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Environmental Influences that May Precede Fertilization: A First Examination of the Prezygotic Hypothesis from Maternal Age Influences on Twins

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The prezygotic hypothesis considers the possibility that development is subject to environmental influences on the oocyte prior to conception. Such influences may occur in the maternal grandmother's uterus where oogenesis is completed or in the mother before fertilization. According to this hypothesis, the separate eggs from which DZ twins are derived may be sensitive to microenvironmental variations within an ovary. As a first approach, we examined same-sex MZ and DZ twins for maternal age effects on differences between pairs in cognitive and behavioral traits. While no differences between MZ and DZ pairs were found that would indicate a major effect of the prezygotic environment, suggestions are made for further experimental studies of this unexplored question in human development.

KEY WORDS: Twins; prezygotic hypothesis; cognition; behavior; oocyte.

INTRODUCTION

We consider how human development may be subject to environmental influences that occur prior to conception. Traditional analyses of environmental effects on human behavioral development largely focus on postnatal domains, with some consideration of prenatal influences, when possible, that include intrauterine exposure to variations of hormones, nutrients, toxins, viruses etc. However, the oocytes supplied by the female of the mating pair are also subject to environmental effects that can extend several decades before the zygote is formed at fertilization. In chronological order, there are two distinct prenatal domains experienced by the oocyte (egg cell) before fertilization (Fig. 1): (i) the environment of the grandmaternal womb, in which the maternal fetus and her ovarian cells develop and (ii) the environment of the maternal ovary after her birth but before fertilization. Subsequently, the individual as a fertilized egg (zygote) is exposed to the environmental domain of the maternal womb (iii) and then the postnatal domain (iv). Thus, a comprehensive analysis of environmental influences on development must consider four distinct environmental domains that are unique to each individual.

It is well established that *all* the oocytes in the human ovary are present by birth. While most oocytes are formed before the third trimester of pregnancy, some are formed as early as 5 months before birth (Byscov, 1982; vom Saal *et al.*, 1994). Thus, the egg that gave rise to each of us was formed in our mother while she was a fetus in our maternal grandmother's womb (Fig. 1). The oocyte in the maternal ovary from birth onward is in a prolonged state of arrested cell division in meiotic prophase,

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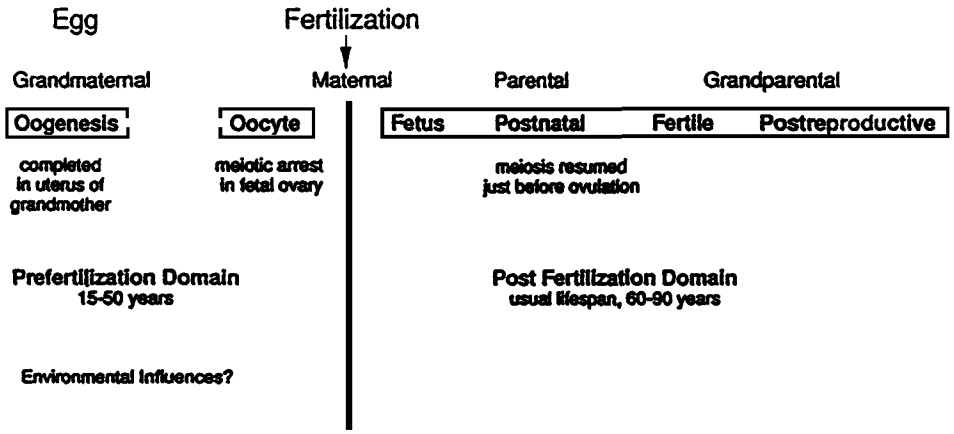

Fig. 1. Pre- and postfertilization domains of life history: the oocyte over four generations. The prezygotic environment. The unfertilized egg (oocyte) may be subject to two distinct environments. In humans, the **grandmaternal environment** is defined before the birth of the mother, when the oocyte is generated as an individual cell in the developing ovary of the fetus. The differentiation of primary oocytes as distinct cells begins in the developing ovaries of fetuses that are about 2 months old and continues until about the time of birth. Oocytes in the maternal ovary could have been formed at any time in this phase, lasting 0–7 months.

known as the dictyate or dictyotene stage. Meiotic cell division is eventually completed in postpubertal humans just before ovulation. For a typical human maternal age of 30 years, the oocyte as a cell has already existed for up to 5 months in the grandmaternal uterine environment and then for another 30 years in the mother.

