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Infant leukemia and parental infertility or its treatment: a Children's Oncology Group report

Susan E. Puumala[1], Logan G. Spector[2,*], Melanie M. Wall[3], Leslie L. Robison[4], Nyla A. Heerema[5], Michelle A. Roesler[1], and Julie A. Ross[2]

[1]Division of Epidemiology/Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, MN 55455, USA [2]Division of Epidemiology/Clinical Research, Department of Pediatrics and Masonic Cancer Center, University of Minnesota, Minneapolis, MN 55455, USA [3]Division of Biostatistics, University of Minnesota, Minneapolis, MN 55455, USA [4]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN 38105, USA [5]Department of Pathology, College of Medicine, Ohio State University, Columbus, OH 43210, USA

*Correspondence address. E-mail: spector@umn.edu

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BACKGROUND: Little is known about the potential risk factors for infant leukemia. With its very young age at diagnosis, exposures occurring in the perinatal period are suspected. Parental infertility and infertility treatment have been studied with regard to childhood cancer in general, but rarely in individual cancer subtypes.

METHODS: A case–control study of infant leukemia was conducted through the Children's Oncology Group, including cases diagnosed from January 1996 to December 2006 and controls selected through random digit dialing and birth certificate tracing. Maternal phone interviews were conducted to obtain information about infertility, infertility treatment and demographic factors. All cases as well as subgroups defined by mixed lineage leukemia (MLL) translocation status and leukemia subtype were examined. Statistical analysis was performed using multivariate logistic regression models.

RESULTS: No significant associations between infertility or its treatment and combined infant leukemia were found. In subgroup analyses, there was a significant increase in the risk of MLL− leukemia for children born to women not trying to conceive compared with those trying for <1 year for all types combined [odds ratio (OR) = 1.62, 95% confidence interval (CI) = 1.01–2.59] and for acute lymphoblastic leukemia (OR = 2.50, 95% CI = 1.36–4.61).

CONCLUSIONS: There were no positive associations between parental infertility or infertility treatment and infant leukemia. While this is the largest study to date, both selection and recall bias may have impacted the results. However, for infant leukemia, we can potentially rule out large increases in risk associated with parental infertility or its treatment.

Key words: infant leukemia / infertility / childhood cancer / MLL translocations

Introduction

Infant leukemia, diagnosed prior to 1 year of age, is a rare subtype of childhood leukemia with an incidence of ~40 cases per million infants in the USA in 1992–2004 (Linabery and Ross, 2008). Leukemia in infants differs from leukemia in older children with variation in type of diagnosis [acute myeloid (AML) and acute lymphoblastic (ALL)], clinical symptoms, tumor genetics and response to treatment (Zweidler-McKay and Hilden, 2008). Another feature which sets infant leukemia apart is that the majority of cases have somatic mutations in the mixed lineage leukemia (MLL) gene. In infant leukemia, ~80% of ALL and 50% of AML have a recombination event within the MLL gene (Reaman, 2003). Mutations in the MLL gene appear to occur *in utero* since rearrangements in the MLL gene have been identified in neonatal blood spots collected at birth (Gale *et al.*, 1997; Greaves, 2003). The distinction between subtype and MLL status is important in infant leukemia, since many studies indicate a potential difference in risk factors for disease based on these subgroups, thus most studies examine each combination of subtype and MLL status separately. Given its differences from leukemia in older children, it is necessary to study this subtype separately in order to discover factors which might lead to improved treatment or lower

incidence rates. Also, since the relevant exposure(s) most likely occurs *in utero*, the study of infant leukemia could help uncover important information about carcinogenesis in general and specifically about carcinogenic exposures before or during pregnancy (Greaves, 2005).

