THE EFFECTS OF PATERNAL AGE ON PREVALENCE OF SELECTED BIRTH DEFECTS

THESIS

Presented to the Graduate Council
of Texas State University-San Marcos
in Partial Fulfillment
of the Requirements

for the Degree

Master of SCIENCE

by

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San Marcos, Texas
December 2005

ACKNOWLEDGEMENTS

I would like to thank my husband, Larry Archer, for all of his encouragement and support. I know I couldn't have achieved any of this without him. I would also like to thank Dr. Peter Langlois at the Texas Department of State Health Services for letting me use vital statistics and Texas Birth Defects Registry data, and for helping me implement the Poisson regression analyses in SAS. Many thanks to the members of my thesis committee, Dr. Jean Brender, Dr. Ram Shanmugam, and Dr. Lucina Suarez. Thank you all for so selflessly agreeing to give of your time to help me complete my thesis.
This manuscript was submitted on October 26, 2005.

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ABSTRACT

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Even though the effect of maternal age on a host of different birth defects has been studied quite extensively, the effect of paternal age on birth defect rates has not been as well studied. This study analyzed Texas birth defect registry cases from 1996 to 2002 to ascertain whether or not paternal age was associated with the prevalence of selected groups of structural birth defects. The following types of birth defects were analyzed: ventricular and atrial septal defects, neural tube defects (anencephaly, spina bifida, and encephalocele), trisomy disorders (trisomies 21, 13, and 18), craniosynostosis, cleft palate, and cleft lip (with or without cleft palate). First, paternal age-specific prevalence rates were calculated for each of the specific birth defects to be analyzed, using Texas

live births from 1996 to 2002 as the denominator data. Poisson regression was then used to determine if there was an association between the paternal age groups and each of the specific birth defect rates, while adjusting for maternal age, maternal and paternal race/ethnicity, and parity. The study results showed a significant association between different paternal age groups and ventricular septal defects, atrial septal defects, cleft lip (with or without cleft palate), trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome), and trisomy 18 (Edwards syndrome). Overall, this study showed little evidence of increased risk of these birth disorders for advanced paternal ages. However, the results did indicate that younger paternal ages of 24 or less are associated with an increase in birth defect rates for ventricular and atrial septal defects, cleft lip, and the trisomy disorders. Especially for the trisomy disorders, this increase in risk is large enough that it might be worthwhile to investigate this association further.

CHAPTER 1

INTRODUCTION

Background

Most birth defect research up to the present has focused on maternal factors (Olshan & Faustman, 1993). The effect of maternal age on a host of different birth defects has been studied quite extensively, and strong associations have been found between maternal age and the prevalence of certain birth defects, such as Down syndrome (Thacker, 2004). However, as with many other paternal factors, the effect of paternal age on birth defect rates has not been as well studied, and for most birth defects for which paternal age has been studied at all, analyses have yielded inconsistent results.

Theoretically, as paternal age increases, birth defect rates should also increase. The scientific basis for expecting an increase in birth defect rates with increasing paternal age is Penrose's "copy-error" theory (1955). Penrose hypothesized that there is a higher rate of mutations in the male germ line than in the female germ line, because male germ cells are continuously replicating through spermatogenesis, and therefore have a greater chance to accumulate mutations with each new division (Penrose, 1955). Female germ cells only undergo about 24 cell divisions total through oogenesis, all of which happen before birth. Male germ cells, on the other hand, have undergone 30 cell divisions by puberty, and then go through one cell division approximately every 16 days, or about 23 times a year. So the older men get, the more divisions the spermatozoa undergo (Risch,

Reich, Wishnick, & McCarthy, 1987). Therefore, if an increase in mutations is due to an increase in germ cell replications (Penrose, 1955), then more mutations should occur in male germ cells than female germ cells. Moreover, as paternal age increases, there should be a linear increase in mutations, and therefore birth defect rates. Although it is not likely that the probability of every type of birth defect increases with more replications (Crow, 2000; Risch et al., 1987), some evidence exists that mutations associated with certain birth defects do increase with an increasing number of replications. These birth defects should have a higher prevalence in children born to older men. Evolutionarily, it also makes sense that the mutation rate of sperm may increase with age, because in the distant past, very few males survived to reproduce in their 40s or 50s. Therefore, there was probably little evolutionary need to reduce the high mutation rates that arose with advanced age (Crow, 2000). A few studies have also shown that a higher percentage of sperm with damaged DNA (double-strand breaks) has been found in older men (Singh, Muller, & Berger, 2003). If there is an association between an increase in damaged sperm and birth defect outcomes, this would also suggest that advanced paternal age may result in an increase in birth defect outcomes.

Numerous studies have suggested that the rates of autosomal dominant disorders are correlated with paternal age (Glaser et al., 2003; Penrose, 1955; Singer, Bower, Southall, & Goldblatt, 1999; Thacker, 2004; Vogel & Rathenberg, 1975). Autosomal dominant disorders that require a single-gene mutation for expression are most commonly thought to be related to paternal age (Crow, 2000; Stene & Stene, 1977). Indeed, the only two disorders that authors seem to consistently agree increase with advanced paternal age are de novo cases of Apert syndrome and achondroplasia (Glaser

et al., 2003; Hurst & Ellegren, 2002; Risch et al., 1987; Singer et al., 1999; Thacker, 2004), which are both single-gene, autosomal dominant mutations. One study (Glaser et al., 2003) concluded that about 99% of all Apert syndrome cases were caused by mutations in the male germ line. Even though the cases that have been associated most strongly with paternal age thus far are all caused by single gene mutations, there is no reason not to believe that these patterns cannot also hold true for more complex defects (Crow, 2000). Autosomal dominant single-gene defects are simply inherited traits, and therefore are much easier to observe than more complex traits (Crow, 2000). However, mutation rates would most likely still increase with age, regardless of the complexity of the disorder.

There may be other scientific explanations for an increase in mutations, and therefore birth defects, as paternal age increases. One study has suggested that the rate of apoptosis, or programmed cell death, in sperm decreases as men age. This would mean that more damaged sperm are able to survive to fertilize eggs as paternal age increases (Singh et al., 2003). This is very plausible, because there is also evidence that DNA repair mechanisms in somatic cells fail more often with advanced age (Singh, Danner, Tice, Brant, & Schneider, 1990). Since both apoptosis of sperm cells and DNA repair of somatic cells serve to eliminate error in transmission of genetic information, it is likely that these two pathways exhibit the same decline in function with increased age (Singh et al., 2003). Also, it may be possible that sperm with specific mutations also may possess some other beneficial quality that would make them more likely to be selected for fertilization over other, non-damaged sperm (Glaser et al., 2003; Hurst & Ellegren, 2002).

The distribution of paternal ages is positively skewed. This is because there are no real biological limitations on paternal age as there are for maternal age (Risch et al., 1987). If a paternal age effect for some birth defects is independent of maternal age effects, the health care implications could be great. Couples with a father of a relatively advanced age may want to opt for genetic counseling before deciding to conceive.

From previous studies, it seems as if some groups of birth defects may be associated with advanced paternal age, but these disorders have not been studied enough to conclusively tell whether or not they are correlated with paternal age. Examples include ventricular and atrial septal defects, neural tube defects, trisomy disorders (Down, Edward, and Patau syndromes), craniosynostosis, and cleft palate/cleft lip (Balgir, 1984; Erickson & Bjerkedal, 1981; Glaser et al., 2003; Hook et al., 1981; Kazaura, Lie, & Skjaerven, 2004; McIntosh, Olshan, & Baird, 1995; Olshan, Schnitzer, & Baird, 1994; Singer et al., 1999). These groups of disorders seem to have some genetic factors, and therefore, it seems scientifically plausible that advanced paternal age could cause an increase in these specific types of birth defects.

