Published in final edited form as:

Cancer Epidemiol. 2011 October ; 35(5): e25–e31. doi:10.1016/j.canep.2011.01.009.

Pediatric germ cell tumors and parental infertility and infertility treatment: a Children's Oncology Group Report

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Abstract

Background—Few risk factors have been established for childhood germ cell tumors (GCT). Parental infertility and infertility treatment may be associated with GCT development but these risk factors have not been fully investigated.

Methods—A case-control study of childhood GCT was conducted through the Children's Oncology Group (COG). Cases, under the age of 15 years at diagnosis, were recruited through COG institutions from January 1993 to December 2002. Controls were obtained through random digit dialing. Information about infertility and infertility treatment along with demographic factors was collection through maternal interviews. Subgroups created by gender, age at diagnosis, and tumor location were examined separately. Statistical analysis was performed using multivariate logistic regression models.

Results—Overall, no association between GCT and infertility or its treatment was found. In subgroup analysis, females whose mothers had two or more fetal losses were found to be at increased risk for non-gonadal tumors (Odds ratio (OR) = 3.32, 95% Confidence interval (CI) = 1.12–9.88). Younger maternal age was associated with a lower risk of gonadal GCT in females (OR = 0.52, 95% CI = 0.28–0.96). There was an increased risk of all GCT and gonadal GCT in males born to older mothers (OR = 2.88, 95% CI = 1.13–7.37 and OR = 3.70, 95% CI = 1.12–12.24).

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Conflict of interest

None.

Conclusion—While no association between parental infertility or its treatment and childhood GCT was found overall, possible associations with maternal age and history of recurrent fetal loss were found in subgroups defined by gender.

Keywords

Germ cell tumor; infertility; pediatrics; epidemiology

Introduction

Childhood germ cell tumors (GCT) are a group of heterogeneous diagnoses with a common origin in the primordial germ cell[1]. There is a distinctive U-shaped incidence curve by age with incidence rates of 21.0, 3.9, 2.2, 7.4, and 29.0 per million for age groups <1, 1–4, 5–9, 10–14, and 15–19 years, respectively, in the United States from 1992–2004[1]. In addition to the wide variance with age, there is a difference in the location of the tumors by sex. In females below the age of 4 years, the most common type of GCT is non-gonadal GCT, whereas in boys testicular GCT and non-gonadal GCT have approximately equal incidence rates in infancy and, after that, gonadal GCT predominates until age four[1]. Incidence is low for both males and females until around puberty when the incidence of ovarian GCT in females and testicular GCT in males rises dramatically [1].

The literature on the etiology of GCT in children under the age of 15 years is sparse, and associations with potential risk factors have been noted only inconsistently [2–12]. Parental infertility and infertility treatment have not been studied previously in pediatric GCT; however, there are reasons that an association would be plausible. For example, superovulation has been shown to disrupt acquisition and maintenance of genomic imprinting in developing embryos [13]. This abnormal imprinting could potentially lead to tumor development.

There are also factors associated with infertility or infertility treatment that could increase risk of GCT. Congenital abnormalities of the genital organs have been found to be associated with childhood GCT [5,6,8,11] and studies have indicated increased risk of these abnormalities following intracytoplasmic sperm injection (ICSI) [14,15]. Another study noted an increased risk of cryptorchidism after intrauterine insemination, although there was no increase after in vitro fertilization or ICSI [16]. An increase in congenital abnormalities could suggest an increase in cancer. Risk of testicular GCT could also be increased through transmission of infertility to children born through the use of ICSI procedures [17–19]. Male factor infertility has been shown to increase risk for adult GCT [20–22] and if male children of infertile males are more likely to be infertile themselves, their risk for testicular GCT could also increase. However, it is not clear that the link between GCT and male infertility could be extended to childhood GCT, given their histological and cytogenetic differences that imply distinct etiologies. Thus more research is needed into parental infertility and risk of childhood GCT.