Little is known from epidemiological studies about infertility or its treatment as possible risk factors for infant leukemia. One study of leukemia in infants (up to 18 months of age at diagnosis) looked at medication recorded in the mother's medical record during pregnancy (Ross *et al.*, 2003). This study found a non-significant inverse association with clomiphene, an ovarian stimulant, but the analysis was only based on two cases with reported use. Other studies examining indication or treatment of infertility and childhood leukemia overall have been mixed with some finding an indication of increased risk (van Steensel-Moll *et al.*, 1985; Roman *et al.*, 1997; Schuz *et al.*, 1999; Puumala *et al.*, 2007) and others finding no association (Cnattingius *et al.*, 1995; Shu *et al.*, 2002; Wen *et al.*, 2002; Shaw *et al.*, 2004). However, all suffered from relatively low power, since there were few cases or controls reporting infertility or infertility treatment.

Many studies have been conducted to examine the association between infertility and infertility treatment and childhood cancer. Although several large cohort studies have examined assisted reproductive technology (ART) and childhood cancer, few have looked at specific diagnoses. Most studies have found that the total number of cancer cases observed in a cohort of children born after ART were similar to what would be expected (Doyle *et al.*, 1998; Bruinsma *et al.*, 2000; Lerner-Geva *et al.*, 2000; Klip *et al.*, 2001; Kallen *et al.*, 2005; Lidegaard *et al.*, 2005), but have been based on small numbers of cancers overall. All studies have examined children with similar ART procedures; primarily *in vitro* fertilization (IVF) or IVF with intracytoplasmic sperm injection (ICSI). Children have been followed to observe a cancer diagnosis before the age 15 with average follow-up times ranging from 3 years 9 months to 8.6 years. Case–control studies have examined the history of infertility or infertility treatment in general and have found some increases in risk for leukemia, hepatoblastoma, neuroblastoma and retinoblastoma (Lightfoot *et al.*, 2005; McLaughlin *et al.*, 2006; Puumala *et al.*, 2007). Rarer diagnoses or subsets of diagnoses have not been frequently examined with respect to infertility or infertility treatment.

Infant leukemia and parental infertility or its treatment are potentially linked through aberrant epigenetic mechanisms. Several studies have found that children born after ART are more prone to severe disorders caused by abnormal genomic imprinting (Olivennes *et al.*, 2001; Cox *et al.*, 2002; DeBaun *et al.*, 2003; Gicquel *et al.*, 2003; Maher *et al.*, 2003; Halliday *et al.*, 2004; Chang *et al.*, 2005; Sutcliffe *et al.*, 2006; Bowdin *et al.*, 2007; Doornbos *et al.*, 2007). Other studies have found that epigenetic defects after ART could be due to parental infertility rather than ART treatment (Ludwig *et al.*, 2005; Doornbos *et al.*, 2007). Although imprinting disorders in these children are still very rare in an absolute sense, the fact that imprinting diseases are more common could indicate a more widespread disruption of epigenetic mechanisms. These disruptions could potentially manifest themselves as an increased propensity for childhood leukemia which has been shown to be epigenetically mediated (Stam *et al.*, 2006).

Taken as a whole, the previous literature supports further investigation of infertility and/or infertility treatment and risk of infant leukemia. Thus, the current study addresses this need while adding to the sparse literature on infant leukemia and infertility and is the first study to look at this exposure within MLL subtypes.

Materials and Methods

Data for this analysis were from a Children's Oncology Group (COG) case–control study of infant leukemia. Cases were collected in two phases for this study. Both phases required cases to have a confirmed diagnosis of acute leukemia prior to 1 year of age. Patients could be diagnosed with either ALL or AML. Cases who died before the study period were eligible for study participation, since the main source of data collection was the child's mother. Children were eligible if they were not diagnosed with Down syndrome, had a biological mother who spoke English or Spanish (phase II only), had a biological mother available by telephone and were treated or diagnosed at a participating COG institution in the USA or Canada. Once cases were identified, the treating physician was contacted and asked to provide permission to contact the child's mother or parental consent to contact was obtained directly. Mothers with physician approval or consent were sent a letter explaining the study and notifying them that they would be contacted by phone. The first phase of recruitment included cases diagnosed between 1 January 1996 and 13 October 2002; the second phase included cases diagnosed between 1 January 2003 and 31 December 2006. In Phase I, 348 cases were confirmed eligible from 126 participating COG institutions and 240 of these (69%) completed interviews. In Phase II, 345 cases were identified by 133 participating COG institutions as potentially eligible for the study. Of those eligible, 203 (59%) completed interviews.

