Paternal Age and Preeclampsia

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Background. Paternal aging is associated with premeiotic damage to spermatogonia, a mechanism by which new point mutations are introduced into the gene pool. We hypothesized that paternal age might contribute to preeclampsia.

Methods. We studied the incidence of preeclampsia in 81,213 deliveries surveyed in 1964–1976 in the Jerusalem Perinatal Study. We controlled for maternal age, parity and other risk factors using logistic regression.

Results. Preeclampsia was reported in 1303 deliveries (1.6%). Compared with fathers age 25–34 years, the odds ratios (ORs) for preeclampsia were 1.24 (95% confidence interval = 1.05–1.46) for age 35–44 and 1.80 (1.40–2.31) for age 45+. For fathers age <25, the OR was 1.25 (1.04–1.51). Although weaker than maternal age effects, paternal effects were consistent within subgroups of other variables.

Conclusions. These findings support the hypothesis that a modest proportion of preeclampsia might be explained by new mutations acquired from fathers and add to a growing body of evidence for paternal age effects in birth defects, neuropsychiatric disease and neoplasia.

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Key words: preeclampsia, paternal age, maternal age, spermatogenesis, new mutations, risk factors.

A man's constantly dividing reproductive stem cells (spermatogonia), like somatic cells, are vulnerable to mutations over his lifetime. *De novo* mutation, associated with male aging, is believed to be common, and in humans, as in other mammals, it is the males who introduce the overwhelming majority of new mutations into the gene pool.[1] In the testis, premeiotic DNA in stem cells may be altered by ionizing radiation,[2] whereas the somewhat different mechanisms for DNA repair during male meiosis and postmeiotic activation[3] may be disturbed more by chemical mutagens, heat and/or oxidative stress and are less clearly related to aging.[4] Therefore, although some mutations related to paternal age will have been accumulated over a man's lifetime, including his childhood, other sporadic mutations may result from paternal exposure to mutagens shortly before conception. The mechanisms behind these two components of risk are believed to be independent.[4,5]

Advanced paternal age is known to be associated with sporadic (nonfamilial) occurrence of certain birth defects, malignancies and neurodegenerative conditions. In a 21- to 33-year follow-up of the Jerusalem Perinatal Study, paternal age has emerged as a strong risk factor for schizophrenia[6] and, because preeclampsia has been proposed as a risk factor for schizophrenia, we questioned whether paternal age was related to this complication of pregnancy. Preeclampsia, a complex disease involving placental pathology, has been traditionally associated with risk factors in mothers. The syndrome is usually manifest after the 20th week of pregnancy by altered maternal vascular permeability, hypertension and proteinuria.[7,8] Not much is known about its epidemiology; previous studies have identified nulliparity and nulligravidity as risk factors, together with increasing maternal age, diabetes, urinary tract infection, autoimmune disease and obesity.[9–11] Smoking is protective.[12] Fetal risk factors include multiple gestations, hemolytic disease, trophoblastic disease and major malformations.[13]

Recent work has also indicated a contribution to preeclampsia from the father. Genetic studies have shown both maternal and paternal transmission of risk,[14,15] and various candidate loci have been investi-

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gated.[16–18] Other findings thought to be attributable to effects of the male partner have included an increased risk associated with recent marriage, shorter periods of cohabitation before conception, barrier contraception or assisted reproduction with donor sperm,[19–21] whereas previous abortion may reduce the risk.[22,23]

Methods

This investigation is based on the Jerusalem Perinatal Study, a research cohort established in 1964–1976. The original purpose was to investigate hypertension in pregnancy,[24] but the study was expanded to capture other obstetric information.[25] The design and methods have been described previously.[26] Briefly, in 1964–1976, the Jerusalem Perinatal Study recorded all births to Israeli residents of the city of Jerusalem and its rural county; the study also undertook active surveillance of infant mortality and birth defects, as reported from multiple sources. Antenatal and intrapartum care were free and equally accessible; all births occurred in hospitals (or en route), and all women were under the care of midwives, whether or not an obstetrician was also present. For women giving birth in the city's three largest obstetric units, the Jerusalem Perinatal Study collected data on maternal conditions and obstetric complications by abstracting information each week from the logbooks in the labor-and-delivery wards. The mothers and offspring are now being traced for mortality (EF Funai, Y Friedlander, O Paltiel, *et al.*, unpublished data, 2002) and a variety of other endpoints including cognitive outcomes (D Malaspina, A Reichenberg, M Weiser, *et al.*, unpublished data, 2002). The present study was approved by the institutional review boards of New York University School of Medicine and the Hadassah Medical Organization/Hebrew University of Jerusalem.