We used data from a Children's Oncology Group (COG) case-control study to evaluate the potential association between parental infertility and its treatment and GCT in children.

Materials and Methods

The methods for this study have been detailed previously [3,4]. Briefly, a total of 84 member institutions of the COG provided cases for this study. Cases were eligible if they had a newly diagnosed GCT under the age of 15 years from January 1993 to December of 2002. Specific GCT diagnoses included germinoma, embryonal carcinoma, yolk sac tumor,

choriocarcinoma, immature teratoma, and mixed GCT. Patients with tumors located in the brain were excluded. Cases were required to have a biological mother available who spoke English and have a telephone in their residence. The treating physician gave approval for study coordinators to contact the case's mother.

Controls were selected through random digit dialing and were frequency matched to cases based on sex, age, and telephone exchange. Using methods similar to those of Waksberg [23,24], potential control phone numbers were generated from case phone numbers. The area code and exchange of the case phone number were retained and the last four digits were randomly selected in order to obtain a control number. If a residential number was reached, screening questions were asked to determine whether or not a child under the age of 15 was present in the household. Case-control ratios were different based on sex; for males the ratio was 1:2 and females 1:1 since GCT in children is more common in females.

Approval for this study was granted by the institutional review boards at each participating institution as well as from the University of Minnesota.

Information on potential exposures was collected for cases and controls through maternal interview. The interview included questions about pregnancy history, maternal exposures during pregnancy with the index child, family history of cancer and other diseases, and information about the medical history of the mother. In the maternal questionnaire, several questions about infertility and infertility treatment were asked including length of time to index pregnancy, history of infertility (more than one year of trying without becoming pregnant), visit to a doctor by mother or index biological father due to non-pregnancy, specific infertility treatment, use of ovulating stimulating drugs in the year before or during pregnancy, history of multiple birth, and history of recurrent pregnancy loss.

Unconditional logistic regression was used to explore the association between infertility and infertility treatment and GCT. Exposures were included in the logistic analysis if at least four cases and controls were represented in all exposure categories. Matching factors sex and year of birth were included in all analyses. In addition, after exploration of potential confounding variables, the following variables were included in all models: maternal age, maternal race, household income, maternal education, and child's gestational age. Results are reported as odds ratios (OR) and 95% confidence intervals (CI). Subgroup analysis was performed for age at diagnosis (<5, 5+) and tumor location (non-gonadal, gonadal), and gender. A sensitivity analysis was performed in subgroups limited to children with white, non-Hispanic mothers to assess the influence of race/ethnicity on results. Gender was analyzed in subgroups rather than through interactions since the etiology of GCT may differ by gender. All analysis was performed using SAS 9.1 (SAS institute, Inc, Cary, NC).

An additional method for assessing infertility was explored based on latent class analysis (LCA) [25]. The variables used in the latent class analysis were maternal age, history of infertility, use of female hormones before or during pregnancy, history of multiple birth, and history of recurrent pregnancy loss. While each variable individually has the potential for misclassification of the true exposure of interest, using all variables together may mitigate this misclassification. Models with and without maternal age were explored to determine if the effect of infertility was only through maternal age or if there was an independent risk factor for infertility apart from age. LCA was conducted using M-Plus software [26]. Predicted class membership was dichotomized and used as a predictor in a logistic regression model along with potential confounders.

Results

Out of 344 eligible cases, 278 completed the maternal interview. Controls were obtained from a total of 17,292 randomly selected phone numbers with 5,912 residential numbers identified. There were 634 households with confirmed eligible children, of which 422 completed maternal interviews (67%).

Demographic characteristics of cases and controls are presented in table 1. Cases were more likely to be non-white and have a high school education or less. Cases and controls were similar with regard to gestational age and birth weight.

