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ORIGINAL ARTICLE

Estimate of genetic variants using CNV-Seq for fetuses with oligohydramnios or polyhydramnios

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Abstract

Background: Oligohydramnios or polyhydramnios, is associated with chromosomal aberrations, particularly aneuploidy. However, its correlation with copy number variation (CNV) remains unclear.

Methods: We retrospectively analyzed 428 cases with an abnormal level of amniotic fluid, comprising of 139 cases of single ultrasound findings (SU group) and 289 cases of multiple ultrasound findings (MU group), by CNV sequencing (CNV-Seq) and followed their pregnancy outcomes.

Results: The overall detection rate of clinically significant findings was 8%, with 5% in the SU group and 11% in MU group. Besides, 18 microdeletion/microduplication syndromes were detected, with the highest rate of renal cysts and diabetes syndrome (22%, 4/18). Also, the rate of termination of pregnancy in MU group was much higher than that in the SU group (29% vs. 10%, $^{***}p < 0.001$), and in the MU-oligohydramnios subgroup, it was the highest (34%), regardless of cases with chromosomal anomaly and lost to follow-up.

Conclusion: Our results showed that the abnormal level of amniotic fluid, especially combined with other ultrasound abnormalities, is closely related to chromosomal abnormalities and genetic CNVs. CNV-Seq may be useful in investigating pregnancies with an abnormal amniotic fluid level.

KEYWORDS

aneuploidy, copy number variation, oligohydramnios, polyhydramnios, pregnancy outcome

1 | INTRODUCTION

Amniotic fluid plays an important role in protecting the fetus, maintaining fetal metabolism, and promoting fetal lung development (Fitzsimmons & Bajaj, 2022). Amniotic fluid is produced by fetal urination and fetal lung fluid production, and is reabsorbed through fetal deglutition and intramedullary and intravascular absorption (Hamza et al., 2013; Underwood et al., 2005). Oligohydramnios or polyhydramnios is a pathological process in which the dynamic equilibrium between the production and resorption of amniotic fluid is disturbed (Hwang & Bordoni, 2022; Keilman & Shanks, 2022). Oligohydramnios refers to the situation in which the amniotic fluid volume (AFV) is less than 300 ml during pregnancy, with an incidence of 0.4%–4% (Hou et al., 2020); whereas, polyhydramnios refers

to the situation in which the AFV is more than 2000 ml, and with an incidence of 0.2%–1.6% (Hamza et al., 2013). Many factors, such as fetal structural abnormalities, placental dysfunction, maternal factors, and so forth can lead to abnormal amniotic volume; however, 60%–70% of the causes are unknown (Hwang & Bordoni, 2022; Keilman & Shanks, 2022). Recently, copy number variation sequencing (CNV-Seq) has been recommended as first tier diagnostic test in prenatal diagnosis for significant chromosome anomalies (Wang et al., 2018b). Nevertheless, the correlation between amniotic fluid abnormality and CNVs has rarely been reported. Here, we focus on the analysis of CNVs in fetuses with oligohydramnios or polyhydramnios to identify possible chromosome anomalies, and to evaluate the pregnancy outcome of these fetuses.