Definition of Preeclampsia

For the purpose of this study, we have relied on the record in the labor-ward logbook for a diagnosis of preeclampsia. In those days, preeclampsia was defined by the onset, after 24 weeks' gestation, of a combination of hypertension, proteinuria and edema of the face or arms. Hypertension was defined as a rise in systolic blood pressure of 30+ mmHg, a rise in diastolic pressure of 15+ mmHg, or two consecutive measurements more than 6 hours apart of 140+ mmHg (systolic) or 90+ mmHg (diastolic). The data do not distinguish preeclampsia from eclampsia, but the latter was extremely rare. Preexisting hypertension and rare diagnoses such as renal or autoimmune disease were coded into a rubric for "other maternal conditions." This study is based solely on the rubric for preeclampsia.

Data Analysis

We analyzed the data using unconditional logistic models employing SAS.[27] Maternal age was modeled initially in 5-year groups; however, it fit better as a continuous variable, after expressing age in deviations from the mean (age 27). Unknown maternal age (N = 64) was set to the mean. Most other variables were treated as dichotomies or sets of dummies. Unless otherwise stated, all models controlled for the following: hospital (B or C *vs* A), primiparity (*vs* multiparity), insulin-dependent diabetes mellitus or gestational diabetes (either *vs* neither), multifetal deliveries (*vs* single), and fetal hemolytic disease (any *vs* none). The models also controlled for social class based on occupation of father (low or medium *vs* high), status as rabbis or students in Talmudic academies (*vs* others), paternal education (unknown, 0–4, or 5–12 *vs* 13+ years), maternal religion (Moslem *vs* non-Moslem), year of delivery (an ordinal variable), and season (sine transformation of day of the year). These variables were included because they were related both to the incidence of preeclampsia and to the distribution of paternal age. We also tested other correlates of paternal age: paternal education, paternal and maternal immigration (*vs* born in Israel), paternal and maternal ethnic groups (continents of birth of their fathers), and duration of marriage; but as these were not independently related to preeclampsia the models did not control for them.

Numbers and Exclusions

There were 91,252 deliveries recorded, with 92,408 offspring. For this study, we excluded 8,816 (9.7%) with incomplete data on obstetric conditions; these were deliveries during the first 90 days of 1964 (N = 1,363, 1.5%) and those in the city's smallest obstetric unit (N = 6003, 6.6%), in hospitals in other areas (N = 1524, 1.7%), or at an unknown place of delivery (N = 9). From the 82,436 deliveries potentially available for study, we excluded 1,223 (1.5%) with unknown paternal age. Among these, the incidence of preeclampsia was 1.3%; the adjusted odds ratio (OR) comparing unknown with known paternal age was 0.84 (95% confidence interval [CI] = 0.51–1.41).

Results

There were 1,303 (1.6%) deliveries associated with preeclampsia. The fathers' ages ranged from 16 to 77 years (mean = 30.5 ± 6.8 standard deviation). There were only 233 births to fathers age <20 (fewer than 0.3%), whereas there were 3,589 (4.4%) to those age 45+ and 1,157 (1.4%) to those age 50+. Table 1 shows the distribution of fathers' age in relation to other variables. In addition to its strong relation to maternal age