Controls were selected in two phases for this study coinciding with the case periods. In Phase I, controls were selected though random digit dialing (RDD). Numbers were generated using a modification of the methods proposed by Waksberg (Robison and Daigle, 1984). Potential phone numbers were generated from case phone numbers at diagnosis. 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. For each number, up to nine contact attempts were performed. If the number resulted in no contact, a refusal or an ineligible household, subsequent numbers were generated until an eligible control agreed to participate in the study. The mother's name and address were then obtained along with permission to send a letter. Controls were obtained from 25 516 telephone numbers selected using RDD, of which 11 713 were identified as residential numbers. Using the method outlined by Slattery *et al.* (1995), the RDD household screening response rate was 67%. Maternal telephone interviews were successfully completed for 254 out of 430 potential eligible controls, giving a field response rate of 59% and an overall response rate of 40%.

Phase II controls were selected through state birth registries. Sixteen states that could release birth records and registered a large number of infant leukemia cases in Phase I were approached about participation, 15 of which ultimately provided rosters of birth certificate (BC) data. Controls were frequency matched to cases on year of birth and region of residence based on Phase I case distribution. The 15 states were allocated to regions to facilitate geographical matching. An introductory letter was sent to 270 potential controls providing information about the study and indicating that an interviewer would contact them by phone. Phone contact was attempted for each potential control successively until an eligible control agreed to participate. In both phases, controls were required to have a biological mother who spoke English or Spanish (Phase II) and was available by telephone. Initial contact letters were sent to mothers of 270 children from randomly selected BCs of which 267 were found eligible. A total of 70 mothers completed the interview and one partially completed the interview, giving a total field response rate of 27% (71/267).

Information was collected for cases and controls through maternal interview. The maternal interview included questions about pregnancy history, maternal exposures during pregnancy with the participating (index) child, family history of cancer and other diseases, and information about the medical history of the mother. Several questions about infertility and infertility treatment were also asked, including length of time to index pregnancy, history of infertility (more than 1 year of trying without becoming pregnant), history of doctor's visits by mother or index biological father due to non-pregnancy, specific infertility treatment, use of female hormones for ovulation stimulation, and use of female hormones for infertility or conditions related to infertility.

MLL status was determined using the case's file from his or her initial COG institution. Information about molecular or cytogenetic testing for MLL gene rearrangements at the time of diagnosis was collected and reviewed by three independent reviewers. Infants were ultimately classified into three classes: MLL+ by molecular or cytogenetic methods, MLL− by molecular or cytogenetic methods, or not enough information to determine MLL status. A total of 69 cases had unknown MLL status after review.

The institutional review boards at the University of Minnesota and the participating COG institutions approved this study. In addition, health departments for the states providing BCs also reviewed and approved this study. All participants provided informed consent prior to participating in the study.

Exposures of interest in this study included maternal age (continuous), history of recurrent pregnancy loss (2 or more, 1 or none), time to index pregnancy (not trying, <1 year, ≥ 1 year), specific infertility treatment (medication, surgery, or other) (yes/no), use of ovulation-stimulating drugs before or during early pregnancy (yes/no).

In addition, a composite infertility variable was constructed based on latent class analysis (LCA), including maternal age, history of recurrent pregnancy loss (2 or more, 1 or none), history of infertility (more than 1 year of trying without becoming pregnant), visit to a doctor by mother or index biological father due to non-pregnancy (yes/no), and use of ovulation-stimulating drugs before or during early pregnancy (yes/no) (Formann and Kohlmann, 1996). This method was used since infertility is difficult to measure and a couple's 'true' infertility status is usually unknown. The LCA combines information from many different variables in order to obtain a better measurement of the unknown 'true' infertility status. Models with and without maternal age were explored in order 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.

The analysis used the conditional independence model which assumes that the observed variables are independent of one another given class membership. This means that once infertility (as defined by the LCA model) is taken into account, the observed variables used to measure infertility are not related to one another. Since more than three observed variables were used, the model was identifiable and no additional constraints were needed. LCA was conducted using M-Plus software (Muthen and Muthen, 1998–2004). Both two and three class models were fit to the data and model selection relied on the BIC value for model fit. Predicted class membership was categorized and used as a predictor in a logistic regression model along with potential confounders.