Overall results suggested little relationship between infertility or infertility treatment and GCT (table 2). Gonadal and non-gonadal subgroup results were fairly concordant with the overall results. However, analysis for each gender separately indicated some potential differences between cases and controls (tables 3 and 4). For females, there was an increased risk of non-gonadal GCT in children born to women with two or more fetal losses (OR = 3.32, 95% CI = 1.12–9.88, $p = 0.03$). Maternal age <27 was found to be significantly associated with a lower risk of gonadal GCT in females (OR = 0.52, 95% CI = 0.28–0.96, $p = 0.04$). Finally, in males there appeared to be an increased risk of GCT in children born to mothers aged 35 years or greater both overall (OR = 2.88, 95% CI = 1.13–7.37, $p = 0.03$) and in gonadal tumors (OR = 3.70, 95% CI = 1.12–12.24, $p = 0.03$). Findings were similar in analysis limited to children of white, non-Hispanic mothers (data not shown).

No notable associations were observed in analysis stratified by age at diagnosis (data not shown).

Discussion

While parental infertility or treatment was not found to be a risk factor for childhood GCT overall, there were some associations in clinically relevant subgroups. Specifically, we found that history of recurrent pregnancy loss elevated risk of non-gonadal GCT in females. Although the American Society for Reproductive Medicine defines recurrent pregnancy loss as a separate disease than infertility [27], other evidence shows that repeated pregnancy loss may be related to infertility, particularly in the male [28]. Still, there are many potential causes of recurrent pregnancy loss including a large percentage with no known cause [29]; thus possible underlying reasons for this association would be difficult to determine. However, the association found in this study could represent a novel risk factor for non-gonadal GCT in females which may warrant further examination.

The associations with maternal age in female and male gonadal GCT are in opposite directions with young and old maternal age protective in females and detrimental in males. This type of qualitative interaction is more likely to be due to chance than represent a real biological phenomenon since it seems unlikely that the effect of maternal age would be opposite for male and female gonadal GCT. As others have noted, it is usually biologically implausible for a single exposure to both cause and protect from the same disease in different subgroups, but is more likely a statistical anomaly [30]. In addition there is little evidence for a maternal age effect in GCT both in childhood [31] and in adolescent and adult testicular cancer [32].

Very few studies of pediatric GCT have been conducted. Of those that have been carried out, this study includes the largest number of cases. The relatively large size allowed us to examine subgroups within GCT which potentially have different etiologies and is the study's greatest strength.

Several limitations also apply to this study. First, even though the number of GCT case was relatively large it was still small in absolute number, particularly in subgroup analysis, leaving us with limited ability to detect moderate associations. Many associations were examined in this study as well, which could lead to false positive findings due to chance alone. There is also the potential for selection bias to influence the study results. Our controls were more likely to be white and have higher income and education compared to cases which may indicate some level of selection bias. However, since these factors are antecedents to both the exposure and disease, adjusting for them in the model may be expected to reduce selection bias [33].

Selection of cases through COG may also have introduced bias, as the proportion of children with cancer seen at COG institutions decreases as the age of the child increases [34]. However, most cases of childhood GCT occur before the age of 5 so that COG institutions would be likely to see a majority of cases; in the current study over half of the cases in this study were diagnosed at 5 years of age or younger. In addition, in this study, a higher proportion of girls with GCT participated as well as a higher percentage of children who were white [3]. This might indicate some differential selection in the cases; however, since controls are also expected to have a higher proportion of children with white race, this could, in fact, mitigate the impact of selection bias. In any case, COG is the only organization which could practicably facilitate case recruitment for such a rare disease in North America.

Another limitation is the potential for recall bias since the exposures of interest could have taken place many years prior to the study. Other studies have examined the possibility of recall bias relating to infertility and infertility treatment. History of infertility was found to be self-reported less often than on medical records as well as slightly more often by cases than controls in one study [35]. Another study showed little difference in the sensitivity of reporting previous spontaneous abortion in cases and controls in a study on sudden infant death syndrome [36]. In this study, the only significant associations were found for maternal age and history of recurrent fetal loss both of which appear to be less subject to recall bias.