Objective

The objective of this study was to ascertain whether or not paternal age is associated with the prevalence of selected groups of structural birth defects, using Texas birth defect registry data from 1996 to 2002. The following types of birth defects were analyzed: ventricular and atrial septal defects, neural tube defects (anencephaly, spina bifida, and encephalocele), trisomy disorders (trisomies 21, 13, and 18), craniosynostosis, cleft palate, and cleft lip (with or without cleft palate). Eleven groups of birth defects

were looked at overall. The null hypothesis for this analysis was the assumption that there is no paternal age effect for any of these specific birth defects.

Benefits of the Study

Paternal age tends not to be a critical factor of concern among most parents-to-be. If this study and others like it find a strong paternal age effect for one or more birth defects, then the implications could be substantial. If an association between increasing paternal age and an increased rate of birth defects is detected, it would hopefully encourage a greater number of older men to seek genetic counseling before trying to have a child. Currently, there are a large number of older fathers in the United States (Risch et al., 1987). If there is in fact an association between paternal age and birth defect rates, and more studies can link advanced paternal age to an increased risk of birth defects, then this knowledge may alter paternal decisions regarding delayed child-bearing. On the other hand, if no association can be found between paternal age and birth defect rates, this information would provide some reassurance to men regarding fathering children later in life. Either way, the birth defects registry that is used in this study is one of the largest birth defects data sets to be analyzed for this particular association, and will therefore have much power to discriminate whether or not advanced paternal age is truly associated with these specific birth defect rates.

CHAPTER 2

METHODS

The Texas Department of State Health Services (DSHS) has maintained a database of birth defect cases in Texas from 1994 to the present (Forrester & Canfield, 2000). Only selected health regions in Texas were monitored using active surveillance before 1999, when birth defect monitoring became statewide (Forrester & Canfield, 2000). Even though, because of inclusion requirements, not all Texas structural birth defects are listed in the Texas Birth Defects Registry (TBDR), it is still a fairly complete listing of birth defect cases, and it is the most comprehensive source of birth defect data in Texas. Actually, in terms of the number of birth defect cases added per year (about 13,000), the Texas Birth Defects Registry is currently the largest active surveillance birth defects registry in the United States, and the second largest in the world (personal comm., Peter Langlois, 7/13/05). Therefore, the numbers of birth defect cases analyzed in this study were larger than in almost any other articles published thus far on the topic of paternal age and birth defect rates.

Dr. Peter Langlois, the senior epidemiologist of Texas DSHS's Birth Defects Epidemiology and Surveillance Branch, granted permission for Natalie Archer, a graduate student, to have access to TBDR and Texas birth certificate information that had

all identifiers removed (a copy of the letter is attached). Identifiers were not needed for this study, and all data used were appropriately abstracted.

Research Design

This was a descriptive epidemiological study designed to examine the relationship between different paternal age groups and rates of eleven specific birth defects.

Study Population

The population for the denominator data (to calculate prevalence rates of the selected birth defects) consisted of all live births in Texas (determined from birth certificates) from 1996 to 2002. Since all liveborn infants in Texas are required by law to have a birth certificate, the denominator population should have come reasonably close to encompassing all live-birth infants born in Texas. The Texas birth certificate cases included live births both with and without birth defects. The birth defect case populations used for the numerator data included all cases of the specific birth defect types to be analyzed (the septal defects, trisomy disorders, neural tube defects, craniosynostosis, and cleft palate/cleft lip) that were listed in the Texas Birth Defects Registry between January 1, 1996 and December 31, 2002. This TBDR data encompasses both liveborn infants and fetuses. To be included in the TBDR, an infant or fetus must have a reported structural birth defect or developmental disability that is diagnosed either prenatally or within one year after delivery, and must have a maternal residence in an area covered by the registry at the time of delivery (Forrester & Canfield, 2000; Texas Department of State Health Services, 2004).

Data Collection

The data used in this study had already been collected between 1996 and 2002 by the Texas Department of State Health Services. This data included demographic information about the parents of each child, such as paternal and maternal ages and race/ethnicities, as well as a wealth of medical information, including whether or not each child had a birth defect, and if so, the type of disorder. All information that was needed for this study was available in either the Texas Birth Defects Registry or the Texas Vital Statistics database of Texas birth certificates.

Confounding Factors

Any factors that were thought to have an impact on the relationship between paternal age and the rate of birth defects were adjusted for in this analysis. Previous studies listed maternal age and parity as potential confounding factors (Kazaura et al., 2004; McIntosh et al., 1995; Olshan et al., 1994). It is possible that parity may be associated with both maternal and paternal age. Maternal age, parity, and maternal and paternal race/ethnicity were all examined as confounding factors in the analysis.

Analysis

First, age-specific prevalence rates were calculated for each of the specific birth defects to be analyzed. Prevalence rates were found for six paternal age groups – age less than 20, 20-24, 25-29, 30-34, 35-39, and age 40 and over. Other studies used eight paternal age groups rather than six, splitting up the highest age group into three different groups: 40-44, 45-49, and 50+ (Kazaura et al., 2004; McIntosh et al., 1994; Olshan et al., 1994). Six groups were used instead of eight in this analysis because some of the birth defects had very small numbers of cases for the advanced paternal ages. With the highest

age group separated into three groups, there were insufficient numbers of cases to draw the correct associations between those paternal age groups and birth defect prevalence, especially when the other confounding factors were taken into account. The numerator values were the number of cases of each specific birth defect for each paternal age group, obtained from the Texas Birth Defects Registry. The denominator values were the total number of births for each paternal age group, obtained from the Texas birth certificate database. SAS was used to find the crude prevalence rates for the different paternal age groups. SPSS version 13.0 ("SPSS," 2004) was then used to generate some descriptive statistics about the different paternal age groups.

Finally, Poisson regression was used to determine if there was an association between the paternal age groups and each of the specific birth defect rates with adjustment for maternal age, maternal and paternal race/ethnicity, and parity. SAS, version 9 ("SAS," 2004), was used to perform the Poisson regression analyses. In addition to giving overall Chi-square values and corresponding p-values for each factor, this regression yielded prevalence ratios for each paternal age group, which represented the likelihood of each paternal age group to have a child affected with a birth defect relative to the reference paternal age category of 25-29. The paternal age group 25-29 was chosen as the reference age category because the greatest number of fathers belonged to this age group. Also, the choice of an age group in the middle of the possible paternal ages made it possible to look at prevalence ratios for the very young as well as older paternal age groups. A number of other similar studies also used this paternal age group as the reference category (Kazaura et al., 2004; McIntosh et al., 1994; Olshan et al., 1994). A prevalence ratio is basically the same as a relative risk, but instead of knowing

the incidence of the defects, the prevalence of the defects is known. Prevalence is used instead of incidence when referring to birth defect rates, since some fetuses with defects that are spontaneously aborted cannot be counted, and since the denominator only includes live births.

Poisson regression was chosen over other types of regression because the dependent variable in this analysis only had non-negative integer values, which represented counts of the number of certain birth defects per age group. Because count data such as this tends to be skewed, its distribution is usually not normal, and instead follows a Poisson distribution. Assumptions for Poisson regression are not affected by skewness of the distribution, whereas a normal distribution is an assumption that must be met when using traditional regression methods (Allison, 1999; Stene & Stene, 1977).