Descriptive methods were used to assess the appropriateness of statistical analysis and the functional forms of the relationship between exposures and outcome. Multivariate models were constructed after considering matching variables as well as confounders including maternal age (continuous), maternal education, maternal race, smoking during pregnancy, household income, gestational age and birthweight. Exposures were included in the logistic analysis if at least four cases and controls were represented in all exposure categories. Birth year was included in all analysis as a matching factor. Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs).

In addition to the combined leukemia analysis, subgroups based on subtype (ALL, AML) and by MLL status (MLL+, MLL−) were examined separately. Each subgroup of cases was compared with the entire control set since there was no basis for selecting a subset of control children and using all of the controls maximized power. Model-based analysis was performed if there were at least two cases and controls in each exposure category within the subgroup. All logistic regression analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 443 cases and 324 controls completed interviews when both phases of recruitment were combined. We had limited data on non-respondents. As reported previously, in Phase II, non-participants had lower levels of maternal education, lower maternal age and marginally lower birthweight compared with our participants (Puumala *et al.*, 2009). For cases, only gender and race were available for both phases. While the percentage of males did not differ (44.2 versus 49.2, $P = 0.2$), there was a significantly lower percentage of whites in the non-respondent group (64.0 versus 78.3, $P < 0.01$).

Descriptive statistics for baseline characteristics of participants are presented in Table I. Case mothers were more likely to be Hispanic, have lower education levels and have lower household income than control mothers. Case children were similar to control children with respect to gender, gestational age and birthweight.

The final selection of confounders included household income as well as maternal race, age, education, smoking during pregnancy, birthweight and gestational age. Although geography was a matching variable, it did not have an impact on the overall results and was not included in the final models (data not shown).

Multivariate analysis for the latent class-derived infertility variable is presented in Table II. The classification did not change based on whether or not age was included in the model. No statistically significant associations were found either in combined leukemia or within any subgroup. Table III presents the results for measures of infertility which have been examined in previous studies. There was a statistically significant increased risk of MLL− infant leukemia for those who reported not trying to become pregnant compared with those trying for <1 year (OR = 1.62, 95% CI = 1.01–2.59). Subgroup analyses revealed that this statistically significant association was confined to the ALL MLL− subgroup (OR = 2.50, 95% CI = 1.36–4.61). For the AML subgroup, while not significant, the OR was <1 in women who reported using ovulation-stimulating drugs prior to or before knowledge of pregnancy (OR = 0.44, 95% CI = 0.13–1.44).

Discussion

We found little evidence of a link between infertility or its treatment and infant leukemia in this study. In fact, some of the statistically significant observed associations were in the opposite direction than hypothesized (e.g. an increased risk for those not trying to become pregnant). Even though the sample size of this study was relatively small, we can generally rule out large positive effects of infertility and infertility treatment on infant leukemia.

The only other study which has examined the association between infertility treatment and infant leukemia specifically evaluated medication recorded in the mother's medical record during pregnancy

Table I Baseline characteristics.

	Controls		Cases		OR[a]	95% CI
	n	(%)	*n*	(%)		
Maternal characteristics						
Race/Ethnicity						
White	273	(84.5)	334	(75.6)	Ref	
Black	18	(5.6)	18	(4.1)	0.65	0.31–1.33
Hispanic	15	(4.6)	55	(12.4)	2.62	1.42–4.83
Other	17	(5.3)	35	(7.9)	1.66	0.88–3.11
Education						
≤High school	91	(28.2)	149	(33.7)	1.46	1.00–2.13
Some post-HS	112	(34.7)	125	(28.3)	Ref	
College graduate	120	(37.2)	168	(38.0)	1.10	0.76–1.58
Household income						
≤ $30 000	95	(29.6)	157	(35.8)	Ref	
$30 001–$75 000	145	(45.2)	189	(43.1)	0.80	0.56–1.13
>$75 000	81	(25.2)	93	(21.2)	0.56	0.37–0.84
Smoking during pregnancy						
Yes (at least 1 cig/day)	65	(20.1)	74	(16.7)	0.90	0.61–1.32
No	258	(79.9)	368	(83.3)	Ref	
Child characteristics						
Gender						
Male	156	(48.1)	218	(49.2)	Ref	
Female	168	(51.9)	225	(50.8)	0.97	0.72–1.31
Gestational age (weeks)						
<37	24	(7.4)	32	(7.2)	0.79	0.44–1.43
37–40	259	(79.9)	360	(81.3)	Ref	
≥41	41	(12.7)	51	(11.5)	1.03	0.65–1.62
Birthweight (g)						
Mean (SD)	3436.33	(591.76)	3477.26	(572.45)	1.12[b]	0.98–1.28