Possible influences from the prezygotic environments have not been addressed in humans. However, analysis of twins in other species of mammals indicates unexplained variance in monozygotes (MZ) that, we suggest, could include prezygotic environmental influences. Mammals in general have the same schedule of ovarian development as found in humans, with most oocytes also being formed before birth (Franchi *et al.*, 1962; Tokarz, 1978; vom Saal *et al.*, 1994). Transfer of blastocysts (preimplantation embryos) into foster mothers was used to compare MZ twins derived from a single artificially cleaved ovum *vs.* dizygous (DZ) twins derived from separate ova in studies of inbred mice (Gärtner and Baunack, 1981, 1982; Baunack *et al.*, 1984; Papaioannou *et al.*, 1989), cattle (Gärtner *et al.*, 1991), and pigs (Reichelt and Nieman, 1994). Most of the considerable variance between twin pairs in rates of postnatal development could not be attributed either to the uterine environment or to residual genetic variations. Gärtner (1990) proposed that this unexplained variance was "inborn and effective at or before fertilization."

In considering the nonshared environment of MZ twins, the usual focus is on individual differences in postnatal experience (Plomin, 1994). However, some consideration has been given to prenatal effects on twins that may arise from differential vascularization of MZ twins through mono- vs dichorionic placentae (Davis *et al.*, 1995). In addition to these mechanisms, we suggest other mechanisms as candidates through which lasting effects of the environment may impact a particular oocyte as an innocent bystander.

The ovary consists of diverse cell types with different patterns of gene expression (Khan-Dawood *et al.*, 1996). Little is known about the factors that select a given follicle for complete maturation, the influences from neighboring atretic (dying) or growing follicles, or even whether DZ oocytes come from the same or both ovaries in humans. Oocytes and the surrounding primordial follicle cells are exposed to microenvironmental influences from neighboring cell deaths of two types. (i) Cell death during atresia of oocytes begins before birth at the earliest stages of ovarian development *in utero* and continues postnatally until the ovary is depleted of oocytes at menopause (Baker, 1963; Gosden, 1985). Atretic cell death of oocytes is a major ongoing process that causes the spontaneous death of most (>99%) oocytes. (ii) Cell death through the involution of corpora lutea cells occurs during each fertility cycle. Exposure of individual oocytes to chemical influences from

neighboring cell death is unlikely to be evenly distributed.

Cell death, from precedents in numerous other tissues, is anticipated to produce local chemical changes that could damage an oocyte and its molecules. Proteins and DNA are subject to diverse chemical modifications during cell death through production of free radical damage by dying cells (Stadtman, 1992; Smith *et al.*, 1991). Ovaries also have resident macrophages and other inflammatory cell types that produce cytokines and other locally diffusible (paracrine) chemical factors (Hume *et al.*, 1984; Bukovský *et al.*, 1995; Flaws *et al.*, 1995) that are associated with free radical production.

Another class of damage that may arise independently of neighboring cell death is cross-linking of proteins through spontaneous chemical reactions with glucose and other metabolites (nonenzymatic glycation) (Vlassara *et al.*, 1994). Furthermore, mitochondrial DNA (mtDNA) accumulates damage during aging in the human brain in association with deficits in mitochondrial energy metabolism (Gupta *et al.*, 1990; Mecocci *et al.*, 1993; Soong *et al.*, 1992; Wallace, 1992). Thus, it is plausible that oocytes also accumulate damaged mtDNA over time that could be a component of ooplasmic variations.

As a likely example of molecular damage to individual oocytes that persists for years, the risk of Down syndrome is increased by maternal exposure to X-rays before pregnancy, with the greatest risk incurred by those irradiated ≥10 years before pregnancy (Alberman *et al.*, 1972). Down syndrome (trisomy 21) is the most common chromosomal aneuploidy and increases exponentially with maternal age (Hook, 1986). It presents a special case of maternal age effects on brain functions of the offspring, because all Downs' adults eventually show cognitive decline and the neuropathology of Alzheimer disease (e.g., Hof and Morrison, 1994). Late maternal age is also associated with increased risk of Alzheimer disease in the absence of Down's in chromosomally normal offspring (Breteler *et al.*, 1992).

As a first (and limited) attempt to detect prezygotic environmental influences on human development, we looked for maternal age effects in twins. DZ twins have existed as separate prezygotic cells for the extensive time since they were formed during the grandmaternal pregnancy, which is >30 years in the present sample. In contrast, MZ twins come from a single prezygotic cell that separated *after* fertilization. We hypothesized that DZ twins might reveal differences in maternal aging effects because of their origins as independent cells in the maternal ovary. Based on the precedents considered above, we speculated that the individual follicles that eventually gave rise to separate ova and DZ twins might be exposed to different microenvironments, which would differ increasingly as a function of maternal age. Of course, broad environmental conditions that equally affected all the mother's oocytes would not be detected by this approach.