While we did not find any association with infertility or infertility treatment and pediatric GCTs, we did find some possible associations with maternal age and recurrent pregnancy loss in sex and location specific subgroups. These associations are likely due to chance but could be considered in future studies.

Acknowledgments

This work was supported by the National Institutes of Health [R01CA067263, U10CA98413, U10CA13539 and U10CA98543]; and the Children's Cancer Research Fund (Minneapolis, Minnesota).

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Table 1

Demographic characteristics

	Overall		Males		Females	
	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)
Mother's race						
White	356 (84.4)	213 (76.9)	152 (84.0)	70 (84.3)	203 (84.6)	143 (73.7)
Non-white	66 (15.6)	64 (23.1)	29 (16.0)	13 (15.7)	37 (15.4)	51 (26.3)
Mother's education						
≤ High school	166 (39.3)	138 (49.8)	66 (36.6)	39 (47.0)	100 (41.7)	99 (51.0)
Some post HS	97 (23.0)	53 (19.1)	40 (22.1)	16 (19.3)	57 (23.8)	37 (19.1)
College graduate	159 (37.7)	86 (31.0)	75 (41.4)	28 (33.7)	83 (34.6)	58 (29.9)
Household income						
≤ \$30,000	192 (45.9)	145 (52.9)	81 (44.8)	40 (50.0)	111 (47.0)	105 (54.1)
\$30,001–\$50,000	124 (29.7)	63 (23.0)	53 (29.3)	21 (26.3)	70 (29.7)	42 (21.6)
> \$50,000	102 (24.4)	66 (24.1)	47 (26.0)	19 (23.8)	55 (23.3)	47 (24.2)
Index child's gestational age						
< 37 weeks	44 (10.4)	35 (12.6)	16 (8.8)	10 (12.0)	27 (11.2)	25 (12.8)
37–41 weeks	343 (81.1)	220 (79.1)	150 (82.9)	67 (80.7)	193 (80.1)	153 (78.5)
≥ 42 weeks	36 (8.5)	23 (8.3)	15 (8.3)	6 (7.2)	21 (8.7)	17 (8.7)
Index child's birth weight Mean (SD)	3373.72 (590.31)	3354.27 (680.58)	3462.77 (607.81)	3499.00 (644.45)	3309.19 (569.33)	3292.67 (687.78)
Index child's gender						
Male	181 (42.9)	83 (29.9)				
Female	241 (57.1)	195 (70.1)				
Index child's age at diagnosis						
<1 years		57 (20.5)		22 (26.5)		35 (17.9)
1–4 years		91 (32.7)		42 (50.6)		49 (25.1)
5–9 years		41 (14.7)		4 (4.8)		37 (19.0)
10–15 years		89 (32.0)		15 (18.1)		74 (37.9)
Type of tumor						

	Overall		Males		Females	
	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)
Gonadal		144 (53.1)		47 (58.0)		97 (51.1)
Non-gonadal		120 (44.3)		31 (38.3)		89 (46.8)
Metastatic		7 (2.6)		3 (3.7)		4 (2.1)

Table 2

Association between childhood GCT and parental infertility and infertility treatment