[a]Logistic regression models were adjusted for year of birth (quartiles).
[b]Per 500 g increase.

and found a non-significant inverse association with clomiphene (Ross *et al*., 2003). In the current study, while no association was found for combined leukemia, there was an indication of a 58% decrease in the odds of AML with medication used for infertility and a similar, but non-significant, OR for the use of ovulation-stimulating drugs. The inverse association was unexpected. It could be due to a 'healthy user' effect, in which those who seek out infertility treatments have better health and dietary intake than women who did not use medical intervention to achieve pregnancy. However, if this were the case, we would expect to see this inverse association across all groups examined, which we did not.

We also found an increased risk in the MLL− group both in combined leukemia and for the ALL MLL− subgroup for women who indicated that they were not trying to become pregnant when they conceived the index child. With few significant findings and many comparisons, however, some significant results could be due to chance alone.

There are several strengths to this study. First, this study represents one of the largest case–control studies assembled for infant leukemia. In addition, this is one of the few studies of infant leukemia that has incorporated the presence of MLL translocations into the analyses. Finally, the exposures used in this analysis are specific to infertility or infertility treatment and, as such, can better evaluate the relationship between this exposure and infant leukemia.

There are also several limitations to this study. First, as it uses the case–control design, it is subject to recall bias. Case–control studies are uniquely prone to recall bias, which occurs when cases recall past exposures differently from controls, leading to an OR that reflects a difference between the two groups based on recall rather than an actual difference in exposure (Schlesselman and Stolley, 1982). Several studies have assessed the magnitude of maternal recall bias and have found varying levels, which were dependent upon the exposure studied (Werler *et al*., 1989; Drews *et al*., 1990). One study on malformations that examined the history of infertility found that women reported malformations much less than what was reported in medical records. Cases in this study were slightly more likely to report a history of infertility than controls (Werler

Table II Association between infant leukemia and latent class measure of infertility.

		Controls		Cases		OR[a]	95% CI	MLL+		OR[a]	95% CI	MLL−		OR[a]	95% CI
		n	(%)	*n*	(%)			*n*	(%)			*n*	(%)		
Combined leukemia	Latent class infertility														
	No	266	(82.1)	372	(84.0)	Ref		192	(84.2)	Ref		121	(82.9)	Ref	
	Yes	58	(17.9)	71	(16.0)	0.97	0.63–1.48	36	(15.8)	0.98	0.58–1.65	25	(17.1)	1.13	0.63–2.01
ALL	Latent class infertility														
	No	266	(82.1)	217	(82.2)	Ref		131	(83.4)	Ref		62	(80.5)	Ref	
	Yes	58	(17.9)	47	(17.8)	1.27	0.79–2.05	26	(16.6)	1.20	0.68–2.13	15	(19.5)	1.40	0.69–2.85
AML	Latent class infertility														
	No	266	(82.1)	149	(86.6)	Ref		59	(86.8)	Ref		56	(84.8)	Ref	
	Yes	58	(17.9)	23	(13.4)	0.65	0.36–1.18	9	(13.2)	0.70	0.29–1.67	10	(15.2)	0.89	0.40–2.02

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MLL, mixed lineage leukaemia.
[a]Logistic regression models were adjusted for year of birth (quartiles), maternal age (continuous), maternal education, maternal race, smoking during pregnancy, household income, gestational age and birthweight.

et al., 1989). Another study showed little difference in the sensitivity of reporting previous spontaneous miscarriage in cases and controls in a study on sudden infant death syndrome (Drews *et al.*, 1990). Other exposures of interest such as time to conception cannot be easily validated. We do note that the young age at diagnosis allowed information on exposures during pregnancy to be assessed after only a short period of time had passed, which may help to minimize errors in recall.

