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Hereditary Hemorrhagic Telangiectasia and Risks for Adverse Pregnancy Outcomes

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Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia characterized by epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations (AVM) in the brain, lung, liver, gastrointestinal tract, or spine. While pregnant women with HHT are known to have increased risks due to pulmonary AVMs, little is known about any increased risk for fetal birth defects or other adverse pregnancy outcomes. To investigate potential increased risk, individuals with a clinical diagnosis of HHT were asked to complete a survey composed of four sections: demographics, personal history of HHT, personal history of birth defects (modeled after state registries), and reproductive history. A total of 226 participants reported outcomes of 560 pregnancies, as well as self-reported personal history of birth defects. Of the 560 pregnancies, 450 (80.4%) resulted in 457 live births and 63 (13.8%) were pre-term. Of the 110 pregnancy losses, 80 (72.7%) were first trimester and five were stillborn. Anomalies considered to be medically or cosmetically significant were reported in 17 babies (3.7%). The presence of significant anomalies was not significantly associated with whether the baby had an HHT diagnosis ($P = 0.55$) or the gender of the parent with HHT ($P = 0.32$). Four liveborn babies and one stillborn had a cerebral AVM or hemorrhage in the perinatal period. Prevalence of uterine hemorrhage, pre-eclampsia, placental abnormalities, low-birth weight, and infertility did not appear increased over the general population. These data provide some reassurance that HHT does not lead to an appreciable increased risk for birth defects or other adverse pregnancy outcomes. © 2012 Wiley Periodicals, Inc.

Key words: HHT; pregnancy; birth defects; malformation; miscarriage; stillbirth; risk; genetic counseling

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a genetically heterogeneous autosomal dominant vascular dysplasia characterized by recurrent epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations (AVM) in the brain, lung, liver, gastrointestinal tract, or spine. It is most often caused by mutations in the *ENG* or *ACVRL1* genes which result in haploinsufficiency. Mutations in *SMAD4*, which is typically associated with juvenile polyposis, can also lead to an HHT phenotype in some individuals. Deleterious mutations in *ENG*, *ACVRL1*, and *SMAD4* are identified in approximately 85–90% of individuals with a clinical diagnosis of HHT [McDonald et al., 2011]. Additionally, linkage analysis indicates that there are at least two additional loci known to be associated with HHT in some families [McDonald et al., 2011].

Currently available data regarding pregnancy complications and HHT have mainly focused on maternal health issues and include a series of 484 pregnancies in 199 women with HHT [Shovlin et al., 2008], a series of 161 pregnancies in 47 women with HHT [Shovlin et al., 1995], as well as several case reports of maternal health complications, such as stroke, hemorrhage, and high output cardiac failure due to pulmonary and hepatic AVMs [Worda et al., 2007; Goussous et al., 2009; Lai et al., 2010; McDonald et al., 2011]. Two reports of uterine AVMs have been described in association with presumed HHT, although neither patient met clinical criteria for HHT [Shanberge, 1994; Dahlgren et al., 2006]. The most significant and well-documented risk during pregnancy is due to pulmonary AVMs (PAVM). Shovlin et al. [2008] reported that, of the 484 pregnancies in their series, 1% experienced a major PAVM bleed,

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and 1% of pregnancies resulted in maternal death due to myocardial infarction, hemoptysis, or hemorrhagic strokes. All maternal deaths occurred in women with no prior knowledge of HHT and prior knowledge was associated with improved survival [Shovlin et al., 2008]. It is, therefore, now recommended that women complete any necessary treatment for PAVMs prior to pregnancy if possible [McDonald et al., 2011]. If a PAVM is detected during pregnancy, treatment can also take place during the second trimester if necessary [McDonald et al., 2011]. Additionally, two retrospective series of women with HHT report no increased rate of miscarriage or other abnormal outcome [Goodman et al., 1967; Shovlin et al., 1995]. Goodman et al. [1967] reported 97 pregnancies in 40 women with HHT and found no statistically significant increase in miscarriage or stillbirths compared to 80 matched controls. In the 161 pregnancies reported by Shovlin et al. [1995], 11 miscarriages occurred which was not considered increased above population rates. The authors also noted that there was no statistically significant difference in miscarriage between women with and without PAVMs.