CHAPTER 3

ANALYSIS RESULTS

In the Texas Birth Defects Registry, 1,496 cases were listed as having a neural tube defect, 15,786 with a ventricular or atrial septal defect, 3,181 with cleft palate/cleft lip, 716 with craniosynostosis, and 2,976 with a trisomy disorder from 1996 to 2002. Of those 24,155 potential cases, 4,528 of them were missing paternal age information. Therefore, these cases had to be excluded, and 19,627 cases were actually analyzed in this study. Almost all of the cases with missing parental race/ethnicity information were excluded after excluding cases with missing paternal ages, and none of the cases had any missing maternal age or parity information. Overall, 18.7% of the cases were missing paternal age information and had to be excluded from the analysis. However, some birth defect types had a smaller percentage of cases with missing information, and many had a larger percentage of missing information. Specific numbers of cases both excluded and used for each birth defect type are shown in Table 1.

The total number of Texas birth certificate records for live births from 1996 to 2002 was used as denominator information for the analyses. There were 2,042,554 live birth certificate records in the database. Of these, 302,083 (14.8%) had missing paternal age information, leaving 1,740,471 live births in the denominator.

Table 1. Total number of specific birth defect cases, number and percentage missing, and total number used in the analysis.

Birth Defect	Total (N)	Missing Paternal Age (%)	Total used in analysis (N)
Anencephaly	551	303 (55.0)	248
Spina bifida	753	189 (25.1)	564
Encephalocele	192	74 (38.5)	118
Ventricular septal defect	8113	1323 (16.3)	6790
Atrial septal defect	7673	1270 (16.6)	6403
Cleft palate alone (without cleft lip)	1118	198 (17.7)	920
Cleft lip (with or without cleft palate)	2063	406 (19.7)	1657
Craniosynostosis	716	80 (11.2)	636
Trisomy 21 (Down syndrome)	2335	465 (19.9)	1870
Trisomy 13 (Patau syndrome)	225	82 (36.4)	143
Trisomy 18 (Edwards syndrome)	416	138 (33.2)	278
All defects combined	24,155	4528 (18.7)	19,627

Crude prevalence rates were found by using SAS programs. First, crosstabs, or frequencies, of the six paternal age groups and the number of birth defect outcomes for each paternal age were calculated. This data was then merged with denominator data for all Texas births (the number of births for each paternal age group), as well as with Poisson probability information, which was provided by the Texas Department of State

Health Services (Peter Langlois, 2005). With the numerator and denominator data as well as the Poisson probability data, crude prevalence rates and 95% confidence intervals were calculated. These paternal age group prevalence rates, which are unadjusted for other confounding factors, are shown in Table 2. The confidence limits in the table show the possible range of each of the prevalence rates. From this table, it can be seen that some of the paternal age groups appeared to have higher prevalence rates than other age groups for particular birth defects. These higher prevalence rates usually tended to occur among either the youngest or the oldest paternal age groups. However, since the crude prevalence rates do not take into account any other factors that may play a part in the differences seen among the age groups, such as maternal age, these crude rates cannot really be used to determine whether or not there is a true association between paternal age and rates of the selected birth defects.

Table 2. Crude prevalence rates of selected birth defects by paternal age group, Texas births from 1996 – 2002.*

Birth Defect Type	Paternal Age Group	Number of Cases	Prevalence Rate	95% Confidence Limits
Anencephaly	< 20	15	1.44	0.81 – 2.38
	20-24	56	1.50	1.13 – 1.95
	25-29	82	1.73	1.38 – 2.15
	30-34	55	1.32	1.00 – 1.72
	35-39	24	0.99	0.64 – 1.47
	40 +	16	1.21	0.69 – 1.96
Spina bifida	< 20	28	2.69	1.79 – 3.89
	20-24	119	3.19	2.61 – 3.76
	25-29	163	3.45	2.92 – 3.98
	30-34	132	3.18	2.63 – 3.72
	35-39	78	3.22	2.55 – 4.02
	40 +	44	3.32	2.41 – 4.45

Table 2 (Continued).

Birth Defect Type	Paternal Age Group	Number of Cases	Prevalence Rate	95% Confidence Limits
Encephalocele	< 20	8	0.77	0.33 – 1.51
	20-24	24	0.64	0.41 – 0.96
	25-29	33	0.70	0.48 – 0.98
	30-34	26	0.63	0.41 – 0.92
	35-39	17	0.70	0.41 – 1.12
	40 +	10	0.75	0.36 – 1.39
Ventricular septal defect	< 20	391	37.58	33.85 – 41.30
	20-24	1362	36.48	34.54 – 38.42
	25-29	1781	37.68	35.93 – 39.43
	30-34	1591	38.29	36.41 – 40.17
	35-39	1001	41.34	38.78 – 43.90
	40 +	664	50.03	46.23 – 53.84
Atrial septal defect	< 20	377	36.23	32.58 – 39.89
	20-24	1310	35.09	33.19 – 36.99
	25-29	1652	34.95	33.27 – 36.64
	30-34	1453	34.97	33.17 – 36.76
	35-39	956	39.48	36.98 – 41.98
	40 +	655	49.35	45.57 – 53.13
Cleft palate alone (without cleft lip)	< 20	50	4.81	3.57 – 6.34
	20-24	181	4.85	4.14 – 5.55
	25-29	250	5.29	4.63 – 5.94
	30-34	221	5.32	4.62 – 6.02
	35-39	126	5.20	4.29 – 6.11
	40 +	92	6.93	5.59 – 8.50
Cleft lip (with or without cleft palate)	< 20	104	10.00	8.07 – 11.92
	20-24	401	10.74	9.69 – 11.79
	25-29	442	9.35	8.48 – 10.22
	30-34	351	8.45	7.56 – 9.33
	35-39	235	9.70	8.46 – 10.95
	40 +	124	9.34	7.70 – 10 99

Table 2 (Continued).

Birth Defect Type	Paternal Age Group	Number of Cases	Prevalence Rate	95% Confidence Limits
Craniosynostosis	< 20	22	2.11	1.33 – 3.20
	20-24	91	2.44	1.96 – 2.99
	25-29	161	3.41	2.88 – 3.93
	30-34	168	4.04	3.43 – 4.65
	35-39	123	5.08	4.18 – 5.98
	40 +	71	5.35	4.18 – 6.75
Trisomy 21 (Down syndrome)	< 20	65	6.25	4.82 – 7.96
	20-24	254	6.80	5.97 – 7.64
	25-29	318	6.73	5.99 – 7.47
	30-34	432	10.40	9.42 – 11.38
	35-39	386	15.94	14.35 – 17.53
	40 +	415	31.27	28.26 – 34.28
Trisomy 13 (Patau syndrome)	< 20	11	1.06	0.53 – 1.89
	20-24	22	0.59	0.37 – 0.89
	25-29	28	0.59	0.39 – 0.86
	30-34	37	0.89	0.63 – 1.23
	35-39	33	1.36	0.94 – 1.91
	40 +	12	0.90	0.47 – 1.58
Trisomy 18 (Edwards syndrome)	< 20	9	0.86	0.40 – 1.64
	20-24	32	0.86	0.59 – 1.21
	25-29	53	1.12	0.84 – 1.47
	30-34	56	1.35	1.02 – 1.75
	35-39	64	2.64	2.04 – 3.37
	40 +	64	4.82	3.71 – 6.16

*The number of cases, the prevalence rate, and the 95% confidence limits for each paternal age group are shown. Prevalence rates are per 10,000 live births.

Next, paternal age group prevalence ratios were calculated and examined for each of the eleven birth defects of interest. A reference category needed to be defined for the prevalence ratios, because the prevalence ratios would reflect the likelihood of each of the paternal age groups to have a child affected with a specific birth defect relative to a reference paternal age category. As mentioned previously, the reference category chosen to compare the other age groups with was the paternal age group of 25-29. The 95% confidence limits were also calculated for each prevalence ratio. In addition to the prevalence ratios and 95% confidence intervals for each age group, the overall F-values, Chi-square values, and their corresponding p-values for the paternal age groups were found for each birth defect analyzed. This was all calculated using Poisson regression.

