	280.44	16.01
Born after 2 female preg	3	123	278.17	14.93
Born after 3 female preg	4+	83	277.48	14.79
Female neonate				
Primiparous	1	1152	280.96	17.73
Born after 1 male preg	2	455	280.38	15.80
Born after 2 male preg	3	127	280.55	15.90
Born after 3 male preg	4+	75	280.89	14.04