The putative prezygotic environmental effects could bias the estimation of trait heritability through the comparison of the resemblance of MZ and DZ pairs. Therefore, some of the difference within DZ pairs might not be due to genetic differences but might arise through different microenvironments during the prolonged existence of the two ova before fertilization. This difference can not exist for MZ pairs who arose from a single ovum that separated into two individuals after fertilization. Thus, a sample of MZ and same sex DZ twins was analyzed for maternal age effects on behavioral and cognitive traits. We reasoned that the separate oocytes of DZ twins might retain influences from different prezygotic microenvironments that accumulated with maternal age.

METHODS

The sample consisted of twins identified among 600,000 U.S. high-school juniors who were administered the National Merit Scholarship Qualifying Test in 1962. For details, see Loehlin and Nichols (1976). In brief, twins were contacted by mail; they and a parent agreed to fill out questionnaires, including items that permitted a diagnosis of the twins as identical or fraternal. The final sample consisted of 850 same-sex sets of twins, of which 336 were typed as DZ; the latter constitute the primary sample for this study. In general, the twins were similar to nontwins among National Merit Scholarship test takers. Both groups are necessarily above average in cognitive ability and academic achievement; the mean class rank of members of the twin sample was at about the 79th percentile of their high-school classes (±18.3%, SD). For personality measures, the average scores tended to lie between those of typical high school

Table I. Study Measures

Scale	Item	Reliability[a]	Mean[b]	SD[b]
NMSQT total score[c]	5[d]	0.88	102.35	21.86
CPI Dominance[e]	46	0.68	27.50	5.92
CPI Socialization[e]	54	0.67	40.40	4.92
Externalizing behavior	5	0.57	6.30	1.30
Internalizing behavior	6	0.53	7.62	1.38
Left-handedness	2	0.95	2.85	2.01
Anxiety/tension symptoms	6	0.62	14.95	1.09
Mother's age[f]	1			
DZ			47.27	5.36
MZ			46.09	5.32

[a] CPI scales, 1-year test–retest reliabilities from the CPI Manual (Gough, 1957); NMSQT, Alpha Reliability based on five subtest scores; others, alpha calculated from items via SPSS reliability (SPSS Inc., 1990).

[b] Mean based on all twins for the first three measures, with SD calculated within sex and zygosity; mean based on one score per pair for remaining measures, with simple SD.

[c] NMSQT, National Merit Scholarship Qualifying Test.

[d] Subscales.

[e] CPI, California Psychological Inventory.

[f] Maternal ages were as reported at the time of the study. The parent questionnaire was filled out in the summer after the twins' senior year in high school, i.e., when twins were typically 18 years old. Thus, the average maternal ages at the birth of the twins would be 28–29 years; 96% of the mothers were within the range 20 to 40 years, compared with 86% of all U.S. mothers in 1946.

and college students on the scales of the California Psychological Inventory (CPI) (Gough, 1957). This sample, by its nature, has a somewhat restricted range of maternal ages. The SD of 5.35 (Table I) may be compared with the SD of 6.53 for all U.S. mothers giving birth in 1945, when the majority of this sample was born (U.S. Bureau of the Census, 1975, Series B 11-19). This represents a reduction of about 18%. The variability of ages in the present sample should, however, be adequate to detect any major effects of maternal age.

From the very large set of variables available in the National Merit study, we chose a small but representative group for the present analysis. As an index of intellectual performance, we used the National Merit Scholarship Qualifying Test (NMSQT) score. As personality measures, we selected the Dominance and Socialization scales from the California Psychological Inventory. These scales are, respectively, typical of Gough's (1957) scale categories I and II: measures of poise, ascendancy, and self-assurance and measures of socialization, maturity, and responsibility. We derived two short a priori scales of childhood psychopathology from the parents ratings, to correspond roughly to Achenbach's Externalizing and Internalizing behaviors (Achenbach and Edelbrock, 1978). The Externalizing scale includes such items as temper tantrums, disobedience, and fighting; the Internalizing scale, such items as shyness, fears, and dependency. Finally, we used handedness (assessed by self-rating and parent rating) and the twins' self-report of physical symptoms of anxiety or tension (sweaty palms, dizziness, trembling, heart pounding, headaches, excessive fatigue). Mother's age was as reported on the parent's questionnaire. Table I provides some psychometric properties of the measures.