Patients with HHT seen in the Mayo Clinic HHT Center have presented with a history of miscarriage or birth defects in themselves or offspring and have raised the question as to whether they may have an increased risk for congenital birth defects, either personally or in their offspring, due to placental anomalies or abnormal blood vessel formation in a fetus. However, to our knowledge, there are no empiric data to provide to couples who are planning for or expecting a child regarding birth defects. In this study, we present self-reported reproductive outcomes from 226 individuals with HHT, a total of 560 completed pregnancies, as well as personal history of birth defects for a subset of 118 participants for whom a retrospective, blinded chart review was completed.

MATERIALS AND METHODS

Participants were eligible for this study if they were 16 years of age or older and had a clinical or genetic diagnosis of HHT. Participants were recruited through the Mayo Clinic HHT and Medical Genetics Clinics and through the HHT Foundation International. Patients identified through the Mayo Clinic were mailed a recruitment letter, survey, and consent form. The HHT Foundation International included recruitment information on its website (www.hht.org) and in newsletters, and participants were invited to complete an online version of the survey. Participants could indicate permission to be contacted if clarification was necessary. All responses were reviewed to ensure that a participant did not complete multiple submissions. The study was approved by the Mayo Clinic Institutional Review Board.

The survey consisted of four parts: demographics, personal history of HHT symptoms, personal history of birth defects (modeled after state birth defect registries), and reproductive history (see Survey in Supporting Information online). The majority of survey items asked for a Yes/No/Don't Know response. Items related to personal history of HHT asked about known symptoms or complications associated with HHT, as well as genetic test results, and were used to confirm either a genetic diagnosis or a clinical diagnosis based on the presence of at least 3 of the 4 following criteria: recurrent epistaxis, mucocutaneous telangiectasia, AVMs in the brain, lung, liver, or spinal cord, and positive family history. Participants were excluded if under 16 years of age or if they did not have a clinical or genetic HHT diagnosis. To assess for a personal history of birth defects, a list of congenital anomalies was created using birth defects commonly reported to national and state birth defects registries [Canfield et al., 2006; Minnesota Department of Health, 2009]. Reproductive history was asked for both male and female participants and included history of infertility and miscarriage. For each pregnancy, participants were asked to provide the delivery type, gestational age, infant's biometrics, a description of any pregnancy complications, whether each child had been diagnosed with HHT, and a description of any birth defects present. Space was provided for the participants to provide additional detail in a free text format.

For participants recruited through the Mayo Clinic, medical records were reviewed by the principal investigator (K.W.), who was blinded to the survey responses at the time of the review. Charts available for review contained imaging studies and consultation notes consistent with the HHT work-up, often including neurology, medical genetics, and ENT records. Additional records were reviewed if available. Pediatric and obstetrical records were not available for review as most patients travel to Mayo Clinic for an HHT evaluation and receive routine care in their hometown; therefore this was not considered a complete validation of the survey data. The data abstracted from the chart review was compared with the survey responses to confirm personal histories of birth defects when possible, and to identify birth defects that the participant failed to report.

The data were summarized using standard descriptive statistics using the SAS version 9.2 software package (SAS Institute, Inc., Cary, NC). Additional analysis of reported reproductive outcomes included a comparison of responses between female and male participants. This was done to assess for an increased risk for adverse events due to maternal HHT as opposed to fetal HHT. Since many of the participants reported on the outcomes for multiple pregnancies, the observations (i.e., pregnancies or live births) were not independent. Therefore, these tests for statistical significance were based on fitting separate logistic regression models for each outcome measure using the generalized estimating equation (GEE) methodology in SAS PROC GENMOD to model the correlation structure between the multiple observations from the same participant. All calculated P-values were two-sided and P-values <0.05 were considered statistically significant.

