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A multicenter study of maternal and neonatal outcomes in individuals with Prader-Willi syndrome

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Abstract

Introduction—Prader-Willi syndrome (PWS) is a complex genetic disorder associated with three different genetic subtypes: deletion of the paternal copy of 15q11-q13, maternal uniparental disomy (UPD) for chromosome 15, and imprinting defect (ID). Patients are typically diagnosed because of neonatal hypotonia, dysmorphism and feeding difficulties, however data of the prenatal features of PWS are limited.

Objective—The aim of the study was to identify and compare frequencies of prenatal and neonatal clinical features of PWS amongst the three genetic subtypes.

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Contributorship Statement

All authors have participated in revising it critically and give their final approval of the version to be submitted. Study conception and design: Daniel J. Driscoll. Acquisition of data: June-Anne Gold, Jennifer L. Miller, Virginia Kimonis, Merlin Butler, Daniel J. Driscoll. Analysis and interpretation of data: Preeti Singh and Ranim Mahmoud, Roy Tamura, Virginia Kimonis. Drafting of manuscript: Preeti Singh, Ranim Mahmoud, and Virginia Kimonis. Critical revision: Virginia Kimonis, Merlin Butler, Daniel J. Driscoll, Roy Tamura.

Competing interests

No conflict of interest.

Methods—Data from 355 PWS patients from the Rare Diseases Clinical Research Network (RDCRN) PWS registry was used to analyze multiple maternal and neonatal factors collected during an eight-year multi-site study.

Results—Amongst our cohort of 355 PWS patients (61% deletion, 36% UPD and 3% IC defect) 54% were born by Cesarean section, 26% were born prematurely and 34% with a low birth-weight (frequencies 32%, 9.6% and 8.07% respectively in the general population). Fetal movements were reported as decreased in 72%. All babies were hypotonic, and 99% had feeding difficulties. Low Apgar scores (< 7) were noted in 17.7% and 5.6% of patients respectively compared to 1% and 1.4% respectively in the general population. Maternal age and pre-pregnancy weight were significantly higher in the UPD group (p value 0.01, <0.001 respectively).

Conclusion—We found a higher rate of perinatal complications in PWS syndrome compared to the general population. No significant differences in the genetic subtypes were noted except for a higher maternal age and pre-pregnancy weight in the UPD subgroup

INTRODUCTION

Lack of expression of genes on the paternally inherited chromosome 15q11-q13 region causes Prader-Willi syndrome (PWS).[1] This complex neurobehavioral condition affects about 1 in 10,000–15,000 live births.[2] Most patients with PWS have a paternal deletion of 15q11-q13 (70%), approximately 25–30% have maternal uniparental disomy (UPD) 15 and 1–3% have an imprinting defect (ID). Babies with PWS present with hypotonia, poor suck and feeding difficulties, dysmorphic features and hypogonadism. Later, obesity and hyperphagia results if caloric intake is not controlled.[3,4,5] These findings may be subtle in the immediate newborn period or may be masked by prematurity and other neonatal complications.[6,7,8]

Perinatal features of PWS reported in the literature include decreased fetal movements, polyhydramnios, malpresentation, and fetal heart rate abnormalities.[6,9–13] These obstetric complications frequently result in assisted vaginal deliveries with forceps or vacuum and Cesarean sections. Perinatal features have been described in the literature as clinical reports or small case series. In this study, we aimed to characterize these findings in a large well-studied cohort of 355 subjects enrolled in the NIH Rare Disease Clinical Research Network (RDCRN) PWS registry with special emphasis on natural history and genotype-phenotype correlations. The goal of this study was to provide an accurate incidence of the maternal and neonatal features of PWS. We believe that increased awareness among obstetricians and health care providers would allow earlier diagnosis and treatment of PWS by pediatricians/neonatologists with subsequent reduction of morbid obesity and other comorbidities impacting on quality of life

METHODS

We analyzed de-identified data from 355 PWS patients from the RDCRN PWS registry. The registry patients were enrolled by PWS experts following signed consent of IRB approved forms at four different clinical sites: University of California, Irvine, CA; Kansas University Medical Center, Kansas City, KS; Vanderbilt University, Nashville, TN and University of

Florida, Gainesville, FL. All data from this registry were managed by the Data Management Coordinating Center in Tampa, FL (DMCC). The DMCC facilitated the generation of electronic forms for data entry, data retrieval, and statistical analyses. Our multicenter longitudinal observational natural history study was supported by the NIH. We analyzed data on maternal and neonatal features collected through standardized natural history questionnaires completed by the registry team and compared variables to the existing general population with their PWS genetic subtypes (Table 1).