2 | MATERIALS AND METHODS

2.1 | Subject

It is a retrospective study that reviewed singleton pregnancies that underwent prenatal CNV sequencing (CNV-Seq) testing due to oligohydramnios or polyhydramnios, accompanied with or without other ultrasound abnormalities between January 2017 and December 2021 at the Genetic and Prenatal Diagnosis Center of the First affiliated hospital of Zhengzhou University. Oligohydramnios was defined as the amniotic fuid index (AFI) below 5 cm or the maximal vertical pocket (MVP) below 2 cm; whereas, AFI above 24 cm or MVP above 8 cm were classified as polyhydramnios. In this study, single ultrasound findings group (SU) includes cases with only oligohydramnios or polyhydramnios index, and multiple ultrasound findings group (MU) contains cases with oligohydramnios or polyhydramnios accompanied with other ultrasound abnormalities. As a results, the enrolled 428 fetuses were classified into SU group ($N = 139$) and MU group ($N = 289$). Then, four subgroups based on the amniotic fluid volume were listed as SU-oligohydramnios ($N = 86$), SU-polyhydramnios ($N = 53$), MU-oligohydramnios ($N = 143$), and MU-polyhydramnios ($N = 146$). In addition to ultrasound abnormalities, other prenatal invasive indications, cases with advanced maternal age and high risk of Down screening were also listed in Table S1. The mean maternal ages of the SU group and MU group were 30.0 ± 5.2 and 29.0 ± 5.1 years old, respectively. Also, the mean gestation age on invasive week was 26.8 ± 4.3 and 27.9 ± 3.7, respectively ($^*p < 0.05$). Detailed demographic characters were presented in Table S1. In the MU group, ultrasound soft indicators includes: thickened nuchal translucency (NT) or nuchal fold (NF), single umbilical artery, fetal growth delay or restriction, echogenic fetal bowel, mild hydronephrosis, mild ventriculomegaly, renal pelvis dilatation, absent or hypoplastic nasal bone, and pleural effusion.

In our study, all the subjects provided the informed consent, and CNV-Seq testing was performed later, which was done on Next Seq CN 500 platform with unique reads ≥2.5 Mb. CNV pathogenicity was assessed according to the latest guidelines from the American College of Medical Genetics (ACMG) (Riggs et al., 2020) and using DGV, Decipher, Ensemble, OMIM, PubMed database, and our local database.

The data were analyzed by Graphpad Prism 9, and statistical comparisons were performed using the Chi-square (and Fisher's exact) test, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | The chromosomal abnormalities ratio of MU group was much higher than in SU group

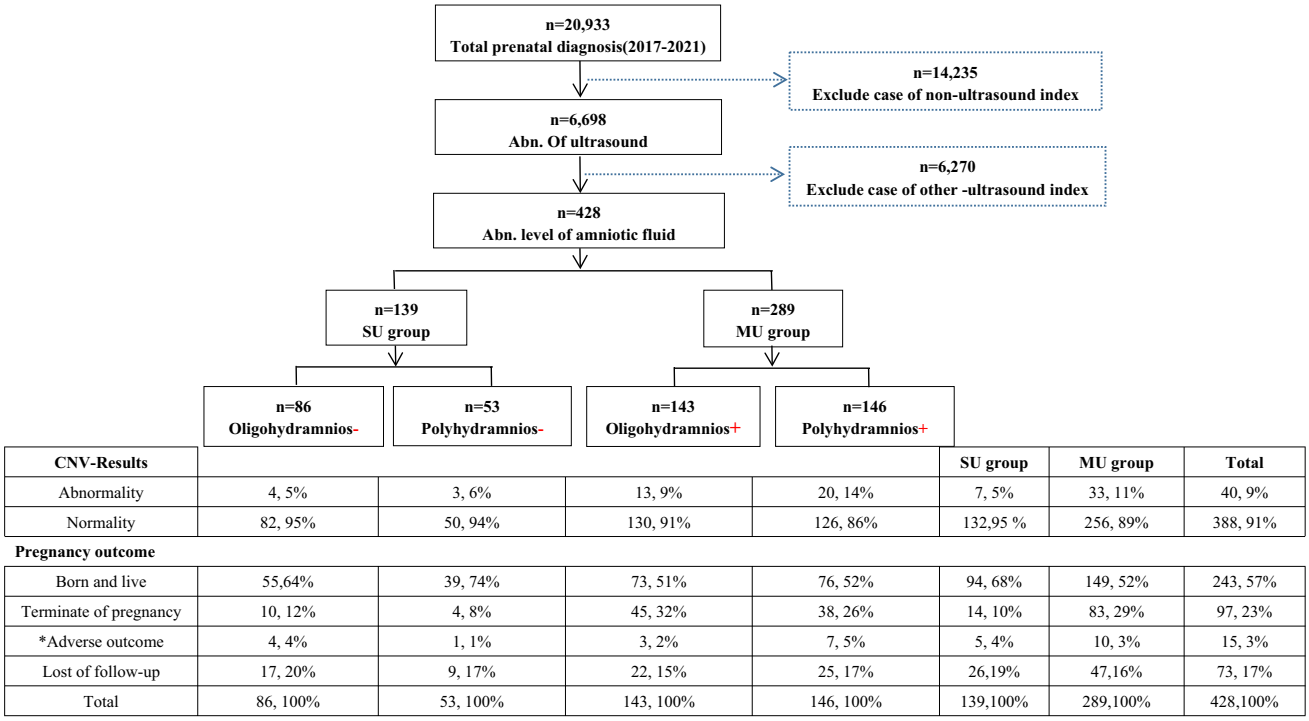
In total, 20,933 prenatal tests were performed, of which 6698 cases were ultrasound abnormalities. Then, 428 fetuses with abnormal amniotic volume were enrolled. Chromosomal abnormalities were detected in 40 (9%) cases, including 14 cases of aneuploidies, 22 cases of pathogenic or likely pathogenic CNVs, and four cases of VUS (variant of unknown significant). Therefore, the overall detection rate of clinically significant findings was 8% (36/428) (Figure 1).