RESULTS

Demographics and HHT History

Of the 243 patients who had been seen at either the Mayo Clinic's HHT Clinic or Medical Genetics Clinic, 118 returned a completed survey for a response rate of 49%. An additional 108 online surveys were completed for a total of 226 participants. The mean participant age was 49 years (range: 17–87) and 78.7% (177/225) were female. Two hundred twelve participants (95.5% of 222) described themselves as White, 74.4% (166/223) had at least a 2-year college degree, and 82.1% (184/224) were married.

Of the 113 (50.2%, 113/225) participants who reported having genetic testing, 96 (85%) indicated that a mutation had been identified, and 72 (63.7%) knew which gene was responsible for their HHT. Forty-one (56.9%, 41/72) mutations were in *ENG*, 26 (36.1%, 26/72) were in *ACVRL1*, and 5 (6.9%, 5/72) were in *SMAD4*. There was a known family history in 86.3% (189/219).

Reproductive History

A total of 564 pregnancies were reported, including nine twin pregnancies. Four individuals (or their partner) were currently pregnant at the time of survey completion, resulting in 560 completed pregnancies for analysis. Of these, 450 (80.4%) resulted in 457 liveborn babies and 110 (19.6%) pregnancies results in pregnancy loss or stillbirth. Of liveborns, 381 (83.4%) were full-term (378 pregnancies), 63 (13.8%) were pre-term (59 pregnancies), and 13 (2.8%) were unknown gestational age. Vaginal births were reported in 336 (73.5%) liveborns (332 pregnancies), Cesarean sections in 94 (20.6%) liveborns (91 pregnancies), and delivery type was unknown for 27 (5.9%). Gender was equally divided. Only 155 liveborn babies (33.9%) were reportedly diagnosed with HHT at some point. Of the 110 pregnancy losses, 80 (72.7%) were first trimester, 14 (12.7%) were second trimester (including two twin pregnancies), 11 (10%) were ectopic or unknown trimester, and 5 (4.6%) were stillborn.

Overall, there were 49 reports of congenital anomalies or neurologic impairment in 35 liveborns (7.7%) and two stillborns (Supplemental eTable I—see Supporting Information online). Of these, 17 babies (3.7%) had significant anomalies (considered medically or cosmetically significant) and four liveborn babies (0.9%) and one stillborn had a reported cerebral AVM in the perinatal period (Table I). None of these babies were siblings. Of the cerebral AVMs found in the four liveborn babies, all were detected after an intracranial hemorrhage or infarction and two occurred prenatally. Of these two, one child had resulting hydrocephalus which resolved and had normal development, and the other child had significant brain atrophy and died after 11 hr. The cause of death for the stillborn baby was intracranial hemorrhage. The baby with the AV canal defect also had a diagnosis of Down syndrome. There were no other known etiologies provided for other babies with anomalies or functional impairment. There was no significant difference in the presence of significant anomalies between babies with or without an HHT diagnosis [4.5% (7/155) of live births with HHT vs. 3.3% (10/302) of live births without HHT, $P = 0.55$, after taking into account correlation]. Thirty-seven liveborns (10.7% of 346 with available data) had low-birth weight, defined as less than 2,500 g. Twenty-two of these were also pre-term.