TABLE 1. Percent Distribution of Father's Age, by Selected Variables

Variable	Number of Births	All Fathers (N = 81,213) %	Age of Father (Years) <25 (N = 11,093) %	25–34 (N = 46,378) %	35–44 (N = 20,153) %	45+ (N = 3,589) %
Mother's age (years)						
<20	2,895	3.6	16	2	<1	<1
20–24	24,861	30.6	75	34	4	2
25–29	26,196	32.3	9	46	18	5
30–34	16,193	19.9	1	16	41	19
35–39	8,476	10.4	<1	2	31	40
40+	2,246	2.1	<1	<1	6	33
Unknown	64	0.1	<1	<1	<1	<1
Birth order						
1	23,538	29.0	71	30	7	6
2–6	49,554	61.0	28	67	69	47
7+	7,986	9.8	1	3	23	47
Unknown	135	0.2	<1	<1	<1	<1
Complications of pregnancy						
IDDM and gestational diabetes	633	0.8	0.3	0.6	1.2	2.1
Fetal hemolytic disease	576	0.7	0.5	0.7	0.9	0.6
Twins and triplets	1,027	1.3	0.8	1.2	1.6	1.4
Occupation of father						
Rabbis and students in Talmudic academies	10,482	12.9	26	13	7	5
Social class (ranked by father's occupation)						
(High) 1 + 2	29,274	36.0	42	39	28	19
(Med) 3 + 4	30,253	37.3	36	38	38	33
(Low) 5 + 6	21,686	26.7	22	23	33	48
Mother's education (years)						
0–4	7,770	9.6	2	6	18	24
5–8	19,873	24.5	23	23	28	28
9–12	27,301	33.6	45	36	26	16
13+	20,682	25.5	22	30	19	11
Unknown	5,587	6.9	7	6	8	11
Religion of father						
Muslim	1263	1.6	1.4	1.4	1.9	2.4
Christian	140	0.2	0.1	0.2	0.2	0.2
Jewish	79,810	98.2	98.5	98.5	97.9	96.4
Ethnic group (birthplace of paternal grandfather)						
Israel	13,192	16.2	20	16	15	10
Other West Asia	25,195	31.0	25	31	34	36
North Africa	17,356	21.4	22	20	23	29
Europe and other developed countries	25,470	31.4	34	33	28	24
Birthplace of father						
Israel	34,619	42.6	55	45	35	18
Abroad	46,594	57.4	46	55	65	82
Duration of marriage (years)						
<1	2,314	2.8	10	2	1	1
1–2	13,412	16.5	48	16	4	7
3–9	44,785	55.1	41	71	32	18
10+	19,671	24.2	<1	9	63	74
Unknown and not married	1,031	1.3	2	1	2	3
Year of delivery						
1964–1968	25,485	31.4	25	31	33	41
1969–1972	25,447	31.3	33	31	32	31
1973–1976	30,281	37.3	42	38	34	29

IDDM = Insulin-dependent diabetes mellitus.

and parity, paternal age was correlated with pregnancy complications. There were strong relations to social and ethnic variables, with the older fathers tending to have less prestigious jobs and less educated wives (Table 1) and to be themselves less educated (not shown). Older fathers were more likely to be immigrants, especially from Islamic countries, or to be Muslims. Their wives had very similar ethnic characteristics (not shown). The youthful fathers (age <25) were more likely to be students in Talmudic academies, who at that time were mainly of European origin. Births to these students, and so to the youngest fathers, increased over time, whereas the proportion of fathers age 45+ decreased.

Table 2 shows the relation of paternal age to preeclampsia. The crude incidence of this condition was lowest in fathers age 25–29. With this age set as the reference group, there was an increased odds ratio estimated for fathers age 20–24, adjusted for the distribution of nulliparity and other variables. There was no difference between fathers age 25–29 and 30–34 but fathers older than 34 were at increased risk. There was a stepped increase in the risk of preeclampsia for paternal age 35–44 and 45+,

TABLE 2. Incidence of Preeclampsia by Age of Father

Age of Father (Years)	Deliveries	% Preeclampsia	Adjusted OR*	95% CI
Total	81,213	1.6		
5-year age groups				
<20	233	0.9	0.66	0.15–2.66
20–24	10,860	1.6	1.28	1.05–1.66
25–29†	25,953	1.2	1.00	
30–34	20,425	1.3	1.00	0.84–1.20
35–39	13,341	2.0	1.30	1.05–1.59
40–44	6,812	2.1	1.08	0.83–1.40
45–49	2,432	4.2	1.89	1.39–2.56
50–54	747	4.0	1.54	0.98–2.41
55–59	236	4.7	1.41	0.70–2.41
60+	174	3.5	1.12	0.47–2.69
10-year age groups				
15–24	11,094	1.6	1.25	1.04–1.51
25–34†	46,378	1.2	1.00	
35–44	20,109	2.1	1.24	1.05–1.46
45+	3,581	4.2	1.80	1.40–2.31

* Odds ratios and 95% confidence intervals adjusted for age of mother (continuous), primiparity, diabetes, multiple pregnancies, fetal hemolytic disease, hospital, maternal education, religion, social class and occupation of father, and year of delivery and season.
† Reference category.

compared with reference group 25–34. Although this pattern was less consistent in the comparisons of the 5-year age groups, a trend test from age 25 based on paternal age as a continuous variable gave $P < 0.02$.