STATISTICS

The categorical variables were summarized using frequencies and continuous variables with calculated average ± SD scores. Pearson Chi-square test was used to compare categorical variables and student t-test for comparison of continuous variables. Fisher's exact test was used to compare categorical variables when the expected cell count was less than 5. SPSS 20 software (Armonk, NY) was used for statistical analysis and p-values less than 0.05 were considered statistically significant.

RESULTS

The descriptive statistics of maternal and neonatal outcome variables are summarized in Table 2. Out of 355 PWS patients enrolled in the registry, 217 patients had the 15q11-q13 deletion (61%); of these 98 were males (45.2%) and 119 females (54.8%); 127 patients had maternal UPD (36%) comprising of 52 males (40.9%) and 75 females (59.1%), and 11 had imprinting defects (3%), this group was comprised of 8 males (72.7%) and 3 females (27.3%).

Seventy-eight percent of PWS mothers reported decreased fetal movements during their pregnancy and 99.7% of the babies had hypotonia postnatally. Fifty-five percent of PWS babies were born by Cesarean section, significantly higher than the Cesarean section rate of 32% for all deliveries in the United States as reported in 2017 by the CDC[14] (Table 2).

We also found a higher incidence of low birth weight babies (34%) in our study group compared with 8.1% incidence of low birth babies in the United States (CDC 2017)[14] (Table 2). We found 5% (16/322) from our individuals had a very low birth weight (<1500 g). The 5% incidence of very low birth weight babies in this PWS group is approximately three times higher than the 1.4% for the overall incidence of extremely low birth weight infants in the United States[14] (Table 2).

Ninety-nine percent of babies with PWS had difficulty feeding (Table 2) and 75% needed supplementation with feeding tube (Table 2). Among the babies with PWS who needed help with a feeding tube, 25% required invasive gastrostomy tube placement and 75% needed a nasogastric or orogastric tube (Table 2). Only 22% of the babies were breastfed in our study population.

We found that PWS babies were born to mothers with a mean age of 31.4 (range 16 to 47) years, a mean pre-pregnancy weight of 63.8 kg and a mean weight gain of 13.9 kg during pregnancy. Eighteen percent of mothers reported polyhydramnios during the pregnancy and

5% had oligohydramnios. Four percent of mothers had gestational diabetes, 6% with high blood pressures during pregnancy but only 1% had pre-eclampsia. Eight percent of mothers reported premature rupture of membranes, 4% had an abnormal placenta (4 had abnormal placental location (3 placenta previa and 1 with low-lying placenta), three had placental insufficiency, two had calcified placentae, one had a post mature placenta, two had abruptio placenta, one had a thickened placenta, and two had unspecified placental abnormalities. Gestational age at birth ranged from 25 to 44 weeks with a mean of 37.9 weeks and 25% of the babies were born prematurely (<37 weeks). Mean Apgar scores were 6.5 at 1 minute and 8 at 5 minutes. Babies with PWS had a range of birth length from 17 to 60 cm (mean of 48.7 cm) and head circumference of 25 to 42 cm (mean of 34.2 cm). A weak cry was noted in 95%, hypotonia in 99.7% and feeding difficulty in 99% the most consistent clinical features in our study. Although most of these babies suffered from failure to thrive (77%) and several with gastroesophageal reflux disease (24%), about 5% were overweight before their first birthday (Table 2).

Comparison of the Variables by Genetic Subtype

We compared all maternal and neonatal outcome variables by their PWS genetic subtype (Deletion, UPD or IC defect). No significant differences were found in incidence of maternal complications across the three genetic subtypes except for a significant difference in the mother's pre-pregnancy weight ($p=0.01$) and maternal age ($p < 0.0001$) with an increased weight and age noted in the mothers of those babies with UPD. There was no difference in the neonatal outcomes in the three genetic subtypes (Table 3).