Selection bias occurs in a case–control study when the probability of participation or selection into the study is different based on case–control status and the underlying exposure of interest (Savitz, 2003). It is of particular concern in a study, such as ours, with low control response rates. An analysis of potential selection bias in our study found that controls differed from the underlying population of interest in terms of maternal age, maternal education level, birthweight, gestational age, race and marital status (Puumala *et al.*, 2009). In the current analysis, maternal age, education and income were found to be confounders of the association between infertility measures and infant leukemia. Since these factors are also related to selection and are antecedent to the exposure and disease, selection bias due to these factors should be mitigated in the adjusted analysis (Greenland, 1996).

Another potential limitation was the recruitment of controls in two different time periods by two different methods. Controls could be different from one another and lead to problems in estimating an overall effect by combining the two study phases. However, in a study examining possible differences between the two control populations, the controls from each time period were found not to differ significantly from one another except for reported smoking during pregnancy (Puumala *et al.*, 2009). The difference in smoking rates could be due to a temporal trend since reported smoking during pregnancy appears to be declining over time (Ananth *et al.*, 2005; Okah *et al.*, 2005). Thus, it was necessary to include controls from both study phases, so that differences between cases and controls would not be influenced by temporal trends.

Finally, even though this study was comparatively large, the sample size was still small in absolute terms, which may have resulted in imprecisely estimated parameters. Also, with several exposure variables of interest and multiple subgroup analyses, our results are likely to include some false positives. Taken together, our results must be interpreted with caution and considered exploratory.

We found little evidence of an association between infertility and infertility treatment and infant leukemia in the largest study of infant leukemia yet conducted. Although there are several limitations both of the study itself and the study design used, it is unlikely that a strong association was missed.

Authors' roles

S.E.P. contributed to data analysis, interpretation of results, drafting and editing of the final manuscript. L.G.S. contributed to study design, acquisition of data, interpretation of results, drafting and editing of the final manuscript. M.M.W. contributed to interpretation of results and critical editing of the final manuscript. L.L.R. contributed to study conception and design, acquisition of data, interpretation of results and critical editing of the final manuscript. N.A.H contributed to study design, acquisition of data and critical editing of the final manuscript. M.A.R contributed to acquisition of data and critical

Table III Association between infant leukemia and additional infertility-related factors.