RESULTS AND DISCUSSION

As an exploratory test of the hypothesis of prezygotic environmental effects, we compared MZ and DZ twins for effects of maternal age on a number of typical cognitive and behavioral traits that might be sensitive to environmental influences on brain development. Assuming that the DZ oocytes were exposed to different local environments in the maternal ovary that, in turn, subtly modified brain development, we predicted that increasing maternal age might be associated with greater mental differences between DZ *vs.* MZ twins. In particular, the hypothesis would predict appreciable positive correlations for the differences between twins and maternal age for DZ but not for MZ twins. Correlations for each of the seven measures between the absolute DZ twin pair difference and maternal age are in Table II. Also shown are corresponding correlations for MZ twins. However, no significant correlations were found in either case. All are numerically near zero, with as many negative as positive correlations.

The data were also analyzed for maternal age effects, because late maternal age has shown an association with risk of Alzheimer disease in normal (non-Downs' individuals; see the Introduction). Only Externalizing behavior (including problematic behaviors) showed a maternal age effect, with younger mothers reporting significantly more (Table II). One anonymous reviewer suggested that this effect could arise as a behavioral epiphenomenon, if the younger mothers were less experienced in rasing teenagers and more reactive to their children's behaviors.

Although the prezygotic hypothesis was not supported by the present analysis, its sensitivity may be limited by the restriction in the range of maternal ages, or (in some unknown way) the selected nature of the twin sample, or the traits examined. Most twins were born when their mothers were between 22 and 40 years (Table I, footnote *f*). However, at limiting ages of childbearing with endogenous ova, the lifetime of an oocyte that survived to maturation and fertilization could vary more than four fold, from 12 years (preteen pregnancy) to >50 years (perimenopausal pregnancy).

More direct tests of the prezygotic hypothesis may be made with mice derived from *in vitro* fertilization. For example, oocytes could be obtained from the same mouse at different ages, and the oocytes could be fertilized *in vitro* and stored frozen for future transplantation into the same host as a test of effects of maternal aging on behavioral measures (Gosden *et al.*, 1993). Moreover, ovaries of fetal mice can be induced to form mature oocytes during transplantation into adult hosts, which would allow discrimination of maternal age environmental effects on the primary oocyte from the later stages of its maturation and ovulation. Portions of the ovary could be obtained from females at different ages as sources of oocytes for *in vitro* fertilization as above. Alternatively, to test effects of environmental toxins, the ovaries could be exposed to chemical agents that modify proteins or nucleic acids and the exposed oocytes could be fertilized and examined in the same surrogate mother. As a precedent, maternal smoking induces chemical adducts in placental DNA (Everson *et al.*, 1986); there is no information on whether smoking alters the DNA of the ovary within the fetus, however. Other studies might use mouse embryo transfer to examine embryos derived from one vs. two eggs for mitochondrial energy metabolism and mtDNA damage. We predict that variations in numbers of damaged mtDNA molecules accumulated in the prefertilized oocyte would result in a greater variance of growth rates for DZ twins (see Gärtner and Baunack, 1981, 1982; Gärtner, 1990).

The prezygotic environment could have less impact on male gametes. In contrast to oocytes, the spermatogonia that give rise to mature sperm proliferate continuously from puberty onward and are estimated to undergo many hundreds of divisions from the primordial germ cells (Vogel and Motulsky, 1986). Thus, by comparison with oocytes, the life span of germ cells in males is relatively short. Despite the lack of persistence of individual cells that parallels the status of the oocyte, the spermatogonial stem cells could acquire DNA damage that might be inherited by the sperm produced.

Table II. Correlations with Maternal Age

Scale	Absolute difference		Maternal age, 1st twin of each pair[c]
	DZ pairs[a]	MZ pairs[b]	
NMSQT total score	0.048	−0.040	0.033
CPI Dominance	−0.022	0.083	−0.008
CPI Socialization	0.078	−0.090	0.026
Externalizing behavior	−0.031	−0.060	−0.072*
Internalizing behavior	−0.037	0.070	−0.050
Left-handedness	0.011	0.015	0.049
Anxiety/tension symptoms	−0.092	−0.010	0.048

[a] Number of pairs, 300–317.
[b] Number of pairs, 468–495.
[c] Number of *S*'s, 768–812.
* $p = 0.041$; *N*'s, 811.

In conclusion, we described features in oogenesis that define two prezygotic environments: one that is relatively brief in the grandmaternal uterus and the other in the maternal ovary, which may extend many decades up to the limit of childbearing. While we did not find in our data any indications that differences between MZ and DZ same-sex twins reflect the prezygotic environment, the analysis performed cannot be considered conclusive. We believe that the possibility of prezygotic environmental influences merits further inquiry in humans and in experimental studies with animal models because the persistence of environmental effects on the oocyte during the two generations that precede conception is a great unknown in human development.

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