Maternal hemorrhage, pre-eclampsia, or placental problems were noted in 36 of the 560 pregnancies (6.4%). Twenty-eight pregnancies resulted in hemorrhage and six of these were noted as

TABLE I. Live Births With Reported Anomalies

Gender	Gestation	Delivery	Anomaly	Other finding	Known HHT
Female	Full-term	Cesarean	Cleft palate	n/a	Yes
Female	Pre-term	Vaginal	Severe scoliosis	Cerebral palsy	No
Female	Full-term	Vaginal	Congenital hip dysplasia	n/a	No
Female	Full-term	Vaginal	Congenital hip dysplasia	n/a	Yes
Male	Full-term	Vaginal	Hypospadias	n/a	No
Male	Full-term	Vaginal	Hypo/aplasia of upper and lower limbs; choanal atresia	n/a	Yes
Female	Pre-term	Vaginal	Double right-sided aortic arch; cleft palate; esophageal stricture; genital anomalies	Learning disabilities; paralysis	Yes
Female	Full-term	Vaginal	Bilateral club foot	n/a	No
Female	Full-term	Vaginal	Bifid uvula	Sacral dimple	Yes
Male	Full-term	Cesarean	3/4 Finger syndactyly	n/a	No
Male	Full-term	Unknown	Enlarged heart	n/a	No
Male	Pre-term	Vaginal	Tibeal torsion	n/a	Yes
Female	Full-term	Vaginal	Congenital hip dysplasia	n/a	No
Female	Full-term	Vaginal	Facial port wine stain	n/a	No
Female	Pre-term	Vaginal	Enlarged kidney; Hirschsprung disease	n/a	Yes
Female	Pre-term	Cesarean	AV canal defect[a]	n/a	No
Female	Full-term	Unknown	Club foot	n/a	No
Male	Full-term	Vaginal	n/a	Cerebral hemorrhage at 2 months	No
Male	Pre-term	Cesarean	n/a	Intracranial hemorrhage at birth	Yes
Male	Full-term	Cesarean	n/a	Cerebral AVM with evidence of strokes in utero	Yes
Male	Full-term	Cesarean	n/a	Intracranial hemorrhage/infarct	Yes

[a]Baby has Down syndrome.

requiring a blood transfusion. There were three reports of pre-eclampsia and 10 reports of placental abnormalities in liveborns (2.2%), including retained placenta (n = 4), abruption (n = 3), structural abnormality (n = 2), and placenta previa (n = 1). Problems with infertility were reported by 25 (11.1%) of the 226 participants.

A summary of a comparison of reproductive outcomes between female and male participants is provided in Table II. There were no significant differences for pre-maturity, Cesarean delivery, or placental anomalies for the pregnancies that resulted in live births. For liveborn babies, there were no significant differences in low-birth weight, presence of an anomaly (either significant or otherwise), a diagnosis of HHT, or the presence of a cerebral hemorrhage or AVM. All participants who reported maternal hemorrhage during delivery were female (7.3%, 26/152), which reached statistical significance ($P = 0.006$).

Personal History of Birth Defects

When asked about the participants' personal history of birth defects, 41 individuals (18.1%) reported some type of anomaly, including minor anomalies that the participants wrote in themselves (Supplemental eTable II—see Supporting Information online). Of these individuals, 20 were of the subset of 118 participants recruited through Mayo Clinic and charts were available for review. The following significant anomalies were confirmed in four participants (3.4%, 4/118): an obstruction defect and double kidney, a ventricular septal defect (VSD), aortic valve stenosis, and atrial septal defect (ASD).

Cardiac anomalies were reported by 22 individuals overall. Eleven of these were Mayo Clinic patients and, in addition to the three participants with cardiac anomalies mentioned above, three were found to have patent foramen ovale (PFO) on chart review. Some individuals did not know the exact name of their anomaly. For example, one individual reported an AV canal defect but was found to have a PFO on chart review. One individual reported a PFO, VSD, and ASD but only the PFO and VSD were confirmed. Some participants provided written comments in the cardiac section regarding PAVMs and many of the individuals who reported cardiac defects (particularly AV canal defects) had PAVMs. Of individuals whose charts were reviewed but cardiac anomalies were not confirmed, five had a history of PAVMs. Of the 11 individuals with reported cardiac anomalies whose charts were not available for review, six had PAVMs.