	Controls n (%)	Cases n (%)	OR ^a	95% CI	p-value	Gonadal n (%)	OR ^a	95% CI	p-value	Non- gonadal n (%)	OR ^a	95% CI	p-value
Prior fetal loss													
None	332 (78.5)	227 (81.7)	Ref			119 (82.6)	Ref			97 (80.8)	Ref		
One	74 (17.5)	34 (12.2)	0.65	0.41–1.03	0.06	19 (13.2)	0.65	0.37–1.16	0.15	13 (10.8)	0.57	0.29–1.12	0.10
Two or more	17 (4.0)	17 (6.1)	1.30	0.63–2.71	0.48	6 (4.2)	0.96	0.35–2.63	0.93	10 (8.3)	1.51	0.62–3.68	0.37
History of multiple birth prior to index													
None	410 (96.9)	269 (96.8)	Ref			139 (96.5)	Ref			117 (97.5)	Ref		
At least one multiple birth	13 (3.1)	9 (3.2)	1.08	0.43–2.67	0.87	5 (3.5)	1.29	0.43–3.91	0.65	3 (2.5)	c		
Maternal age													
< 27	187 (44.2)	126 (45.3)	0.84	0.59–1.21	0.36	64 (44.4)	0.79	0.50–1.25	0.32	54 (45.0)	0.91	0.55–1.50	0.71
27–34	197 (46.6)	123 (44.2)	Ref			66 (45.8)	Ref			54 (45.0)	Ref		
≥35	39 (9.2)	29 (10.4)	1.23	0.70–2.15	0.47	14 (9.7)	1.23	0.61–2.49	0.57	12 (10.0)	1.05	0.49–2.29	0.90
Use of OS ^d drugs (prior to or before knowledge of pregnancy)													
No	410 (97.4)	273 (98.2)	Ref			139 (96.5)	Ref			120 (100.0)	Ref		
Yes	11 (2.6)	5 (1.8)	0.84	0.28–2.58	0.77	5 (3.5)	1.48	0.48–4.63	0.50	0 (0.0)	c		
No pregnancy after a year or more of trying													
No	334 (79.1)	221 (79.5)	Ref			112 (77.8)	Ref			96 (80.0)	Ref		
Yes	88 (20.9)	57 (20.5)	0.95	0.64–1.41	0.78	32 (22.2)	1.01	0.62–1.63	0.97	24 (20.0)	0.91	0.52–1.57	0.72
Time to index pregnancy													
Not trying	191 (45.3)	134 (48.4)	0.93	0.65–1.32	0.67	68 (47.2)	0.97	0.63–1.51	0.90	58 (48.7)	0.92	0.56–1.52	0.75
< 1 year of trying	183 (43.4)	119 (43.0)	Ref			61 (42.4)	Ref			52 (43.7)	Ref		
≥ 1 year of trying	48 (11.4)	24 (8.7)	0.71	0.40–1.26	0.24	15 (10.4)	0.86	0.44–1.72	0.67	9 (7.6)	0.65	0.29–1.49	0.31
Latent class infertility ^b (with maternal age)													
No	390 (92.2)	254 (91.4)	Ref			130 (90.3)	Ref			111 (92.5)	Ref		
Yes	33 (7.8)	24 (8.6)	1.05	0.56–1.98	0.87	14 (9.7)	1.32	0.62–2.79	0.47	9 (7.5)	0.78	0.32–1.89	0.57

	Controls n (%)	Cases n (%)	OR ^a	95% CI	p-value	Gonadal n (%)	OR ^a	95% CI	p-value	Non- gonadal n (%)	OR ^a	95% CI	p-value
Latent class infertility ^b (without maternal age)													
No	408 (96.5)	267 (96.0)	Ref			138 (95.8)	Ref			115 (95.8)	Ref		
Yes	15 (3.5)	11 (4.0)	1.18	0.51–2.73	0.70	6 (4.2)	1.20	0.43–3.32	0.73	5 (4.2)	1.23	0.39–3.86	0.72

^a Logistic regression models were adjusted for child's age, sex, and gestational age as well as maternal age, race, education, and household income

^b Infertility predicted from the latent class model

^c Sample size too small for logistic regression analysis

^d Ovarian stimulating

Table 3
Association between childhood GCT and parental infertility and infertility treatment (Females only)