When finding the paternal age group prevalence ratios using Poisson regression, the confounding factors of maternal age, maternal race/ethnicity, paternal race/ethnicity, and parity (previous live births) were also examined. Maternal age was deemed to be a large confounder for most of the birth defects that were analyzed. This is because maternal age and paternal age are highly correlated. Since changes in paternal age would most likely be correlated with maternal age, maternal age was adjusted in all analyses. Analyses were performed using maternal age as both a categorical and as a continuous factor; however, the results obtained from the analyses using maternal age as a continuous factor are focused upon. Other studies strongly suggested tightly controlling for maternal age factors by adjusting for by single years of mothers' age (McIntosh et al., 1995; Olshan et al., 1994; Erickson & Bjerkedal, 1981), so it was decided that adjusting for maternal age as a continuous variable would give the most correct results, because it would minimize the possibility of residual confounding within broader categories of

maternal age (Kazaura et al., 2004). Also, Poisson regressions were performed using only maternal age as the independent variable. Poisson regressions were first done using maternal age groups (age as a categorical variable), and then performed using maternal age as a continuous variable. The p-values obtained from maternal age as a continuous variable were better for most birth defects than those obtained when using maternal age groups. Because most of the p-values were more significant when maternal age was used as a continuous variable, and also because using a continuous variable would yield more statistical power in multivariate analysis, a continuous variable was thought to be a better way to represent maternal age than using a categorical one. The only drawback to using maternal age as a continuous variable is that this assumes that the maternal age effect is linear. However, since maternal age was more significant in the regression model for most birth defects when it was represented as a continuous variable, it would seem that a linear assumption in this case was a valid one. Maternal and paternal race/ethnicity (white, African-American, Hispanic, or other) were both adjusted for as categorical variables, and a continuous variable was used for parity.

Because maternal age is closely tied to paternal age, maternal age was always adjusted for in every analysis. However, for the other confounding factors, backwards elimination was used to determine the factors included in the Poisson regression model. For each birth defect type analyzed, all factors were initially included in the regression equation. After the Poisson regression had run, and overall Chi-square values and the corresponding p-values were obtained for all factors, the variable with the largest, or least significant, p value was removed, and the Poisson regression was run again with the remaining variables. Of course, since the independent variable of interest was the

paternal age groups, it was never removed from the analysis, nor was maternal age, because it is an important confounder. The other three confounding factors, however, were removed from the Poisson regression analysis, via backwards elimination, if they were not significant. This removal of factors that were not significant was done because if too many meaningless variables are left in a regression model, this leads to statistical imprecision (Hair, Anderson, Tatham, & Black, 1998). Therefore, all variables that were not statistically meaningful, other than paternal age groups and maternal age, were removed from the equation so that if an association truly existed between the paternal age groups and birth defect rates, it had a greater chance of being found.

First, Poisson regression analyses were performed and prevalence ratios were found using maternal age as a categorical variable. Maternal age was split into the same six age group categories as paternal age: <20, 20-24, 25-29, 30-34, 35-39, and 40+. Maternal and paternal race/ethnicity and parity were also adjusted for as well, if they were significant, using backwards elimination. Table 3 shows the adjusted prevalence ratios, relative to the reference age group of 25-29, and 95% confidence limits for the different paternal age groups for each birth defect type. This table also shows prevalence ratios that have only been adjusted for maternal age as a categorical variable, and no other factors. For many of the birth defects, the prevalence ratios that are adjusted only for maternal age show quite different trends than the crude prevalence rates in Table 2, showing that maternal age is definitely an important confounder for paternal age. When controlling for maternal age as a categorical variable, atrial septal defects, cleft lip, trisomy 21, and trisomy 13 showed higher prevalence ratios at the youngest paternal age groups than the reference age category, and ventricular & atrial septal defects and trisomy

21 had higher prevalence ratios at the oldest paternal age group than the reference category. However, only one birth defect type, cleft lip, had a significant paternal age effect, as ascertained by the Chi-square value for the paternal age groups overall. It was the only birth defect for which one of the paternal age group prevalence ratios had confidence limits that did not encompass 1.

Table 3. Adjusted prevalence ratios for paternal age groups relative to the reference age group of 25-29 for selected birth defects, with maternal age controlled for as a categorical variable.*

Birth Defect Type	Paternal Age Group	Adjusted Prevalence Ratio (95% Confidence Limits)	Prevalence Ratio Adjusted for Maternal Age Only
Anencephaly[6]	< 20	0.59 (0.31 – 1.08)	0.54 (0.26 – 1.09)
	20-24	0.72 (0.50 – 1.03)	0.70 (0.46 – 1.06)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.90 (0.63 – 1.28)	0.91 (0.60 – 1.36)
	35-39	0.80 (0.48 – 1.28)	0.84 (0.47 – 1.44)
	40 +	1.00 (0.54 – 1.75)	1.10 (0.53 – 2.09)
Spina bifida[5]	< 20	0.73 (0.41 – 1.25)	0.72 (0.44 – 1.16)
	20-24	0.91 (0.67 – 1.24)	0.92 (0.70 – 1.21)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.91 (0.68 – 1.22)	0.91 (0.70 – 1.17)
	35-39	0.94 (0.65 – 1.34)	0.93 (0.67 – 1.27)
	40 +	0.90 (0.56 – 1.41)	0.92 (0.61 – 1.36)
Encephalocele[8]	< 20	0.84 (0.24 – 2.55)	0.84 (0.24 – 2.55)
	20-24	0.71 (0.34 – 1.46)	0.71 (0.34 – 1.46)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	1.13 (0.55 – 2.28)	1.13 (0.55 – 2.28)
	35-39	1.23 (0.50 – 2.87)	1.23 (0.50 – 2.87)
	40 +	1.28 (0.41 – 3.50)	1.28 (0.41 – 3.50)
Ventricular septal defect[4]	< 20	0.98 (0.87 – 1.10)	1.01 (0.87 – 1.16)
	20-24	0.96 (0.90 – 1.03)	0.98 (0.90 – 1.07)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.98 (0.92 – 1.05)	0.95 (0.88 – 1.03)
	35-39	0.97 (0.90 – 1.05)	0.93 (0.84 – 1.02)
	40 +	1.05 (0.95 – 1.15)	1.00 (0.89 – 1.11)

Table 3 (Continued).

Birth Defect Type	Paternal Age Group	Adjusted Prevalence Ratio (95% Confidence Limits)	Prevalence Ratio Adjusted for Maternal Age Only
Atrial septal defect[2]	< 20	1.04 (0.88 – 1.22)	1.06 (0.85 – 1.30)
	20-24	1.03 (0.94 – 1.14)	1.04 (0.92 – 1.19)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.94 (0.85 – 1.02)	0.92 (0.82 – 1.04)
	35-39	0.96 (0.86 – 1.07)	0.93 (0.81 – 1.08)
	40 +	1.05 (0.93 – 1.20)	1.03 (0.86 – 1.22)
Cleft palate alone (without cleft lip)[6]	< 20	0.85 (0.62 – 1.15)	0.81 (0.55 – 1.17)
	20-24	0.92 (0.77 – 1.11)	0.91 (0.73 – 1.13)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.97 (0.82 – 1.14)	0.99 (0.81 – 1.21)
	35-39	0.92 (0.75 – 1.14)	0.94 (0.73 – 1.21)
	40 +	1.22 (0.95 – 1.55)	1.22 (0.91 – 1.63)
Cleft lip (with or without cleft palate)[6]	< 20	1.26 (0.98 – 1.60)	1.21 (0.90 – 1.61)
	20-24	1.22 (1.04 – 1.41)	1.20 (1.01 – 1.42)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.91 (0.78 – 1.05)	0.92 (0.77 – 1.08)
	35-39	1.02 (0.85 – 1.21)	1.03 (0.84 – 1.27)
	40 +	0.93 (0.74 – 1.17)	0.95 (0.72 – 1.23)
Craniosynostosis[2]	< 20	0.84 (0.54 – 1.30)	0.76 (0.46 – 1.22)
	20-24	0.94 (0.73 – 1.22)	0.81 (0.62 – 1.04)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.96 (0.73 – 1.25)	1.05 (0.84 – 1.30)
	35-39	1.08 (0.81 – 1.44)	1.21 (0.94 – 1.55)
	40 +	1.12 (0.81 – 1.56)	1.17 (0.86 – 1.58)
Trisomy 21 (Down syndrome)[7]	< 20	1.13 (0.85 – 1.49)	1.14 (0.85 – 1.53)
	20-24	1.16 (0.98 – 1.36)	1.18 (0.99 – 1.40)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	1.08 (0.95 – 1.24)	1.05 (0.91 – 1.22)
	35-39	0.98 (0.84 – 1.15)	0.94 (0.80 – 1.11)
	40 +	1.15 (0.98 – 1.35)	1.11 (0.93 – 1.32)

