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Evaluation of maternal history of miscarriage, infertility, and in-vitro fertilization use as associated factors in PHACE

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The etiology of PHACE (**P**osterior fossa anomalies, **H**emangioma, **A**rtial anomalies, **C**oarctation of the aorta, and **E**ye anomalies) is unknown. A genetic etiology has been proposed but there are no published reports of heritability in families of children with PHACE. PHACE has a female predominance although preliminary X-inactivation studies have not demonstrated significant skewing in affected female patients or their mothers.¹ Copy number variation studies have yet to identify a common pathogenic variant.² We sought to determine if there is an increased prevalence of miscarriage, infertility and/or the use of in-vitro fertilization (IVF) in the mothers of children with PHACE. Several studies have suggested that the incidence of imprinting disorders is increased in patients undergoing IVF. Imprinting disorders occur when either the paternal or maternal normal allele is epigenetically silenced (imprinted) and a mutated allele from the other parent is expressed. Previous studies indicate that IVF may not be the sole cause of imprinting disorders, but rather that the genetic background of subfertile parents plays an important role.³ It has been proposed that IVF may bypass a natural selection mechanism to allow for an imprinting disorder to occur.⁴

The PHACE syndrome International Registry was established in 2006 and had 218 families enrolled at the time of this study. Of those, information regarding maternal history of miscarriage and infertility was only available for 174 at the time of enrollment. To further investigate the rates of maternal history of miscarriage, infertility, and IVF in the registry, an electronic survey was designed using SurveyMonkey Platinum and sent to registry participants for whom email contact information was available (114 families). Fifty-four responses were gathered from December 14th, 2014 to February 4th, 2015. The chi-square test was used to calculate p-values when comparing survey results to rates in the United States (US) for miscarriage, infertility, and IVF use.

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Known or suspected history of miscarriage was reported in 59/174 in the registry database (33.9%) compared with 22/54 survey respondents (40.7%). This difference likely represents an ascertainment bias. Both rates were statistically significantly higher than the estimated miscarriage rate of 10–20% in the US, $p < 0.001$ (Figure 1).⁵ Of the 22 survey respondents, 8 reported a history of 2 or greater pregnancy losses.

Fifteen percent of survey respondents reported a history of infertility (8/54). This rate was not statistically different from the US infertility rate of 12%, $p = 0.67$.⁶ Thirteen percent (7/54) of survey respondents reported receiving fertility therapy for the pregnancy related to the child with PHACE. This is comparable to the 11.9% of women in the US receiving infertility services, $p = 0.97$.⁷

More mothers of children with PHACE had miscarriages when compared to US data. Miscarriage is defined as the spontaneous loss of a known pregnancy before 20 weeks of gestation and recurrent pregnancy loss (RPL) has been defined as two or more failed consecutive pregnancies.⁵ Etiologies include cytogenetic abnormalities in the miscarriage tissue (50% for spontaneous pregnancy loss and 35% for RPL), anatomic uterine anomalies (20%), autoimmune and alloimmune causes (i.e. antiphospholipid antibody syndrome 15–20%), and parental genetic abnormalities (3–5%).⁵ Because cytogenetically abnormal miscarriages may result from a mechanism that impairs chromosome segregation, it is possible that PHACE syndrome results from a similar cause such as smaller, more viable cytogenetic abnormalities, e.g. duplications and deletions, or other molecular aberrations. Anatomic factors such as uterine or placental anomalies may also play a role in the pathogenesis of PHACE. There was not an increased incidence of hypercoagulability disorders in mothers of children with PHACE per maternal report; however, mothers may not have been routinely tested for these.

In contrast, rates of infertility and IVF use did not differ substantially between our study cohort and US national rates, making the hypothesis of PHACE as an imprinting disorder less likely.

Limitations to the study include recall and ascertainment biases and lack of control for confounding factors such as maternal age given the survey based design, parental reporting, and under powering. Another limitation was that the study was not designed to include a severity scale. The clinical features of PHACE in the children of the respondents were similar to those of the registry as a whole, with no significant differences in severity except for a trend toward higher rates of cardiac anomalies in the survey group. Population data was used for comparison, where the cohort may have included individuals with various diseases. In summary, our study demonstrated higher rates of miscarriage in mothers of children with PHACE. Rates of infertility and IVF use between the PHACE cohort and US population did not differ significantly. Larger studies will be beneficial to elucidate the etiology of PHACE.

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Figure 1.