	Controls n (%)	Cases n (%)	OR ^a	95% CI	p-value	Gonadal n (%)	OR ^a	95% CI	p-value	Non- gonadal n (%)	OR ^a	95% CI	p-value
Prior fetal loss													
None	185 (76.8)	157 (80.5)	Ref			80 (82.5)	Ref			69 (77.5)	Ref		
One	48 (19.9)	23 (11.8)	0.59	0.34–1.03	0.07	12 (12.4)	0.48	0.22–1.02	0.06	10 (11.2)	0.61	0.28–1.36	0.23
Two or more	8 (3.3)	15 (7.7)	2.12	0.84–5.36	0.11	5 (5.2)	0.77	0.21–2.87	0.70	10 (11.2)	3.32	1.12–9.88	0.03
History of multiple birth prior to index													
None	235 (97.5)	187 (95.9)	Ref			93 (95.9)	Ref			86 (96.6)	Ref		
At least one multiple birth	6 (2.5)	8 (4.1)	1.65	0.53–5.15	0.39	4 (4.1)	1.55	0.36–6.61	0.56	3 (3.4)	<i>c</i>		
Maternal age													
< 27	119 (49.4)	90 (46.2)	0.67	0.43–1.05	0.08	44 (45.4)	0.52	0.28–0.96	0.04	41 (46.1)	0.87	0.48–1.58	0.64
27–34	97 (40.2)	88 (45.1)	Ref			46 (47.4)	Ref			39 (43.8)	Ref		
≥35	25 (10.4)	17 (8.7)	0.79	0.39–1.61	0.52	7 (7.2)	0.63	0.22–1.76	0.38	9 (10.1)	0.87	0.35–2.20	0.77
Use of OS ^d drugs (prior to or before knowledge of pregnancy)													
No	234 (97.9)	191 (97.9)	Ref			93 (95.9)	Ref			89 (100.0)	Ref		
Yes	5 (2.1)	4 (2.1)	0.99	0.25–3.94	0.99	4 (4.1)	1.79	0.42–7.66	0.43	0 (0.0)	<i>c</i>		
No pregnancy after a year or more of trying													
No	184 (76.3)	155 (79.5)	Ref			76 (78.4)	Ref			70 (78.7)	Ref		
Yes	57 (23.7)	40 (20.5)	0.85	0.53–1.37	0.50	21 (21.6)	1.02	0.53–1.95	0.95	19 (21.3)	0.86	0.45–1.64	0.65
Time to index pregnancy													
Not trying	119 (49.4)	94 (48.5)	0.75	0.48–1.20	0.23	50 (51.5)	0.88	0.48–1.62	0.68	40 (45.5)	0.71	0.37–1.33	0.28
< 1 year of trying	95 (39.4)	82 (42.3)	Ref			37 (38.1)	Ref			40 (45.5)	Ref		
≥ 1 year of trying	27 (11.2)	18 (9.3)	0.77	0.39–1.53	0.46	10 (10.3)	1.21	0.48–3.03	0.69	8 (9.1)	0.67	0.27–1.70	0.40
Latent class infertility ^b (with maternal age)													
No	222 (92.1)	177 (90.8)	Ref			88 (90.7)	Ref			80 (89.9)	Ref		
Yes	19 (7.9)	18 (9.2)	1.23	0.57–2.62	0.60	9 (9.3)	1.52	0.55–4.25	0.42	9 (10.1)	1.19	0.45–3.19	0.71

	Controls n (%)	Cases n (%)	OR ^a	95% CI	p-value	Gonadal n (%)	OR ^a	95% CI	p-value	Non- gonadal n (%)	OR ^a	95% CI	p-value
Latent class infertility ^b (without maternal age)													
No	235 (97.5)	185 (94.9)	Ref			92 (94.8)	Ref			84 (94.4)	Ref		
Yes	6 (2.5)	10 (5.1)	2.35	0.80–6.92	0.12	5 (5.2)	1.75	0.47–6.52	0.41	5 (5.6)	3.06	0.77–12.10	0.11