Table 3 (Continued).

Birth Defect Type	Paternal Age Group	Adjusted Prevalence Ratio (95% Confidence Limits)	Prevalence Ratio Adjusted for Maternal Age Only
Trisomy 13 (Patau syndrome) [1]	< 20	1.91 (0.67 – 5.33)	1.80 (0.86 – 3.67)
	20-24	1.07 (0.49 – 2.37)	1.10 (0.66 – 1.82)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	1.02 (0.49 – 2.23)	1.03 (0.67 – 1.60)
	35-39	1.15 (0.54 – 2.58)	1.06 (0.66 – 1.72)
	40 +	0.50 (0.19 – 1.30)	0.47 (0.24 – 0.88)
Trisomy 18 (Edwards syndrome) [1]	< 20	0.77 (0.31 – 1.78)	0.75 (0.29 – 1.78)
	20-24	0.85 (0.51 – 1.41)	0.85 (0.49 – 1.43)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.83 (0.55 – 1.26)	0.83 (0.54 – 1.29)
	35-39	0.92 (0.59 – 1.45)	0.93 (0.58 – 1.50)
	40 +	0.96 (0.59 – 1.57)	1.00 (0.60 – 1.66)

*Prevalence ratios are based on Texas births from 1996 – 2002. The prevalence ratios and 95% confidence limits for each paternal age group are shown, both adjusted for maternal age plus other significant factors as well as for maternal age alone, as a categorical variable.
[1] Adjusted for maternal age and parity
[2] Adjusted for maternal age and paternal race/ethnicity
[3] Adjusted for maternal age and maternal race/ethnicity
[4] Adjusted for maternal age, paternal race/ethnicity, and maternal race/ethnicity.
[5] Adjusted for maternal age, paternal race/ethnicity, and parity.
[6] Adjusted for maternal age, maternal race/ethnicity, and parity.
[7] Adjusted for maternal age, maternal race/ethnicity, paternal race/ethnicity, and parity
[8] Adjusted for maternal age only.

Next, Poisson regression analyses were performed and prevalence ratios were found using maternal age as a continuous variable. The overall Chi-square and p-values for paternal age, maternal age, and a list of the other factors that the paternal age prevalence ratios are adjusted for in the final regression equation (that had a p-value of .05 or less) for each of the birth defects are shown in Table 4. The prevalence ratios, adjusted for maternal age as a categorical variable, for the different paternal age groups relative to the reference age group of 25-29, are listed in Table 5 for each of the birth

defect types analyzed. Maternal and paternal race/ethnicity and parity were also adjusted for, if they were significant, using backwards elimination. Table 5 also contains a column that shows prevalence ratios that have only been adjusted for maternal age as a continuous factor. The extent of confounding due to factors other than maternal age can be examined by looking at the differences between the two prevalence ratios for each paternal age group.

Table 4. Chi-square and corresponding p-values for paternal age, maternal age, and the other variables adjusted for in the Poisson regression analyses of selected birth defects. Maternal age was controlled for as a continuous variable.

Birth Defect Type	Independent Variables	Chi-square value	P value
Anencephaly	Paternal age	0.76	0.5800
	Maternal age	18.79	<.0001
	Parity	39.61	<.0001
Spina bifida	Paternal age	0.73	0.9811
	Maternal age	0.00	0.9482
	Paternal race/ethnicity	18.63	0.0003
	Parity	7.24	0.0071
Encephalocele	Paternal age	1.94	0.8580
	Maternal age	1.62	0.2030
	Maternal race/ethnicity	8.10	0.0441
Ventricular septal defect	Paternal age	20.98	0.0008
	Maternal age	91.34	<.0001
	Paternal race/ethnicity	32.70	<.0001
	Maternal race/ethnicity	42.72	<.0001
Atrial septal defect	Paternal age	33.68	<.0001
	Maternal age	75.42	<.0001
	Paternal race/ethnicity	52.33	<.0001
Cleft palate alone (without cleft lip)	Paternal age	7.14	0.2102
	Maternal age	0.13	0.7221
	Maternal race/ethnicity	31.82	<.0001

Table 4 (Continued).

Birth Defect Type	Independent Variables	Chi-square value	P value
Cleft lip (with or without cleft palate)	Paternal age	12.10	0.0335
	Maternal age	0.01	0.9254
	Maternal race/ethnicity	26.1	<.0001
	Parity	25.86	<.0001
Craniosynostosis	Paternal age	4.66	0.4587
	Maternal age	9.29	0.0023
	Paternal race/ethnicity	82.49	<.0001
	Parity	4.18	0.0408
Trisomy 21 (Down syndrome)	Paternal age	81.98	<.0001
	Maternal age	456.36	<.0001
	Paternal race/ethnicity	42.66	<.0001
	Parity	6.46	0.0110
Trisomy 13 (Patau syndrome)	Paternal age	12.24	0.0316
	Maternal age	15.46	<.0001
	Parity	6.65	0.0099
Trisomy 18 (Edwards syndrome)	Paternal age	20.46	0.0010
	Maternal age	105.63	<.0001
	Parity	10.31	0.0013

As shown in Table 4, when maternal age was controlled for as a continuous variable, paternal age was found to be a significant factor in the regression model for ventricular septal defects, atrial septal defects, cleft lip (with or without cleft palate), and all three of the trisomy disorders (Down syndrome, Patau syndrome, and Edwards syndrome). It was not a significant factor for any of the neural tube defects, cleft palate alone (without cleft lip), or for craniosynostosis.