Maternal age was more clearly and more strongly related to the risk of preeclampsia than paternal age (data not tabulated). The crude incidence of preeclampsia varied from 1.4% for mothers age <20 through 1.3%, 1.2%, 1.6%, 2.5%, 5.6% and 6.1% in successive 5-year groups and to 8.3% at age 50+. The odds ratios (and 95% CIs), using <20 for the reference group and adjusting for paternal age and other variables, were 1.2 (0.9–1.7) for mothers age 20–24 and 1.5 (1.1–2.2), 2.1 (1.4–3.0), 2.9 (1.9–4.3), 5.7 (3.7–8.7), 6.0 (3.1–11.6) and 6.7 (1.8–24.3) in subsequent 5-year groups.

Table 3 shows paternal age effects estimated for categories of other variables. Within broad groups of maternal age, the ORs were adjusted for maternal age as a continuous variable. There was no obvious difference in the effects of paternal age between mothers of various ages, parities, social classes, ethnic groups or infant genders; within each of these strata the risk of preeclampsia increased consistently with increasing paternal age beyond age 34. Similarly, the pregnancies fathered by the youngest group of men showed increased ORs in most subgroups.

We questioned whether the results might be an artifact attributable to an effect of the difference between maternal and paternal ages. On average, the fathers were 3.8 years older than their wives. After excluding outliers in which the mother was more than 15 years older than her spouse, or he was 30+ years older than the mother, there was no evidence of trend when the parents' age difference was tested in quartiles nor at the more extreme categories. The categories for −15- to −5-year difference (*ie*, fathers younger than mothers), −4 to +1, +2 to +5, +6 to +15 and +16 to +29, gave ORs of 0.92 (CI = 0.53–1.59), 1.00 (reference category), 0.97 (0.83–1.12), 1.01 (0.82–1.24) and 0.74 (0.44–1.22), respectively. For each year of difference between paternal and maternal age as a continuous variable, we derived an OR of 0.92 (0.85–1.00). Inclusion of this variable in the model changed the ORs for paternal age to 1.14 (0.92–1.41) for fathers age <25 years, 1.00 (reference category) for 25–34, 1.44 (1.15–1.81) for 35–44 and 2.54 (1.66–3.90) for 45+. Thus, although there was a large difference in age between the oldest fathers and their wives, it was the absolute age of the father, not the age difference, that predicted preeclampsia. The age difference did, however, account for some of the excess risk in the youngest fathers.

We also considered whether the excess risk of preeclampsia associated with younger fathers might be an artifact attributable to recent marriage. The ORs for intervals of <1, 1–2 and 3–4 years since marriage were 0.81 (CI = 0.54–1.20), 0.94 (0.74–1.20) and 0.99 (0.82–1.19) compared with a reference group of 5+ years since marriage. Similar patterns were seen in first births and in the wives of rabbis and Talmud students (who would not have been sexually experienced before marriage); thus, recency of marriage or conception with a new partner did not account for the paternal age effects. Similarly, the excess risk in younger fathers was not explained by the preponderance of rabbis and students in Talmud academies in this group (Table 3).

Re-analysis of these data after removal of the mothers with diabetes, multiple gestations or fetal hemolytic disease did not alter these conclusions; nor did further adjustment (using data available on a small subcohort) for body mass index, preexisting hypertension, renal disease or urinary tract infection.

Discussion

Our results show father's age related to preeclampsia independently of effects of maternal age. Two trends are discernible: first, an increasing incidence of preeclampsia with increasing fathers' age, supporting our *a priori* hypothesis; second, a higher risk in the pregnancies fathered by youthful fathers, age under 25, compared with the fathers age 25–34. These effects were unlikely to have been attributable to chance and were consistent within demographic sub-