In the MU group, the total detection rate was much higher than that in SU group (11% vs. 5%, $^*p < 0.05$). Also, the main difference lied in the aneuploidies (5% vs. 1%, $^*p < 0.05$), rather than CNVs detection (7% vs. 4%, $p = 0.39$). (Figure 1, Tables 1 and 2).

3.2 | 18/26 cases were associated with CNV syndrome and RACD is the most common one

Among 26 cases detected with CNVs, 18 (69%) cases were associated with the CNV syndrome, and renal cysts and diabetes syndrome (RACD) was the most common type (4/18, 22%).

In the MU group, 16 (6%) pathogenic or likely pathogenic CNVs and 4 (1%) VUS CNVs were detected as shown in Table 2. The size of the 20 cases (case 21–40) ranged from 520 kb to 14.86 Mb, of which 13 were related to clinical syndromes: RACD(#137920, case 34, 39, 40), Angelman syndrome/Prader-Willi syndrome (#105830/176270, case 29, 37), Wolf-Hirschhorn syndrome, (#194190, case 23), 1p36 terminal region (includes *GABRD*) (#607872, case 26),



CNV-Results					SU group	MU group	Total
Abnormality	4, 5%	3, 6%	13, 9%	20, 14%	7, 5%	33, 11%	40, 9%
Normality	82, 95%	50, 94%	130, 91%	126, 86%	132,95 %	256, 89%	388, 91%
Pregnancy outcome							
Born and live	55,64%	39, 74%	73, 51%	76, 52%	94, 68%	149, 52%	243, 57%
Terminate of pregnancy	10, 12%	4, 8%	45, 32%	38, 26%	14, 10%	83, 29%	97, 23%
*Adverse outcome	4, 4%	1, 1%	3, 2%	7, 5%	5, 4%	10, 3%	15, 3%
Lost of follow-up	17, 20%	9, 17%	22, 15%	25, 17%	26,19%	47,16%	73, 17%
Total	86, 100%	53, 100%	143, 100%	146, 100%	139,100%	289,100%	428,100%

FIGURE 1 Patient flow chart with CNV results and corresponding pregnancy outcomes.

TABLE 1 Aneuploidy was detected in 14/428 prenatal cases with abnormal level of amniotic fluid by CNV-Seq