We also combined the UPD and IC defects and compared the frequency of the factors to the 15q11-q13 deletion group. Mother's weight before pregnancy ($p=0.015$) and the maternal age ($p<0.0001$) continued to be significantly different between the two genetic subtype groups. Patients from the combined UPD and IC defect group were born to mothers who were older (34.8 years vs. 29.2 years) and had a higher mean pre-pregnancy weight (66.2 kg vs. 62.3 kg), indicating that advanced maternal age and pre-pregnancy overweight/obesity increases the risk particularly for the UPD group. Additionally, a weak cry was noted to be slightly more frequent in the deletion subtype (97%) babies compared to in the combined group (92%, $p=0.048$). All of the other maternal and neonatal outcome variables showed no differences between the deletion and combined UPD and IC defect subtypes.

DISCUSSION

Prader, Labhart and Willi first recognized and described the Prader-Willi syndrome in 1956[27]. Holm et al. (1981) later established the PWS clinical diagnostic criteria which was revised in 1993[28,29] and again in 2001 due to significant advances in genetic testing and assessments.[18] Gillessen-Kaesbachet et al. (1995) showed that babies with PWS from Germany due to UPD had a significantly higher birth weight; however, Gunay-Aygun et al. (1997) showed that the reverse was true in babies from the United States. Varela et al. (2005) found no statistically significant difference regarding these parameters in babies with PWS from Brazil.[30–33] In term infants the incidence of low birth weight was higher in our PWS cohort group (34%) versus the population rate of 8.1 % in United States.[14] In our study

however, we did not find any significant difference in birth weight, length or head circumference in babies by PWS genetic subtype.

Whittington et al. (2008)[10] reported perinatal features of PWS in 46 UK babies, which was similar to the present study where we found a significant difference between the PWS genetic subtypes for mother's age and birth weight. In our study we also found a similar correlation between UPD and maternal age (35.2 years for UPD vs. 29.1 years for the deletion group) but we did not find any difference in birth weight[10]. Dudley et al. (2007) reported a significantly higher rate of miscarriage, polyhydramnios (27%), induced labor, Cesarean section (53%), low birth weight (37%), hypotonia (97%) and poor nippling (83%) in a French population of PWS. They also found significant differences between PWS genetic subtypes for higher rate of induced labor (79% vs. 48%), prematurity (26% vs. 8%) and older maternal age in UPD (36.4 years vs. 29.3 years) and lower birth weight for newborns with deletion, concluding a significant antenatal complication rate associated with UPD but more significant weight abnormalities associated with the deletion subtype of PWS.[11] Our study confirms similar rates of Cesarean section (55%), hypotonia (99.7%), and low birth weight (34%), but showed a lower risk for polyhydramnios (18%) and a higher risk for feeding difficulty (99%) as in previous studies. Our study also confirms that patients with UPD are born to older mothers with higher pre-pregnancy weights compared to patients with the 15q11-q13 deletion lending support to non-disjunction associated trisomy rescue in in the etiology of PWS UPD; the rates of prematurity and low birth weight however were found to be similar by genetic subtype in our study population. Hiroi et. al. (2000)[34] described abnormal ultradian heart rhythm of fetuses with PWS, which could be an early sign of PWS. Abnormal heart rate or rhythm may increase the risk for preterm induction of labor and emergency delivery by Cesarean section. Our study did not look at incidence of abnormal heart rate but our study had significantly higher rate of Cesarean deliveries compared to the general population per CDC statistics (54% vs. 32%).[14]

High Cesarean section rates can be associated with PWS perinatal complications like polyhydramnios, decreased fetal movements, and abnormal heart rate/rhythm. Polyhydramnios is seen in about 1–3% of pregnancies which could be a sign of underlying maternal or fetal disease and contribute significantly to perinatal morbidity and mortality in both mothers and babies.[16] A recently published retrospective matched case control study by Suleiman et al. (2017) found polyhydramnios to be an independent risk factor for a Cesarean delivery.[35] Our study found 18% of PWS patients had polyhydramnios prenatally which is significantly higher than the general population. Decreased fetal movements were added as one of the minor diagnostic criteria by Holm et al (1993). Decreased fetal movements were also seen in 78% of our study population which is similar to previous reports.[10,11,1736,]

In summary, our study reported the incidence of perinatal features in a large cohort of individuals with PWS. We found a high incidence of decreased fetal movements and delivery by Cesarean section compared to the general population. Babies with PWS were also found to be at a high risk for low birth weight (< 2500 g) in babies delivered at term (34%) and preterm (<37 weeks) (38.2%). Hypotonia, a weak cry and feeding difficulties were the most consistent clinical features of PWS in the newborn period. Most of the babies with feeding difficulties required assistance and the use of a feeding tube with 25% requiring

gastrostomy tube placement. There were no significant intergenetic PWS subtype differences except for maternal age and pre-pregnancy maternal weight being significantly higher in the UPD group supporting meiotic non-disjunction and associated trisomy rescue events in early pregnancy.