^a Logistic regression models were adjusted for child's age, sex, and gestational age as well as maternal age, race, education, and household income

^b Infertility predicted from the latent class model

^c Sample size too small for logistic regression analysis

^d Ovarian stimulating

Table 4
Association between childhood GCT and parental infertility and infertility treatment (Males only)

	Controls n (%)	Cases n (%)	OR ^a	95% CI	p-value	Gonadal n (%)	OR ^a	95% CI	p-value	Non-gonadal ^b n (%)
Prior fetal loss										
None	146 (80.7)	70 (84.3)	Ref			39 (83.0)	Ref			28 (90.3)
One	26 (14.4)	11 (13.3)	0.71	0.30–1.70	0.44	7 (14.9)	1.06	0.37–3.09	0.91	3 (9.7)
Two or more	9 (5.0)	2 (2.4)	<i>d</i>			1 (2.1)	<i>d</i>			0 (0.0)
History of multiple birth prior to index										
None	174 (96.1)	82 (98.8)	Ref			46 (97.9)	Ref			31 (100.0)
At least one multiple birth	7 (3.9)	1 (1.2)	<i>d</i>			1 (2.1)	<i>d</i>			0 (0.0)
Maternal age										
< 27	68 (37.6)	36 (43.4)	1.37	0.70–2.67	0.36	20 (42.6)	1.55	0.66–3.68	0.32	13 (41.9)
27–34	99 (54.7)	35 (42.2)	Ref			20 (42.6)	Ref			15 (48.4)
≥ 35	14 (7.7)	12 (14.5)	2.88	1.13–7.37	0.03	7 (14.9)	3.70	1.12–12.24	0.03	3 (9.7)
Use of OS ^d drugs (prior to or before knowledge of pregnancy)										
No	175 (96.7)	82 (98.8)	Ref			46 (97.9)	Ref			31 (100.0)
Yes	6 (3.3)	1 (1.2)	<i>d</i>			1 (2.1)	<i>d</i>			0 (0.0)
No pregnancy after a year or more of trying										
No	149 (82.8)	66 (79.5)	Ref			36 (76.6)	Ref			26 (83.9)
Yes	31 (17.2)	17 (20.5)	1.30	0.61–2.75	0.50	11 (23.4)	1.80	0.70–4.64	0.23	5 (16.1)
Time to index pregnancy										
Not trying	71 (39.4)	40 (48.2)	1.17	0.64–2.14	0.62	18 (38.3)	0.88	0.41–1.90	0.75	18 (58.1)
< 1 year of trying	88 (48.9)	37 (44.6)	Ref			24 (51.1)	Ref			12 (38.7)
≥ 1 year of trying	21 (11.7)	6 (7.2)	0.56	0.17–1.81	0.33	5 (10.6)	1.09	0.27–4.36	0.90	1 (3.2)
Latent class infertility ^b (with maternal age)										
No	167 (92.3)	77 (92.8)	Ref			42 (89.4)	Ref			31 (100.0)
Yes	14 (7.7)	6 (7.2)	0.72	0.21–2.48	0.60	5 (10.6)	1.68	0.39–7.29	0.49	0 (0.0)
Latent class infertility ^b (without maternal age)										
No	172 (95.0)	82 (98.8)	Ref			46 (97.9)	Ref			31 (100.0)

	Controls n (%)	Cases n (%)	OR ^a	95% CI	p-value	Gonadal n (%)	OR ^a	95% CI	p-value	Non-gonadal ^b n (%)
Yes	9 (5.0)	1 (1.2)	<i>d</i>			1 (2.1)	<i>d</i>			0 (0.0)

^a Logistic regression models were adjusted for child's age, sex, and gestational age as well as maternal age, race, education, and household income

^b Too few cases of non-gonadal for logistic regression analysis

^c Infertility predicted from the latent class model

^d Sample size too small for logistic regression analysis

^e Ovarian stimulating