Case	Age	Gestational week^{+day}	Ultrasound	CNV- results	Pregnancy outcome
1	36	22	Oligohydramnios, echogenic intracardiac focus	47,XN,+13	Termination of pregnancy
2	33	24^{+3}	Polyhydramnios, single umbilical artery, abnormal hand posturing	47,XN,+18	
3	29	18	Polyhydramnios, bilateral choroid cyst	47,XN,+18	
4	23	23^{+5}	Polyhydramnios, ventricular septal defect, single umbilical artery, low conus medulla, spinal canal cyst, small thymus, possible overlapping fingers of right hand	47,XN,+18	
5	29	25	Polyhydramnios, short nasal bone, echogenic left intracardiac focus	47,XN,+21	
6	28	24	Polyhydramnios, no nasal bone, duodenal stenosis or atresia	47,XN,+21	
7	27	31	Polyhydramnios, short nasal bone	47,XN,+21	
8	27	26^{+2}	Polyhydramnios, ventricular septal defect, no nasal bone	47,XN,+21	
9	28	33	Polyhydramnios, pleural effusion, abdominal cavity effusion	47,XN,+21	
10	44	23	Polyhydramnios, poor filling of gastric vesicles	47,XN,+21	
11	40	31	Polyhydramnios, poor filling of stomach bubble, dilation of lateral ventricle	47,XYY	
12	29	24	Oligohydramnios	47,XXY	
13	29	22	Oligohydramnios, NT 2.9 mm	46,XY,+Y(1.3)	
14	25	20	Oligohydramnios, choroid cyst	47,XXY,+X(1.83),−Y(0.12)	

16p13.11 recurrent microduplication (#613458, case 27), 1q43q44 terminal region (includes *AKT3*)(ISCA-37493, case 28), 16p11.2p12.2 microdeletion syndrome(#613604, case 31), 8p23.1 duplication syndrome (Decipher, case 32), 15q24 recurrent microdeletion syndrome (#613406 case 33), and Cat-Eye Syndrome (Type I) (#115470, case 38).

While, in the SU group, 6 (4%) pathogenic CNVs were revealed, containing five syndromes: RACD (#137920, case

TABLE 2 22 pathogenic/likely pathogenic and 4 VUS CNVs were detected in 26/428 prenatal cases with abnormal level of amniotic fluid by CNV-Seq

Case	age	GW^{+d}	Ultrasound	CNVs	Size	Key gene/syndrome	Pathgenicity	Outcome
15	26	24	Oligohydramnios	22q11.21(18880000–21480000)×3	2.6	22q11 duplication syndrome	P	Born
16	32	22	Oligohydramnios	2q12.2q13(106980000–113120000)×3	6.14	/	P	Born
17	37	26	Oligohydramnios	Xp22.31(6460000–8140000)×0	1.68	Steroid sulphatase deficiency (STS)	LP	TOP
18	28	28^{+3}	Polyhydramnios	22q11.21(18900000–2032000)×1	1.42	22q11 deletion syndrome	P	Born
19	30	32	Polyhydramnios	17p12(14100000–15440000)×1	1.34	Hereditary liability to pressure palsies (HNPP)	P	Born
20	28	28	Polyhydramnios	17q12(34820000–36200000)×1	1.38	RCAD	P	TOP
21	29	28	Oligohydramnios, hydronephrosis of right	1p35.3p35.1(29740000–32920000)×1	3.18	/	P	TOP
22	21	29^{+5}	Oligohydramnios, tricuspid regurgitation	14q12(27100000–31680000)×1	4.58	*FOXG1*	P	TOP
23	28	33^{+4}	Oligohydramnios, fetal growth restriction, small kidneys	4p16.3(68345–1962078)×1	1.89	Wolf-Hirschhorn syndrome	P	TOP
24	28	23	Oligohydramnios, fetal growth delay, microcephaly	19p13.3(1360000–4440000)×3	3.08	/	P	TOP
25	32	32	Oligohydramnios, fetal growth delay	4q26q28.1(116000000–124620000)×1	8.62	/	LP	TOP
26	29	26	Oligohydramnios, fetal growth delay	1p36.33p36.32(820000–2700000)×1; 19p13.3(260000–5840000)×3	1.88;0.78	1p36 terminal region (includes *GABRD*)	P	TOP
27	34	28	Oligohydramnios, enlargement of cardiothoracic ratio, the skin of the head is edema and thickened	16p13.11(15520000–16300000)×3	0.78	16p13.11recurrent micro-duplication	VUS	TOP
28	32	35	Oligohydramnios, fetal growth restriction	1q43q44(237560000–249220000)×1	11.66	1q43q44 terminal region (includes AKT3), *ZBTB18,FH*	P	Growth delay
29	27	31	Oligohydramnios, tricuspid regurgitation, fetal growth delay	15q11.2(22500000–23640000)×1	1.14	Angelman syndrome/Prader-Willi syndrome	VUS	NA