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Table 1

Maternal and neonatal variables analyzed in the study

Maternal Variables		Neonatal Variables	
1	Maternal age	**1**	PWS genetic subtype
2	Mother's weight before pregnancy	**2**	Gestational age
3	Maternal weight gain during pregnancy	**3**	Birth weight
4	Maternal body mass index (BMI)	**4**	Birth length
5	Assessment of fetal movements	**5**	Birth head circumference
6	Mode of delivery	**6**	Apgar score at 1 minute
7	Polyhydramnios	**7**	Apgar score at 5 minutes
8	Oligohydramnios	**8**	Failure to thrive
9	Gestational diabetes	**9**	Breastfeeding
10	Preterm labor	**10**	Feeding difficulty
11	High blood pressure	**11**	Gastro-esophageal reflux disease
12	Pre-eclampsia	**12**	Use of feeding tube
13	Premature rupture of membranes	**13**	Type of feeding tube
14	Abnormal placenta	**14**	Weak cry
		15	Hypotonia
		16	Overweight before 1 year of age

Table 2

Descriptive statistics of maternal and neonatal outcome variables in Prader- Willi syndrome.

Maternal and Neonatal Outcomes	**Study Statistics**	**Population Statistics**
Maternal age	16–47 years, mean 31.4 years	26.4 years[14]
Maternal body mass index (BMI) (mean ± SD)	26.5 ± 6	25.6% have BMI 25–29.9[15]
Assessment of fetal movements (N=328)	Decreased - 256 (78%) Normal - 67 (20%) Increased - 5 (2%)	NA
Mode of delivery (N=348)	Cesarean section - 190 (54.6%) Vaginal - 158/348 (45.4%)	32%[14]
Polyhydramnios	62 (18%)	1–3%[16,17]
Oligohydramnios	18 (5%)	11%[18]
Gestational diabetes	14 (4%)	9%[19]
High blood pressure	20 (6%)	9%[20]
Pre-eclampsia	5 (1%)	3.4%[21]
Premature rupture of membranes	30 (8%)	Term-8%, Preterm-3%[22]
Prader-Willi syndrome genetic subtypes (N=355), (M=Males, F=Females)	Deletion 15q11-q13 - 217 (61%) (M/F 98/119, 45.1%/ 54.8%) Maternal uniparental disomy 15–127(36%) (M/F 52/75, 40.9%/59%) Imprinting defect 11 (3%) (M/F 8/3; 72.7%/ 27.2%)	Deletion 15q11-q13 −70% Maternal disomy 15– 25% Imprinting defect - 2–5%
Gestational age in weeks (N=343)		
Preterm (<37 weeks)	90 (26%)	9.6%[14]
Term (37–41.6 weeks)	227 (66%)	83.4%[14]
Post-term (>42 weeks)	26 (8%)	0.4%[14]
Birth weight (N=322) (mean, range)	2713 g (703 – 5000 g)	
Normal birth weight (>2500 g)	212 (66%)	90.6%[14]
Low birth weight (<2500 g)	110 (34%)	8.1%[14]
Very low birth weight (<1500 g).	16 (5%)	1.4%[14]
Birth length (mean ± SD)	48.8 ± 5.8 cm for boys 48.4 ± 3.9 cm for girls	45.9–54.8 cm for boys[23] 45.9–54 cm for girls[23]
Birth head circumference (mean ± SD)	34.5 ± 3.4 cm for boys/33.8 ± 3.2 cm for girls	32.1–38.6 cm for boys[23] 32.3–37.8 cm for girls[23]