Table 5. Adjusted prevalence ratios for paternal age groups relative to the reference age group of 25-29 for selected birth defects, with maternal age controlled for as a continuous variable.*

Birth Defect Type	Paternal Age Group	Adjusted Prevalence Ratio (95% Confidence Limits)	Prevalence Ratio Adjusted for Maternal Age Only
Anencephaly[1]	< 20	0.65 (0.32 – 1.23)	0.55 (0.29 – 1.00)
	20-24	0.72 (0.48 – 1.08)	0.69 (0.47 – 1.00)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.94 (0.62 – 1.41)	0.94 (0.64 – 1.37)
	35-39	0.79 (0.44 – 1.37)	0.83 (0.48 – 1.37)
	40 +	1.02 (0.50 – 1.92)	1.11 (0.58 – 2.00)
Spina bifida[5]	< 20	0.81 (0.45 – 1.37)	0.78 (0.50 – 1.18)
	20-24	0.92 (0.67 – 1.27)	0.93 (0.72 – 1.19)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.93 (0.68 – 1.28)	0.92 (0.72 – 1.17)
	35-39	0.95 (0.64 – 1.40)	0.93 (0.68 – 1.25)
	40 +	0.95 (0.57 – 1.53)	0.95 (0.65 – 1.38)
Encephalocele[3]	< 20	0.84 (0.33 – 1.93)	0.83 (0.34 – 1.84)
	20-24	0.80 (0.44 – 1.42)	0.79 (0.45 – 1.37)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	1.02 (0.58 – 1.78)	1.04 (0.60 – 1.78)
	35-39	1.26 (0.63 – 2.46)	1.30 (0.66 – 2.47)
	40 +	1.51 (0.63 – 3.31)	1.50 (0.64 – 3.22)
Ventricular septal defect[4]	< 20	1.16 (1.03 – 1.31)	1.20 (1.00 – 1.44)
	20-24	1 05 (0.98 – 1.13)	1.07 (0.96 – 1.21)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.95 (0.89 – 1.02)	0.92 (0.83 – 1.03)
	35-39	0.97 (0.89 – 1.05)	0.92 (0.81 – 1.06)
	40 +	1.11 (1.00 – 1.23)	1.06 (0.90 – 1.25)
Atrial septal defect[2]	< 20	1.28 (1.10 – 1.47)	1.30 (1.07 – 1.57)
	20-24	1.12 (1.03 – 1.23)	1.14 (1.01 – 1.28)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.91 (0.83 – 0.99)	0.89 (0.79 – 1.00)
	35-39	0.94 (0.84 – 1.05)	0.92 (0 80 – 1.06)
	40 +	1.10 (0.97 – 1 25)	1.08 (0.91 – 1.27)

Table 5 (Continued).

Birth Defect Type	Paternal Age Group	Adjusted Prevalence Ratio (95% Confidence Limits)	Prevalence Ratio Adjusted for Maternal Age Only
Cleft palate alone (without cleft lip)[3]	< 20	0.98 (0.72 – 1.33)	0.93 (0.71 – 1.22)
	20-24	0.96 (0.79 – 1.15)	0.93 (0.79 – 1.10)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.97 (0.81 – 1.16)	0.99 (0.85 – 1.16)
	35-39	0.94 (0.75 – 1.18)	0.96 (0.79 – 1.17)
	40 +	1.30 (1.00 – 1.68)	1.27 (1.01 – 1.60)
Cleft lip (with or without cleft palate)[6]	< 20	1.19 (0.92 – 1.51)	1.13 (0.91 – 1.38)
	20-24	1.20 (1.03 – 1.40)	1.18 (1.03 – 1.40)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.87 (0.75 – 1.02)	0.88 (0.77 – 1.00)
	35-39	0.98 (0.81 – 1.18)	0.99 (0.84 – 1.16)
	40 +	0.94 (0.73 – 1.19)	0.94 (0.77 – 1.15)
Craniosynostosis[5]	< 20	0.85 (0.52 – 1.33)	0.80 (0.47 – 1.27)
	20-24	0.84 (0.64 – 1.10)	0.82 (0.62 – 1.08)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	1.03 (0.82 – 1.30)	1.05 (0.82 – 1.33)
	35-39	1.20 (0.91 – 1.57)	1.19 (0.90 – 1.57)
	40 +	1.25 (0.89 – 1.73)	1.17 (0.82 – 1.64)
Trisomy 21 (Down syndrome)[5]	< 20	3.01 (2.1 – 4.23)	3.10 (1.97 – 4.71)
	20-24	1.86 (1.50 – 2.30)	1.93 (1.48 – 2.51)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.89 (0.74 – 1.08)	0.86 (0.69 – 1.09)
	35-39	0.86 (0.70 – 1.06)	0.82 (0.64 – 1.06)
	40 +	1.16 (0.93 – 1.45)	1.12 (0.85 – 1.47)
Trisomy 13 (Patau syndrome)[1]	< 20	4.89 (1.84 – 11.93)	4.32 (2.16 – 8.27)
	20-24	1.62 (0.79 – 3.27)	1.61 (0.96 – 2.65)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0 97 (0.53 – 1.83)	0.97 (0.63 – 1.52)
	35-39	1.03 (0.51 – 2.08)	1.05 (0.64 – 1.73)
	40 +	0.53 (0.20 – 1.32)	0.53 (0.27 – 1.03)

Table 5 (Continued).

Birth Defect Type	Paternal Age Group	Adjusted Prevalence Ratio (95% Confidence Limits)	Prevalence Ratio Adjusted for Maternal Age Only
Trisomy 18 (Edwards syndrome) [1]	< 20	2.89 (1.31 – 5.74)	2.65 (0.69 – 7.76)
	20-24	1.48 (0.94 – 2.31)	1.48 (0.70 – 3.00)
	25-29	1.00 (Reference)	1.00 (Reference)
	30-34	0.66 (0.45 – 0.97)	0.66 (0.36 – 1.24)
	35-39	0.79 (0.53 – 1.18)	0.80 (0.42 – 1.55)
	40 +	0.98 (0.63 – 1.53)	1.00 (0.49 – 2.06)

*Prevalence ratios are based on Texas births from 1996 – 2002. The prevalence ratios and 95% confidence limits for each paternal age group are shown, adjusted for maternal age plus other significant factors as well as for maternal age alone, as a categorical variable.
[1] Adjusted for maternal age and parity.
[2] Adjusted for maternal age and paternal race/ethnicity.
[3] Adjusted for maternal age and maternal race/ethnicity
[4] Adjusted for maternal age, paternal race/ethnicity, and maternal race/ethnicity.
[5] Adjusted for maternal age, paternal race/ethnicity, and parity.
[6] Adjusted for maternal age, maternal race/ethnicity, and parity

When maternal age was adjusted for as a continuous variable, many of the same general trends were seen as when maternal age was controlled for as a categorical variable. Encephalocele and craniosynostosis were the only two birth defects whose prevalence ratios seemed to have a trend of positive association with their defect rates throughout all age groups (Tables 3 and 5). However, paternal age was not a significant factor for either of these birth defects, and none of their paternal age groups' confidence limits were significant (did not encompass 1). In Table 5, ventricular septal defects, atrial septal defects, and trisomy 21 all showed higher prevalence ratios for both the youngest and oldest age groups than the reference age category of 25-29. Significantly higher prevalence ratios were also found for the youngest age categories for cleft lip, trisomy 13, and trisomy 18, when compared to the reference age category.

CHAPTER 4

DISCUSSION AND CONCLUSIONS

Discussion

An analysis of the crude prevalence rates for the six different paternal age groups shows that the prevalence rates for several of the selected birth defect types seems to increase with advancing paternal age. As shown in Table 2, the rates for ventricular septal defects, atrial septal defects, cleft palate alone (without cleft lip), craniosynostosis, Down syndrome (trisomy 21), and Edwards syndrome (trisomy 18) all increased with paternal age. For many of these birth defects, the prevalence rates seemed to rise rapidly only for the two oldest paternal age groups, and sometimes just for the oldest age group (of fathers 40 years of age or over). This may indicate that perhaps the prevalence rates of these defects are related to paternal ages of over 35 or 40, but it is just as likely that these prevalence rates increased in these age groups only because the mothers were also older, and advanced maternal age was associated with a higher prevalence of birth defects.

For a small number of birth defects, such as cleft lip (with or without cleft palate) and Patau syndrome (trisomy 13), the youngest or two youngest paternal age groups of <20 and 20-24 had higher prevalence rates than many of the other paternal age groups. Again, however, this trend could have been confounded by maternal age. The adjusted prevalence ratios, which take into account maternal age, maternal race/ethnicity, paternal race/ethnicity, and parity, are needed to determine if an independent association between paternal age and these birth defect prevalence rates exists. However, it is worth noting

that a comparison of the crude prevalence rates, only maternal age-adjusted prevalence ratios, and prevalence ratios adjusted for maternal age as well as other factors seems to show that maternal age was the main confounder, while the other confounding factors did not substantially change the estimated prevalence ratios for most paternal age groups.