TABLE 2 (Continued)

Case	age	GW^{+d}	Ultrasound	CNVs	Size	Key gene/syndrome	CNV level	Outcome
30	41	34	Polyhydramnios, echogenic fetal bowel	13q21.1q21.2(57560000−60340000)×1	2.78	/	VUS	Born
31	23	27	Polyhydramnios, ectopic kidney, aortopulmonary disorder of ration	16p11.2(29660000−30200000)×1	0.54	16p11.2-p12.2 microdeletion syndrome	P	TOP
32	23	20^{+5}	Polyhydramnios, single umbilical artery, permanent umbilical vein, permanent left superior vena cava, aortic arch at right, right polycystic kidney	8p23.1(10840000−11460000)×3; Xq28(153820000−154940000)×1	0.62;1.12	8p23.1 duplication syndrome	LP	TOP
33	36	29	Polyhydramnios, aortic stenosis, persistent left superior vena cava, coronary sinus dilated	15q24.1q24.2(72960000−76100000)×1	3.14	15q24 recurrent microdeletion syndrome	P	Born
34	23	25	Polyhydramnios, enhanced echo in both kidneys	17q12(34800000−36220000)×1	1.36	RCAD	P	Born
35	41	27^{+3}	Oligohydramnios, fetal growth restriction	18p11.32p11.21(120000−14980000)×1	14.86	*TGIF1*, *AFG3L2*	P	TOP
36	18	33	Polyhydramnios, fetal ascites, pleural effusion	46,XX,Xp11.4(40520000−41040000)×3	0.52	*USP9X*	VUS	TOP
37	25	32	Polyhydramnios, the S/D value of umbilical artery increased intermittently	15q11.2q13.1(23683783−28544359)×1	4.86	Angelman syndrome/Prader-Willi syndrome	P	TOP
38	19	31	Polyhydramnios, single umbilical artery, separation of the left renal pelvis	22q11.1q11.21(16079545−18877787)×4	2.78	Cat-Eye syndrome (Type I)	P	TOP
39	37	26^{+2}	Polyhydramnios, separation of the renal pelvis	17q12(34880000−36060000)×1	1.58	RCAD	P	TOP
40	25	26	Polyhydramnios, multiple fingers in front of right axis	17q12(34800000−36260000)×1	1.46	RCAD	P	TOP

Abbreviations: LP, likely pathogenic; NA, not available; P, pathogenic; RCAD, renal cysts and diabetes syndrome; TOP, termination of pregnancy; VUS, variant of unknown significant.

TABLE 3 The pregnancy outcome of 317 fetuses with known follow-up results and normal CNVs

	SU group			MU group			
	Total	Oligo-hydramnios−	Poly-hydramnios−	Total	Oligo-hydramnios+	Poly-hydramnios+	Summary
Birth and live well	91, 86%	54, 83%	37, 90%	145, 69%	72, 66%	73, 72%	236, 74%
Mature birth	69, 65%	36, 55%	33, 80%	108, 51%	43, 40%	65, 64%	177, 56%
Premature birth	22, 21%	18, 28%	4, 10%	37, 18%	29, 26%	8, 8%	59, 19%
Poor pregnancy outcome	4, 4%	3, 5%	1, 3%	10, 5%	3, 3%	7, 7%	14, 56%
Born with death	3, 3%	2, 3%	1, 3%	8, 4%	2, 2%	6, 6%	11, 4%
Born with disease	1, 1%	1, 2%	0	2, 1%	1, 1%	1, 1%	3, 1%
Terminate of pregnancy	11, 10%	8, 12%	3, 7%	56, 26%	34, 31%	22, 21%	67, 21%
Total	106, 100%	65, 100%	41, 100%	211, 100%	109, 100%	102, 100%	317, 100%

Abbreviations: MU, multiple ultrasound findings including oligohydramnios or polyhydramnios; SU, single ultrasound findings (oligohydramnios or polyhydramnios).

20), 22q11 duplication syndrome (#608363, case 15), steroid sulphatase deficiency (STS) (#308100, case 17), 22q11 deletion syndrome (#188400, case 18), and hereditary liability to pressure palsies (HNPP) (#162500, case 19) (Table 2).