Maternal and Neonatal Outcomes	**Study Statistics**	**Population Statistics**
Apgar score at 1 minute (mean) Low Apgar score <7	6.5 ± 2.27 17.7%	Low Apgar score in 1 %
Apgar score at 5 minutes (mean) Low Apgar score <7	8.0 ± 1.7 5.6%	Low Apgar score in 1.4%[24]
Failure to thrive (N=343)	263 (77%)	5–10%[25]
Breastfeeding (N=343) Yes With difficulty/without difficulty	76 (22%) (96%, 4%)	83%[26]
Feeding difficulty (N=344), (Severe, Moderate, Mild)	340 (99%) (68%, 26%, 5%)	NA
Use of feeding tube (N=339)	Yes - 254 (75%) No - 85 (25%)	NA
Feeding tube type (N=236) Gavage (NG/OG) Gastrostomy tube	 177 (75%) 59 (25%)	 NA
Weak cry	328/344 (95%)	NA
Hypotonia (N=340)	339 (99.7%)	NA

Table 3

Maternal and Neonatal outcomes by Prader- Willi syndrome genetic subtype (Deletion vs. UPD - Uniparental Disomy, vs ICD - Imprinting Defect).

Maternal Outcome	**Deletion (217)**	**UPD (127)**	**ICD (11)**	**p-value**
Maternal age (mean ± SD)	29.2 years ± 5.3	35.2 years ± 6.1	30.8 years ± 4.77	**<0.001**
Mother's weight before pregnancy (mean ± SD)	62.3 kg ± 12.9	66.6 kg ± 15.4	61.9 kg ± 8.1	**0.01**
Maternal weight gain during pregnancy (mean ± SD)	14.2 kg ± 6.6	13.56 kg ± 5.7	13.3 kg ± 6.9	0.36
Maternal body mass index (mean ± SD)	26 ± 5.7	27.1 ± 6.2	28 ± 8.3	0.16
Decreased fetal movements	161/209 (77%)	88/124 (71%)	7/11 (64%)	0.33
Cesarean section	120/211 (57%)	66/126 (52%)	4/11 (36%)	0.40
Polyhydramnios	33 (15%)	28 (22%)	1 (9%)	0.21
Oligohydramnios	12 (55%)	6 (5%)	0	0.70
Gestational diabetes	9 (4%)	5 (4%)	0	0.79
Preterm labor	56 (26%)	34 (27%)	0	0.13
High blood pressure	10 (5%)	9 (7%)	1 (9%)	0.56
Pre-eclampsia	3 (1%)	2 (2%)	0	0.91
Premature rupture of membranes	20 (9%)	9 (7%)	1 (9%)	0.79
Abnormal placenta	8 (4%)	7 (6%)	0	0.56
Neonatal Outcome				
Mean birth weight (>37 weeks) ±SD	2752 ± 0.58	2591± 0.67	2857 ± 0.39	0.13
Mean birth weight (<37 weeks) ±SD	2165 ± 0.61	2091± 0.51	2200 ± 0.40	0.12
Low birth weight (<2500 g) >37weeks	46/142 (32%)	32/78 (41%)	1/10 (10%)	0.23
Birth length (mean ± SD) cm.	48.9 ± 3.9	47.8 ± 6.5	51.4 ± 4.5	0.09
Birth head circumference (mean ± SD)cm.	34.8 ± 3.3	33.4 ± 3.2	35.2 ± 2.02	0.11
Apgar score at 1 min (mean ± SD)	6.4 ± 2.2	6.6 ± 2.3	6.6 ± 2.3	0.77
Apgar score at 5 min (mean ± SD)	7.9 ±1.7	8.0 ± 1.8	7.6 ± 1.6	0.86
Failure to thrive	166 (76%)	89 (70%)	8 (73%)	0.23
Breastfeeding	43 (20%)	28 (22%)	5 (45%)	0.15
Feeding difficulty	207 (95%)	122 (96%)	11 (100%)	0.81
Gastroesophageal reflux disease	53 (24%)	31 (24%)	1 (9%)	0.33
Feeding tube used	151/203 (74%)	95/125 (76%)	8/11 (73%)	0.58
Gastrostomy tube	39/151 (26%)	19/95 (20%)	5/8 (63%)	0.25
Weak cry	204 (94%)	113 (89%)	11 (100%)	0.07
Hypotonia	206/207 (99.5%)	122/122 (100%)	11/11 (100%)	0.87
Overweight before 1 year of age	7 (3%)	9 (7%)	1 (9%)	0.23