TABLE 3. Risk of Preeclampsia by Father's Age in Subgroups of Other Risk Factors

Variable	Category	Age of Father (Years) <25	25–34†	35–44	45+
Mother's age (years)					
<25	Cases	158	194	9	1
	OR	1.16	1.0	1.16	1.60
	95% CI	0.92–1.46		0.59–2.29	0.22–11.8
25–34	Cases	16	345	202	19
	OR	1.03	1.0	1.30	1.66
	95% CI	0.61–1.72		1.07–1.60	1.02–2.71
35+	Cases	3	21	61	76
	OR	8.52	1.0	1.05	1.51
	95% CI	1.99–36.4		0.66–1.68	0.92–2.47
Parity					
1	Cases	148	264	58	10
	OR	1.11	1.0	1.52	1.62
	95% CI	0.88–1.38		1.08–2.52	0.79–3.30
2+	Cases	29	297	357	140
	OR	1.45	1.0	1.16	1.68
	95% CI	0.98–2.15		0.96–1.41	1.26–2.23
Father's occupation					
Rabbis and Talmud Students	Cases	50	64	30	9
	OR	1.34	1.0	1.33	1.85
	95% CI	0.85–2.11		0.71–2.49	0.67–5.15
Others	Cases	127	497	385	141
	OR	1.23	1.0	1.22	1.79
	95% CI	0.99–1.51		1.03–1.45	1.38–2.32
Social class					
1–3 (high)	Cases	106	315	182	51
	OR	1.29	1.0	1.26	2.02
	95% CI	1.01–1.66		0.99–1.60	1.36–3.00
4–6 (low)	Cases	71	236	233	99
	OR	1.19	1.0	1.25	1.68
	95% CI	0.89–1.59		0.99–1.57	1.21–2.34
Ethnic group (birthplace of father's father)					
Israel	Cases	26	102	66	15
	OR	0.72	1.0	1.32	1.74
	95% CI	0.45–1.16		0.87–2.00	0.86–3.52
Other West Asia	Cases	44	181	154	54
	OR	1.25	1.0	1.28	1.60
	95% CI	0.87–1.79		0.97–1.69	1.05–2.44
North Africa	Cases	34	83	83	40
	OR	1.61	1.0	1.36	2.17
	95% CI	1.03–2.51		0.92–2.01	1.25–3.78
Europe and other developed countries	Cases	73	195	112	41
	OR	1.42	1.0	1.17	1.99
	95% CI	1.05–1.93		0.86–1.59	1.24–3.20
Infant gender					
Male	Cases	100	304	211	83
	OR	1.30	1.0	1.18	2.02
	95% CI	1.01–1.67		0.94–1.49	1.43–2.84
Female	Cases	77	257	204	67
	OR	1.21	1.0	1.30	1.59
	95% CI	0.91–1.60		1.03–1.66	1.10–2.31
Year of delivery					
1964–1968	Cases	35	201	165	62
	OR	0.94	1.0	1.20	1.43
	95% CI	0.64–1.38		0.93–1.56	0.97–2.12
1969–1972	Cases	71	175	138	48
	OR	1.47	1.0	1.28	1.89
	95% CI	1.08–2.00		0.95–1.72	1.20–2.97
1973–1976	Cases	71	185	112	40
	OR	1.30	1.0	1.28	2.42
	95% CI	0.95–1.77		0.93–1.74	1.50–3.90
Total					
	Cases	177	561	415	150
	OR	1.25	1.0	1.24	1.80
	95% CI	1.04–1.51		1.05–1.46	1.40–2.31

* Odds ratios and 95% confidence intervals adjusted for maternal age (continuous), primiparity, multiple births, diabetes, fetal hemolytic disease, hospital, maternal education, religion, social class and occupation of father, and year of delivery and season.
† Reference category.

groups. There are no previous studies, to our knowledge, of paternal age and preeclampsia.

Our findings indicate a stronger relation with maternal age than previous studies in which, as in the present study, the data have been adjusted for socioeconomic status[28]; studies not so adjusted have found a J-shaped relation between maternal age and preeclampsia (as reviewed by Knuist *et al.* in 1998).[29] Women in the U.S.

who give birth before age 20 are often unmarried and poor and have a life-style that differs from that of the ultrareligious Jews (and Muslims) in our population; these latter groups are strictly segregated before marriage. Previous authors have found recent marriage or a change of partner as a risk factor for preeclampsia,[20] although others have suggested that this is confounded by an increased risk of preeclampsia associated with a longer interval between pregnancies.[30] In our cohort there is no excess risk of preeclampsia in women who recently married. This is true even in the ultra-orthodox wives of rabbis and students in Talmudic academies, where the fervently religious life-style is characterized by arranged marriages and early, uncontrolled fertility, leading to short intervals between births. Thus, the excess risk of preeclampsia in younger men seems inconsistent with previous studies.