3.3 | MU group tends to have a higher proportion of adverse outcomes

The follow-up results shows that, 243/428 (57%) cases were born and live, while 97/428 (23%) cases terminate their pregnancy, 15/428 (3%) cases with poor pregnancy outcomes including born with disease or death, and the rest (73/428, 17%) were lost to follow-up (Figure 1).

Specifically, the rate of termination of pregnancy in the MU group is higher than that in the SU group [83/289 (29%) vs. 14/139(10%), $^{***}p < 0.001$], regardless of cases with loss of follow-up [83/242 (34%) vs. 14/113(12%), $^{***}p < 0.001$]. Also, the ratio of poor pregnancy outcome in the MU group is similar in that in the SU group [10/287 (3%) vs. 5/139 (4%), $p > 0.5$]. On the contrary, the rate of birth and live in the MU group is lower than that in the SU group [149/289 (52%) vs. 94/139 (68%), $^{**}p < 0.01$], regardless of cases with loss of follow-up [149/242 (62%) vs. 94/113 (83%), $^{***}p < 0.001$] (Figure 1, Tables 1 and 2).

Moreover, when both chromosomal anomaly (40 cases) and lost to follow-up (71 cases) were excluded from the data, pregnancy outcomes agree to previous non-excluded results obtained (Table 3). Namely, the MU group even with normal CNV results had a higher rate of termination of pregnancy [56/211 (26%) vs. 11/106 (14%), $^{***}p < 0.001$] (Table 3).

As data showed, except case 29 of lost to follow-up, 14 aneuploidies and 17 CNV-positive cases chose to terminate their pregnancy, and eight cases continued their pregnancy and gave birth to live babies. Except for case 28, where the baby had prenatal fetal growth restriction and showed postnatal growth delay, other seven cases showed no obvious clinical symptoms. This may be related to the younger age of the children, from one year to four years.

4 | DISCUSSION

In the past five years, CNV-Seq testing has been widely applied in prenatal diagnosis, especially for those with ultrasound abnormalities (Wang et al., 2018a, 2018b). A prospective analysis performed by Wang et al. showed that the more the ultrasound abnormality index, the higher the rate of pathogenic CNVs detected (Wang et al., 2018a). Also, the same team demonstrated that CNV-Seq detected an additional 1% pathogenic or likely pathogenic chromosomal aberrations compared to the traditional karyotype in prenatal diagnosis (Wang et al., 2018b). However, no literature retrieved reported the association between amniotic fluid abnormality and genetic anomalies by CNV-Seq analysis. Hence, we first focused on the analysis of CNVs in fetuses with oligohydramnios or polyhydramnios, accompanied with or without other ultrasound indications by CNV-Seq test. Our results showed that the overall detection rate of clinically significant findings was 8%, including 14 (3%) aneuploidies, and 22 (5%) pathogenic or likely pathogenic CNVs. Also, the incremental yield in the SU group and MU group was 5% and 11%, respectively. Therefore, CNV-Seq testing plays a key role in the etiological analysis of both oligohydramnios and polyhydramnios, regardless of the presence of other ultrasound abnormalities.

Wu et al. find that the overall significant abnormality rate was 11% (16/150) in fetuses with polyhydramnios,

with an additional 7% chromosomal aberrations than karyotype, by using another technology, chromosomal microarray analysis (CMA) (Wu et al., 2022). In our study, the total abnormality rate of the polyhydramnios group was 12% (23/199), 6% (3/53) for the SU-polyhydramnios subgroup and 14% (20/146) for the MU-polyhydramnios subgroup. Assuming that the karyotype detects abnormalities larger than 5 Mb, we can detect an additional 7% (13/199) aberrations than karyotype. The total ratio was consistent with the previous study. However, there was a larger difference in the abnormal rate of the SU-polyhydramnios group between the study of Wu's group and our study (6% vs. 9%), which may be related to the small sample size.