The use of Poisson regression analyses of birth defect rates and their association with paternal age provided a method to adjust for these potential confounding factors. The regression results showed which factors were significantly associated with the specific birth defect prevalence rates, and yielded adjusted prevalence ratios for each paternal age group. Even after adjusting for confounders, when maternal age was controlled for as a continuous factor, paternal age was found to be significantly associated (an overall p-value of .05 or less) with the prevalence of ventricular septal defects, atrial septal defects, cleft lip (with or without cleft palate), Down syndrome (trisomy 21), Patau syndrome (trisomy 13), and Edwards syndrome (trisomy 18). Differing paternal age groups were not significantly associated with the prevalence of any neural tube defects (anencephaly, spina bifida, or encephalocele), with cleft palate alone (without cleft lip), or with craniosynostosis. Rather than being associated with paternal age, the prevalence of anencephaly seemed to be most associated with maternal age and parity. The prevalence of spina bifida was found to be associated with parity as well as paternal race/ethnicity, and the prevalence of both encephalocele and cleft palate were significantly associated with maternal race/ethnicity. The significant factors found for the prevalence of craniosynostosis were maternal age, paternal race/ethnicity, and parity.

The birth defect types whose rates were and were not significantly associated with paternal age were a bit unexpected. Penrose's copy-error hypothesis would suggest that

paternal age would not be very associated with prevalence rates for the three trisomy disorders. The trisomy disorders involve gaining an entire extra chromosome, whereas the biological basis of Penrose's hypothesis is that single-gene disorders, which only required a very small genetic mutation, would increase with advanced paternal age (Penrose, 1955). It seems unlikely that advanced paternal age would cause such a large genetic error as chromosomal non-disjunction, at least not according to this hypothesis. Also, even though a link between advanced paternal age and an increase in Apert syndrome is well-documented (Crow, 2000; Thacker, 2004), there was no significant association between the prevalence of craniosynostosis, the birth defect category of which Apert syndrome is a part, and paternal age. This could possibly be due to the fact that the rates of the other birth defects that also result in craniosynostosis may not be associated at all with paternal age, or the paternal ages at which craniosynostosis prevalence rates greatly increase could be at a very advanced paternal age (i.e., over age 55 or 60), and the younger ages in the "40+" category could have weakened the association.

An analysis of the adjusted prevalence ratios for the different paternal age groups also shows some surprising results. Although a few of the birth defects had higher prevalence ratios in the highest paternal age category of 40+ years of age relative to the reference category, all of the birth defects for which paternal age was significantly associated with prevalence showed that the younger paternal age groups (less than 20 and/or 20-24) had higher prevalence ratios, when maternal age was adjusted for as a continuous variable. The expectation was that if paternal age were associated with a birth defect's prevalence at all, increasing paternal age would show an increase in the

prevalence rate. However, atrial septal defects, cleft lip, trisomy 21, and trisomy 13 consistently showed the opposite association – the youngest paternal ages showed an increase in these birth defect prevalence rates. This association was seen whether or not maternal age was adjusted for as a continuous or a categorical variable; however, only when maternal age was used as a continuous variable were these prevalence ratios all significantly higher than the reference paternal age category. Higher prevalence ratios for ventricular and atrial septal defects, as well as for trisomy 21, were also found for ages 40 or over. However, of the birth defects where prevalence rate was significantly associated with paternal age, ventricular septal defect was the only one that showed a significantly higher prevalence ratio (confidence limits do not encompass 1) for the highest paternal age group, when maternal age was used as a continuous variable. When maternal age was adjusted for as a categorical factor, none of the birth defects showed significantly higher prevalence ratios for the oldest paternal age group. Other birth defect types, such as encephalocele, cleft palate alone, and craniosynostosis, appeared to have a trend of higher prevalence ratios among higher paternal age groups, but paternal age was not found to be an overall significant factor for any of these birth defects. Reasons that age was not a significant factor for these defects could include there not being enough cases to be able to have sufficient power to detect a difference that may in fact exist, or that age may have made a difference in prevalence rates, but the difference is very small and cannot be detected without a very large number of cases. For example, too small of a sample size could have been the reason that paternal age was not significant for encephalocele, since there were only 118 cases. The prevalence ratios showed a good

increasing trend for this birth defect, yet none of the prevalence ratios were significant at the .05 level.

Very interesting results were seen when the trisomy disorders were analyzed, and their prevalence ratios were calculated. When maternal age was adjusted for as a continuous variable, the three trisomy disorders had the highest prevalence ratios of all the birth defects at the youngest paternal ages. For the youngest paternal age group of men less than 20 years of age, the prevalence ratios were 2.89 for Edwards syndrome (trisomy 18), 3.01 for Down syndrome (trisomy 21), and 4.89 for Patau syndrome (trisomy 13). This indicates that fathers less than 20 years of age are more likely to have babies with these trisomies than fathers 25-29 years of age, with maternal age adjusted. Unlike mothers, where increasing age is associated with increasing prevalence rate, these results would suggest that for fathers, decreasing age is associated with an increase in prevalence rate for trisomy disorders, after maternal age has been adjusted for. Down syndrome showed a higher prevalence ratio in the highest paternal age group than in the reference group, so it would appear that at paternal ages 40 and above, the prevalence rate might increase slightly. However, the prevalence ratio for this highest age group is not nearly as large as the prevalence ratios of the two youngest paternal age categories. It is very likely that a majority of trisomy disorder cases are linked to increasing maternal age, but perhaps for those trisomy cases that occur among younger women, younger paternal age may be a risk factor for trisomy disorders. The prevalence ratios of trisomy 21 and trisomy 13 were higher in the youngest paternal age groups than in the reference age group when maternal age was adjusted for as a categorical variable, but the rates were not nearly as high as when maternal age was controlled for as a continuous variable.

It is possible that this discrepancy lies in the fact that by modeling maternal age as a continuous and linear variable, there may have been a misspecification of the maternal age effect. If a linear maternal age relationship was controlled for when its relationship was not actually linear, the true impact of maternal age might not have been adequately controlled for. This seems plausible, since younger women tend to have higher birth defect rates than ages 25-29, and very young men are likely to father children with very young women. A misspecification of the maternal age effect as being linear certainly seems like it might be the case for the trisomy 18 rates. For trisomy 18, the crude prevalence rates by maternal age in Texas from 1999 to 2001 showed a rate increase for mothers less than 20 years of age (Texas Department of State Health Services, 2004), and when mother's age was adjusted for as a categorical variable, no increase in prevalence rates was found for the youngest paternal age group, relative to the reference age category. However, for trisomy 13, the crude prevalence rate by maternal age from 1999 to 2001 in the youngest maternal age category was not much greater than the reference age category of 25-29, and for trisomy 21 (Down syndrome), the prevalence rate for the youngest maternal age category was lower than the reference age category (Texas Department of State Health Services, 2004). Therefore, a linear misspecification of the youngest maternal age group may not be the reason why paternal age was not a significant factor for trisomies 21 and 13 when a categorical maternal age variable was used. It is also possible that most of the regression analyses did not find paternal age to be a significant factor when adjusted for maternal age as a categorical variable because this further split the cases up into more groups. This would reduce the sample size in each cell, which would increase the amount of variability. With smaller sample sizes,