Additionally, the chart reviews of the 118 Mayo-recruited participants (52.2% of 226) revealed 39 individuals with congenital anomalies that were not included in the survey responses, although only seven of these individuals (5.9%) had anomalies that might be considered medically significant. These include two individuals (1.7%) with schizencephaly noted on brain MRI, one closed-lipped with polymicrogyria and one open-lipped. Neither of these individuals had any neurologic impairment noted on chart review or their survey. One participant had a bicuspid aortic valve and a possible secundum ASD and another participant had a possible secundum ASD. Three participants had renal anomalies including an extra kidney, a partially duplicated collecting system, and a rotational anomaly. The other mild anomalies or variants noted on chart review (some occurring in the same individual) include five individuals with a PFO, 11 individuals with accessory spleens, nine individuals with duplicated renal arteries or prominent extrarenal pelvis, and 11 individuals with scoliosis or mild skeletal anomalies (Supplemental eTable III—see Supporting Information online).

DISCUSSION

With every pregnancy there is a risk for complications impacting maternal or fetal health. Generally, pregnant women are quoted a 3–5% risk for a child to be born with a major congenital malformation or neurological impairment due to genetic, teratogenic, or other causes [Bhasin et al., 2006; Canfield et al., 2006]. This risk does

TABLE II. Reproductive Outcomes Comparing Female and Male Parents With HHT

Outcome	Female parent[a]	Male parent[a]	*P*-value*
Pregnancies with live birth			
Pre-term delivery[b]	53/341 (15.5%)	6/94 (6.4%)	0.068
Cesarean delivery[b]	72/339 (21.2%)	19/82 (23.2%)	0.75
Placental anomalies	7 (2.0%)	3 (3.1%)	0.56
Livebirths			
Low-birth weight[b]	34/278 (12.2%)	3/66 (4.6%)	0.079
Any reported anomaly	30 (8.4%)	5 (5.2%)	0.24
Significant anomaly	15 (4.2%)	2 (2.1%)	0.32
Cerebral AVM/bleed	4 (1.1%)	1 (1.0%)	0.85
Child HHT diagnosis	119 (33.2%)	35 (36.1%)	0.71
Maternal hemorrhage	26 (7.3%)	0	0.006**

[a]One respondent (two pregnancies) was removed from this analysis because the gender of the respondent was not reported. The 152 female respondents reported 352 completed pregnancies with 358 live births. The 37 male respondents reported 96 completed pregnancies with 97 live births.
[b]The percentages for gestation, type of delivery, and low-birth weight are based on those without missing data.
*The tests for statistical significance were based on fitting separate logistic regression models for each outcome measure using the generalized estimating equation (GEE) methodology in SAS PROC GENMOD to model the correlation structure between the multiple observations from the same respondent.
**The above statistical approach could not be applied to this outcome measure since there were no maternal hemorrhages reported among the partners of the male respondents. This *P*-value is based on the standard chi-squared test ignoring the correlated nature of the data.

not generally include chances for minor anomalies, such as ptosis, strabismus, or hemangiomas. Additionally, some anomalies, such as PFO, scoliosis, and some renal anomalies are very common in the general population and may not come to medical attention or cause impaired health [Kent and Thaler, 2010; Lorenz et al., 2010]. Of all the liveborn infants reported in this study, 7.7% were reported to have a congenital anomaly or neurologic impairment. However, if minor anomalies (PFO, ptosis, strabismus, spina bifida occulta, hemangiomas, and port wine stains) and reports of neurologic symptoms are removed, there were 17 liveborn babies (3.7%) with significant anomalies. This is quite similar to general population rates. Anomalies considered significant were those that would be reported to national or state birth defect registries [Canfield et al., 2006; Minnesota Department of Health, 2009] or those that have severe cosmetic consequences, such as a large facial port wine stain. The majority of babies, with and without reported anomalies, had not received a diagnosis of HHT, although it is not known how many had received formal evaluation. While we would expect that approximately 50% of offspring would inherit HHT, it is quite likely that some of these children have not had genetic testing or a clinical evaluation, or may not have reached an age where clinical features of HHT would be expected. However, there was no statistically significant difference in having an HHT diagnosis between babies with or without a reported anomaly. Babies with a reported cerebral hemorrhage or AVM were considered separately and it is important to note that the risk for such an event is present in infancy [Morgan et al., 2002].