Another retrospective cohort study using CMA technology showed 2% (1/50) clinically significant findings in oligohydramnios cases, which did not differ from a large control group of 5541 fetuses with normal ultrasound (1.4%, 78/5541) (Singer et al., 2019). Here, we found 7% (17/229) risk for clinical significant CNV-Seq findings in cases with oligohydramnios, which differs from the control group of 5005 fetuses in our inner database [7% (17/229) vs. 1.7% (86/5005), $p < 0.001$]. It should be noted that the number of oligohydramnios cases in the previous study (Singer et al., 2019) was small. If our data is compared with their control data, the difference is significant [7% (17/229) vs. 1.4% (78/5541), $p < 0.001$]. In addition, Stoll et al. reported 31 (20%) abnormal karyotypes in 154 fetuses with oligohydramnios, including the same kind of aneuploidy as that in our study (Stoll et al., 1998). In summary, the ratio difference is mainly due to the sample size, testing methods, and regional differences.

In addition to aneuploidy, we also found 22 (5%) pathogenic or likely pathogenic CNVs and 4 (1%) VUS CNVs, which contained 14 kinds of CNV syndromes and three halpoinsufficiency or triplosensitivity genes (case 22, 35, 36). Also, RCAD accounted for the highest proportion in the related syndrome (4/18, 22%). RCAD, also named 17q12 microdeletion, was the most commonly reported syndrome in the polyhydramnios group, comprising a wide clinical spectrum of developmental kidney abnormalities (Mefford et al., 2007), mainly due to insufficient expression of *HNF1B* gene[OMIM 189907] (Ulinski et al., 2006). In our study, 36% (19/53) oligohydrmanios cases and 18% (26/146) polyhydramnios cases combined with kidney abnormalities such as hyperechogenic kidneys and pyelic separation were reported, and the positive rates were 4% (2/53) and 3% (5/146), respectively.

In addition to RACD syndrome, there are syndromes as 22q11 deletion syndrome, 15q24 microdeletion syndrome, and Cat-Eye Syndrome (Type I) that involve cardiovascular defects and urogenital malformations (Besseau-Ayasse et al., 2014; Gajecka et al., 2007; Sharp et al., 2007). Besseau-Ayasse et al. pointed out that 9% fetuses with 22q11 deletion showed kidney abnormalities (all combined with polyhydramnios) in prenatal diagnosis, and 27% in fetal autopsy (Besseau-Ayasse et al., 2014). This implies that there is a connection between oligohydramnios and the 22q11 deletion syndrome. Also, several studies have shown that the 15q24 microdeletion syndrome and 1p36 microdeletion syndrome are associated with hypospadias and cleft lip/palate, respectively (Gajecka et al., 2007; Sharp et al., 2007). These may be the cause of prenatal abnormal amniotic fluid volume, but further exploration is required for confirmation.

Pregnancy outcomes were also estimated in our study, and it showed that 57% cases were born and alive, while 26% cases had poor outcomes. Overall, the SU group fared better than the MU group, and the SU-polyhydramnios had the best outcome, even after removing the data of cases with chromosomal anomaly and lost to follow-up (Figure 1, Tables 2 and 3). Beside, in 317 cases with normal CNV-Seq results and known pregnancy outcomes, the overall ratio of premature, and born with disease or death is 19%, and 4%, respectively. The situation brings great pressure and financial burden to the family, which requires further investigation.

In conclusion, the MU group is inclined to obtained more pathogenicity genetic anomalies and poor pregnancy outcome. CNV-Seq may be useful in investigating pregnancies with an abnormal amniotic fluid level.

AUTHOR CONTRIBUTIONS

Conceptualization: Panlai Shi; writing—original draft preparation: Panlai Shi and Xiangdong Kong; experiment and analysis: Yaqin Hou, Duo Chen, Huanan Ren, and Yanjie Xia; writing—review and editing, and funding acquisition: Panlai Shi. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

The study was approved by The First Affiliated Hospital of Zhengzhou University Scientific and Clinical Research Ethics Committee (Approval number, 2019-KY-418).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the parent to publish this paper.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Zhengzhou University Ethics Committee (protocol code No. 2019-KY-418 and the date of approval, 28 December 2019).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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