		Controls		Cases		OR[a]	95% CI	MLL+		OR[a]	95% CI	MLL−		OR[a]	95% CI
		n	(%)	*n*	(%)			*n*	(%)			*n*	(%)		
Combined leukemia	Prior fetal loss														
	None	241	(74.4)	337	(76.1)	Ref		171	(75.0)	Ref		114	(78.1)	Ref	
	One	64	(19.8)	76	(17.2)	1.10	0.73–1.64	42	(18.4)	1.32	0.80–2.16	22	(15.1)	0.88	0.50–1.57
	Two or more	19	(5.9)	30	(6.8)	1.37	0.71–2.62	15	(6.6)	1.57	0.71–3.47	10	(6.8)	1.46	0.61–3.49
	Maternal age [mean (SD)] (OR for 1 year increase)	29.82	(5.42)	29.08	(5.75)	0.99	0.96–1.02	28.81	(5.53)	0.98	0.94–1.02	28.98	(6.04)	0.99	0.95–1.03
	Use of OS drugs														
	No	309	(95.4)	424	(95.7)	Ref		218	(95.6)	Ref		140	(95.9)	Ref	
	Yes	15	(4.6)	19	(4.3)	1.01	0.48–2.13	10	(4.4)	0.88	0.35–2.22	6	(4.1)	0.98	0.36–2.70
	Time to index pregnancy														
	Not trying	108	(33.4)	170	(38.4)	1.22	0.86–1.74	77	(33.8)	0.98	0.63–1.53	66	(45.2)	1.62	1.01–2.59
	<1 year of trying	175	(54.2)	227	(51.2)	Ref		125	(54.8)	Ref		67	(45.9)	Ref	
	≥1 year of trying	40	(12.4)	46	(10.4)	1.09	0.66–1.80	26	(11.4)	1.10	0.60–2.01	13	(8.9)	0.99	0.47–2.07
ALL	Prior fetal loss														
	None	241	(74.4)	199	(75.4)	Ref		116	(73.9)	Ref		61	(79.2)	Ref	
	One	64	(19.8)	44	(16.7)	1.13	0.71–1.79	29	(18.5)	1.44	0.83–2.49	9	(11.7)	0.62	0.28–1.39
	Two or more	19	(5.9)	21	(8.0)	1.76	0.87–3.59	12	(7.6)	1.85	0.79–4.33	7	(9.1)	2.20	0.80–6.03
	Maternal age [mean (SD)] (OR for 1 year increase)	29.82	(5.42)	28.73	(5.58)	0.98	0.94–1.02	28.71	(5.49)	0.99	0.94–1.03	28.74	(5.98)	0.96	0.91–1.02
	Use of OS drugs														
	No	309	(95.4)	250	(94.7)	Ref		150	(95.5)	Ref		73	(94.8)	Ref	
	Yes	15	(4.6)	14	(5.3)	1.42	0.64–3.15	7	(4.5)	1.08	0.40–2.94	4	(5.2)	1.32	0.40–4.32
	Time to index pregnancy														
	Not trying	108	(33.4)	104	(39.4)	1.32	0.88–1.96	53	(33.8)	1.00	0.61–1.64	38	(49.4)	2.50	1.36–4.61
	<1 year of trying	175	(54.2)	127	(48.1)	Ref		85	(54.1)	Ref		29	(37.7)	Ref	
	≥1 year of trying	40	(12.4)	33	(12.5)	1.32	0.76–2.30	19	(12.1)	1.09	0.55–2.13	10	(13.0)	2.01	0.85–4.78
AML	Prior fetal loss														
	None	241	(74.4)	133	(77.3)	Ref		54	(79.4)	Ref		50	(75.8)	Ref	
	One	64	(19.8)	31	(18.0)	1.01	0.60–1.72	12	(17.6)	1.06	0.48–2.36	13	(19.7)	1.16	0.56–2.40
	Two or more	19	(5.9)	8	(4.7)	0.85	0.33–2.21	2	(2.9)	0.80	0.16–4.09	3	(4.5)	0.88	0.23–3.40
	Maternal age [mean (SD)] (OR for 1 year increase)	29.82	(5.42)	29.68	(5.87)	1.01	0.97–1.05	28.85	(5.60)	0.95	0.88–1.02	29.48	(6.03)	1.02	0.96–1.08
	Use of OS drugs														
	No	309	(95.4)	167	(97.1)	Ref		65	(95.6)	Ref		64	(97.0)	Ref	
	Yes	15	(4.6)	5	(2.9)	0.44	0.13–1.44	3	(4.4)	0.57	0.11–2.88	2	(3.0)	0.63	0.13–3.10
	Time to index pregnancy														
	Not trying	108	(33.4)	65	(37.8)	1.22	0.77–1.95	24	(35.3)	1.28	0.62–2.62	27	(40.9)	1.17	0.61–2.22
	<1 year of trying	175	(54.2)	94	(54.7)	Ref		37	(54.4)	Ref		36	(54.5)	Ref	
	≥1 year of trying	40	(12.4)	13	(7.6)	0.75	0.36–1.55	7	(10.3)	1.36	0.51–3.63	3	(4.5)	0.35	0.09–1.27

[a]Logistic regression models were adjusted for year of birth (quartiles), maternal age (continuous), maternal education, maternal race, smoking during pregnancy, household income, gestational age and birthweight.
OS = ovarian stimulating.

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