Of participants whose personal charts were available for review, four (3.4%) reported a significant anomaly that was confirmed. Additionally, seven participants were found to have an anomaly that may be considered significant, but which they either did not report or they were not aware of. These 11 individuals account for 9.3% of participants with available chart reviews. It is interesting that the majority of individuals reporting cardiac defects either mentioned a PAVM in relation to it or had a PAVM. Since echocardiography is employed to screen for PAVMs, it would not be surprising if some participants confused abnormal shunting with a congenital structural cardiac anomaly. Finally, the rates of incidental minor anomalies and variants, such as accessory spleens, renal variants, and PFOs in the chart-reviewed group were not higher than published background rates [Mortele et al., 2004; Kent and Thaler, 2010; Lorenz et al., 2010].

There does not appear to be any increased risk for pre-maturity, Cesarean delivery, low-birth weight, or miscarriage for this population. The approximate rates of pre-term labor and delivery by cesarean in the general population are 12.3% and 32.3%, respectively, and approximately 8.2% of infants are born with low-birth weight [Mathews et al., 2011]. In this study, overall rates of pre-term births (13.8%) and Cesarean delivery (20.6%) are very similar to general population rates, as is low-birth weight (10.7%). In clinically recognized pregnancies, there is a 10–20% chance of miscarriage, usually occurring in the first trimester [Condous et al., 2003]. Of the 560 completed pregnancies reported in this study, 14.3% resulted in a first trimester loss with an overall loss rate of 19.6%. These results provide further confirmation of the previously reported miscarriage rates by Goodman et al. [1967] and Shovlin et al. [1995] and indicate no increased risk. While participant overlap between this study and Shovlin et al. [1995] cannot be excluded, it is unlikely to be significant since the women in the Shovlin et al. study were all recruited at the Hammersmith Hospital in London and only one participant in the current study was known to be from England. Additionally, placental anomalies and pre-eclampsia did not appear increased over the general population prevalence [Gabbe et al., 1996].

Reproductive outcome responses were compared between male and female participants. Since the partners of the male participants presumably do not have HHT, this serves as a control to assess for the effects of maternal HHT on the fetus. There were no significant differences between the rates of anomalies, low-birth weight, placental anomalies, pre-term delivery, or Cesarean delivery. There were no reports of maternal hemorrhage in pregnancies reported by male participants and 26 reports by female participants. This did reach statistical significance and further studies to assess for this complication specifically may be warranted.

The limitations of this study are several and include small sample size, which is unavoidable in rare disorders of this type. The self-reported nature of these data which could not be completely validated, as well as a lower than desirable response rate (49%), could lead to ascertainment bias, and data were compared to general population rates rather than matched controls. Since the primary aim of this study was to understand fetal outcomes in the setting of HHT, rather than maternal pregnancy events such as those related to maternal PAVMs, our methods did not allow for evaluation of pregnancy complications leading to maternal death.

In this study of self-reported pregnancy outcomes for couples in which one parent has HHT, results provide some basis for reassuring couples that reproductive risks appear to be similar in type and frequency to that of the general population. These data do not indicate an increase in pregnancy loss or anomalies compared with published risk ranges. Counseling families about the natural history of cerebral AVMs and the risks for these as early as the perinatal period should certainly be included in discussions about genetic testing and AVM screening. A larger prospective, case–control study of pregnant women with HHT which includes postnatal follow-up and confirmed knowledge of HHT status in the offspring is recommended to confirm these results.

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