On the other hand, this excess risk in young men might indicate exposure to environmental causes of DNA damage (*eg*, heat, pesticides, smoking or suboptimal diet). In mice, immature males are more likely to sire offspring with adverse outcomes[31] and are believed to be less efficient at apoptosis after DNA damage during meiosis or postmeiotic maturation of spermatozoa. Young human fathers, too, beget offspring with more suboptimal outcomes.[32]

An advantage of our study for investigating effects of paternal age, apart from the large size of the cohort, is that few women were unmarried and the religious life-style of the population makes it less likely, compared with some other studies, that the legal fathers were not the biological fathers. Another advantage is the scope and range of available variables, especially those reflecting ethnicity, socioeconomic status and other maternal conditions. On the other hand, we do not have the benefit of a modern definition of preeclampsia, the certainty of complete ascertainment, or knowledge of preexisting hypertension or body size. We cannot exclude the possibility that the results reflect confounding attributable to these or some other factor associated with paternal age.

With this caveat, our results accord with a body of literature linking advanced paternal age to a variety of pediatric and adult diseases, especially those associated with neurodevelopmental abnormalities and malignancies. (For reviews of paternal age effects in birth defects see Lian *et al.*[33] and Plas *et al.*[34]) In our population, paternal aging is strongly related to schizophrenia.[6] In other countries, epidemiologists have linked advanced paternal age to neural tube defects,[35] pediatric brain neoplasms,[36] adult nervous system malignancies,[37] early-onset Alzheimer's disease,[38] and carcinomas of breast[37] and prostate.[39] In case series, advanced paternal age has been associated with reduced survival[40] and with sporadic (nonfamilial) occurrence of progeria [41,42] and numerous other syndromes (reviewed by Malaspina *et al.*[43]). In molecular genetic studies, *de novo* point mutations have been specifically associated with older fathers for a number of specific genes important in oncofetal development and neoplasia.[41,44–47]

Consistent with this previous literature, our findings can support the hypothesis for a role for paternal age in preeclampsia, acting through new mutations. As an alternative explanation one could postulate that there might be preexisting paternal causes of both preeclampsia and subfertility that would lead preeclampsia to be associated with increased paternal age. But if this were true, one would expect to see the age effect operating mainly in first births and at higher social class. This is clearly not the case in our results.

The effects of paternal age in our study are modest, compared with the effects of maternal age. We estimate that fewer than 12% of cases of preeclampsia in this study might be attributable to the excess risk associated with paternal age over 35. In contrast, approximately half of the cases in this study could be attributable to the excess risk of maternal age over 35. The reason for the strong effect of maternal age on preeclampsia is unknown. Some have suggested nondisjunction affecting chimeric extra-embryonic membranes[48,49] or mutations in mitochondrial DNA,[50] although others negate this.[14]

Although some propose that a single gene might be responsible for most preeclampsia, others take the view that there must be numerous alternative pathways to the disease.[51,52] Placentation draws on a huge variety of genes and, although there may be much redundancy, many genes must be essential. Current views of the pathogenesis of preeclampsia focus on abnormal structure or function at the junction between the fetal trophoblast and the maternal decidua, associated with inadequate invasion of the trophoblast into the maternal spiral arteries.[53] Mutations or polymorphisms suggested to contribute to preeclampsia might include those involving genes active in thrombosis and fibrinolysis (*eg*, coagulation factor V, PAI-1 and prothrombin)[54–56]; folate metabolism (*eg*, MTHFR)[57]; lipid metabolism; cell responses to oxidative stress/anoxia and nitric oxide[58,59]; and systems related to angiogenesis and blood pressure,[51,52,60,61] the immune system,[62,63] and leptin.

De novo changes characteristically associated with paternal aging are point mutations at a single base pair or expansion of DNA triplet repeats; more extensive lesions seem to be efficiently eliminated during male meiosis.[1] Small deletions and inversions tend to be inherited more often from mothers than from fathers. Larger genetic rearrangements (*eg*, chromosome translocations, large deletions or inversions, gain or loss of entire chromosomes, or uniparental disomy) are variously contributed by either parent, often in association with aging.[49,64]

For substitutions at a single base pair, there are estimated to be approximately 64 mutations per genome per generation; however, most occur in noncoding DNA.[65] It is thought that about four point mutations are induced in the coding regions of genes, per genome per generation, with 1.6 deleterious mutations being transmitted to the next generation.[66] Advantageous mutations are thought to be rarer. Although deleterious mutations are common, most are eliminated through infertility, embryo death, fetal loss or early infant death. We speculate that preeclampsia may be another manifestation of this spectrum of loss.

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