power would have been diminished, which could cause fewer significant differences to be found between age groups, even if they did actually exist. As mentioned before, three birth defects for which paternal age was a significant factor did have higher prevalence ratios in the highest paternal age category than the reference category – ventricular septal defects, atrial septal defects, and Down syndrome. For these three defects, it is possible that the reason for the rise in prevalence rates at these higher paternal ages has to do with an increase in mutations in the sperm caused by an increase in germ cell replications. However, when a continuous maternal age variable was used, all of the birth defects for which paternal age was a significant factor showed highest prevalence ratio values for the youngest paternal age categories. Penrose's copy-error hypothesis cannot explain these results. Other studies have found similar associations between increased birth defect rates and younger paternal age, however. McIntosh et al. (1995) found a strong association for Down syndrome – in this study, men less than 20 years of age were found to be 3.8 times more likely to have a child with Down syndrome than men 25-29 years of age. The study also found a slight increase in risk for the youngest paternal age group with regards to cleft lip and cleft palate (McIntosh et al., 1995). Other studies have also found weaker relationships between young paternal age and Down syndrome birth defect risk (Roecker & Huether, 1983). The finding of increased ventricular and atrial septal defect rates associated with younger paternal age was also reported in a couple of studies (Olshan et al., 1994; Zhan, Lian, Zheng, & Gao, 1991). Some studies also found weak positive associations between paternal age and prevalence of ventricular and atrial septal defects (Lian, Zack, & Erickson, 1986; Olshan et al., 1994).

This study did not agree with findings in literature with regard to neural tube defects and craniosynostosis, however. Some studies have found that very young fathers (less than 20 years of age) had an increased risk of having children with neural tube defects (Kazaura et al., 2004; McIntosh et al., 1995), but the current study found no increased risk of neural tube defects for any paternal ages relative to the reference category. Singer et al. (1999) found that an increase in craniosynostosis was associated with infants born to fathers 40 years of age or older. In contrast, although prevalence rates increased with paternal age, this study found no real association between craniosynostosis rates and paternal age of 40 or more years. Also, a study by Hook et al. (1981) found a positive association between Down syndrome rates and paternal age over the whole range of ages. In contrast, although this analysis found a possible weak association between the highest paternal age group and increased Down syndrome rates, it did not find an increasing trend throughout all age groups.

The greatest strength of this study was the relatively large numbers of the different types of birth defect cases. This should give the study adequate statistical power to detect a difference in prevalence ratios, and because of this, the study should have yielded fairly valid results. This study also had a few weaknesses, however. Although all studies in the literature had a percentage of missing cases due to missing paternal age, the overall percentage of missing birth defect cases in this study (18.7%) was higher than most (Kazaura et al., 2004; Lian et al., 1986; Olshan et al., 1994), and the percentage of missing cases for some of the specific birth defects was very high, especially for the neural tube defects and trisomies 13 and 18. The number of neural tube defect cases missing paternal age could be the reason why no paternal age association was found at all

in this study, even though other studies found associations between paternal age and neural tube defect rates (Kazaura et al., 2004; McIntosh et al., 1995). Also, this study placed all paternal ages 40 and above into a single category. This was done because for some of the birth defect types, it was feared that splitting these advanced ages up even more would result in numbers in each category that might be too small to yield any valid results. However, having only one category for all ages 40 and over made it more difficult to find valid and significant associations if the prevalence rates for birth defects increased only after very advanced paternal ages, i.e. after age 55 or 60. If this were the case, having paternal ages of 40 and over in only one category would make associations with advanced paternal age seem weaker than they really were. If these ages were separated into more categories, it is possible than an association that was missed beforehand would become evident.

Conclusion

The results of this descriptive study, adjusting for maternal age as a continuous variable, show a significant association between different paternal age groups and the following birth disorders: ventricular septal defects, atrial septal defects, cleft lip (with or without cleft palate), trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome), and trisomy 18 (Edwards syndrome). Surprisingly, for all of these disorders (and most especially for the trisomy disorders), the findings suggest that the youngest paternal age groups are more likely to have children with these birth defects than the reference paternal age of 25-29. There is no current biological hypothesis for why younger fathers would be associated with higher birth defect prevalence rates, but there could be many other possible explanations. Environmental, lifestyle, or socio-economic risk factors may

have something to do with higher birth defect rates, such as smoking, use of medications, or occupational exposures (Kazaura et al., 2004; McIntosh et al., 1995). Higher prevalence rates have been found in the youngest maternal age group for some birth defects as well (Reefhuis & Honein, 2004), so both younger maternal and paternal age groups may have the same explanations for their relatively high prevalence rates. It may be worthwhile to further investigate this association between young parental ages and an increase in some birth defects' prevalence rates.

Among the birth defects for which a significant (p-value of .05 or less) paternal age association was found, only ventricular septal defects showed a significantly higher prevalence ratio for the oldest paternal age group when compared to paternal ages 25-29, although atrial septal defects and trisomy 21 (Down syndrome) also had slightly higher prevalence ratios in this last age group. When a categorical maternal age variable was used, none of the birth defects had a significantly higher prevalence ratio in the oldest paternal age group. The likelihood of the oldest age group having children with any of these birth defects was not much higher than the reference category in any of the analyses, which would suggest that even if there is an increase in prevalence rates at advanced paternal ages for some these birth defects, it is not a very large increase. Or perhaps, as mentioned before, only very advanced paternal ages are associated with marked increases in these birth defect rates, and a separation of the oldest paternal age group into different age categories would show a more definite increasing trend. However, there were too few cases for many of the birth defects analyzed to be able to split the oldest paternal age group up much more. This would suggest that even if very advanced paternal age is significantly associated with an increase in some birth defect

prevalence rates, there are so few of these fathers that it is probably not a major health concern.

Paternal race/ethnicity was found to be a very significant factor ($p < .001$) in the regression model for five of the eleven defects analyzed: spina bifida, ventricular septal defects, atrial septal defects, craniosynostosis, and trisomy 21 (Down syndrome). As with many paternal characteristics, the association between paternal race/ethnicity and birth defect prevalence rates has not yet been very well studied. The results of this study indicate that further analysis of the effects of paternal race/ethnicity on birth defect rates might be warranted.

Overall, this study showed little evidence of increased risk of the eleven birth disorders analyzed for advanced paternal ages. This study's results indicate that even though there may be a slight increase in a few birth defect prevalence rates for older paternal ages, the increase in risk for the birth defects analyzed is probably not large enough to be a major source of concern for older fathers. However, the results also indicated that younger paternal ages of 24 or less are associated with an increase in birth defect rates for quite a few of the defects analyzed. When maternal age is adjusted for as a continuous factor, the increase in risk of trisomy disorders for the youngest paternal age groups is large enough that it might be worthwhile to investigate this association further. Behavioral factors such as smoking and alcohol use should also be analyzed to see if they can explain the association between young paternal age and increased birth defect rates. If more studies also find an association between an increase in birth defect rates and young paternal age, and if the reason for this association can be ascertained, then perhaps health programs can be put in place to screen very young fathers for their risk of having a

child with a birth defect, or young fathers can be encouraged to seek counseling before deciding whether or not to have a child.

APPENDIX

TEXAS DEPARTMENT OF STATE HEALTH SERVICES

EDUARDO J. SANCHEZ, M D., M.P H
COMMISSIONER

1100 W. 49th Street • Austin, Texas 78756
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June 7, 2005

Natalie Archer
2404 Spring Wagon Lane
Austin, TX 78728

Dear Ms Archer:

This letter is to confirm that you have permission to use data from the Texas Birth Defects Registry for your Master's thesis. I could not find the attached Agreement signed by you in my files; please sign it and mail it back to me at:

Peter Langlois
Birth Defects Epidemiology & Surveillance Branch
Texas Department of State Health Services
1100 West 49th Street, T-707
Austin, TX 78756

Let me know if you have any questions.

Sincerely,

Peter Langlois, PhD
Senior Epidemiologist
Birth Defects Epidemiology & Surveillance Branch

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VITA

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