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Pathology Section

Tracheal Agenesis and Tracheal Stenosis in Perinatal Autopsies: A 13-Year Study

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ABSTRACT

Introduction: Tracheal agenesis and tracheal stenosis are rare, fatal congenital anomalies and are an acute neonatal emergency. It may be an isolated anomaly or may be associated with other congenital anomalies. Affected newborns present with inaudible cry, rapidly developing respiratory distress soon after birth rendering endotracheal intubation impossible. Despite the surgical management in these cases in experienced hands, the survivability of the newborn remains poor. Congenital High Airway Obstruction Syndrome (CHAOS), a clinico-pathological condition, complicates it further leading to fatality even with the absence of airway-oesophageal fistula. Tracheal anomalies usually form a part of VATER/VACTERL association, which includes anomalies of vertebrae (V), anal canal (A), renal (R) with Tracheo-Oesophageal fistula (TE). Radial dysplasia, cardiac anomalies and nonradial limb anomalies were later added to make it VACTERL. Perinatal autopsies performed in these cases give valuable insights to the treating physicians and surgeons about the severity of these anomalies.

Aim: Since this is a very rare and lethal anomaly, we undertook this study to know the hospital based incidence and to carry out a detailed autopsy study to look for type of tracheal anomaly and other associated abnormalities.

Materials and Methods: All the dead newborns and aborted fetuses which were sent for autopsy to Pathology department were examined for tracheal anomalies after obtaining the informed consent. Anthropometry was measured with respect to gestational age and analysed for external anomalies and a detailed dissection of the body was carried out. The anatomic relations of each visceral organ, structural abnormalities and histopathologic examinations were examined. Faro classification was used for type of tracheal agenesis.

Results: Of the 1152 perinatal autopsies performed over a 13-year period, five cases were identified of having agenesis or stenotic tracheal anomaly. Of these, four had tracheal agenesis and one had tracheal stenosis. Three of the tracheal agenesis cases were syndromic; first was associated with VACTERL and caudal regression type V, second with VATER and third with CHAOS. As per Faro classification, two cases of type C and one each of type B and F tracheal agenesis were identified. The tracheal stenosis case also was syndromic, having VATER, CHAOS and persistent mullerian duct syndrome. Maternal ultrasound examination revealed oligo/polyhydramnios in three of these cases.

Conclusion: This study highlights the significance of poly or oligohydramnios during routine anomaly scan. When present, the fetuses should be examined for anomalies in trachea and other organs by radiologic investigations especially with MRI.

Keywords: Caudal regression, CHAOS, Persistent mullerian duct syndrome, Tracheal agenesis, Tracheal stenosis, VACTERL

INTRODUCTION

Both tracheal agenesis and tracheal stenosis are very rare and fatal anomalies of the fetus. These anomalies may be isolated or associated with other systemic anomalies in the newborn which compromise further survivability or defer surgical repair of the airway defect. High degree of suspicion is necessary in pregnancies complicated by polyhydramnios or oligohydramnios. Sonographic anomaly scan and MRI aid in early detection of the abnormality, and in counselling the parents for termination of pregnancy. Surgical repair is successful only in few cases and long-term survival is disappointing [1]. Since this is a very rare and lethal anomaly, we undertook this study to know the hospital based incidence and to carry out a detailed autopsy study to look for any other associated abnormalities.

MATERIALS AND METHODS

The study was undertaken at SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India. All the dead newborns and aborted fetuses which were sent for autopsy to Pathology department were examined for tracheal anomalies. Informed, signed consent for the autopsy was obtained from the parents. Ethical committee clearance was obtained for the study. This was a prospective study and study period was for 13 years (from 1st January 2005 to 31st December 2017). We included only the cases of tracheal agenesis or tracheal stenosis based on autopsy confirmation. The cases selected were independent of gestational age and associated anomalies in other systems. Those cases having anomalies other than tracheal agenesis and tracheal stenosis were excluded from the study. The clinical history and delivery notes for each case was retrieved from medical records department. For all the autopsies performed, anthropometry was measured with respect to gestational age and analysed for external abnormalities and anomalies. A detailed dissection of the body was carried out and fetuses were checked for effusions, and anatomic anomalies of the organs. After identifying carotid vessels, the visceral organs were en-block eviscerated from thorax, abdomen and pelvis. The anatomic relations of each visceral organs, structural abnormalities and histopathologic examinations were carried out. The skull was opened and brain was removed and examined grossly and histologically. The organs histologically examined included thymus, lungs, heart, liver, gall bladder, pancreas, spleen, kidneys, testes,

uterus, ovaries, brain, other endocrine organs (adrenals, thyroid, pituitary) and abnormally formed structures (such as cloaca, diverticuli) whenever encountered.

RESULTS

Of the 1152 perinatal autopsies performed over a 13-year period, five cases were identified of having agenesis or stenotic tracheal anomaly. The maternal details, investigations and delivery methods are given in [Table/Fig-1]. The autopsy data of these five fetuses was analysed and details mentioned in [Table/Fig-2].

Case1

The fetus was 6th pregnancy of 21-year-old lady with bad obstetric history. Her 1st, 2nd and 3rd pregnancies were aborted in 3rd, 5th and 6th months of gestation respectively. Fourth pregnancy ended as premature stillborn child. Fifth pregnancy was aborted in 5th month. During the 6th pregnancy she was treated with aspirin 75 mg OD, from 10 weeks of gestation, underwent cervical encirclage at 14th week and was diagnosed to have oligohydramnios and Intrauterine Growth Restriction (IUGR) by sonography. She was referred to this institution at 28 weeks of gestation for further management. Serologic tests for VDRL, HBsAg were negative. Glucose Challenge Test (GCT) and Glucose Tolerance Test (GTT) were impaired. Patient underwent caesarean section as induction of labour was not successful. Intraoperatively there was absence of liquor and fetus was noted in extended breech presentation. Baby had multiple external anomalies and heart rate of 60 beats/min. Child did not cry after birth. Breathing was assisted with ambubag and baby succumbed 1 hour later.

At autopsy, baby weighed 1060 grams. The anomalies included low set ears, presence of two upper prenatal teeth, bilateral contractures at elbows, absence of right hip and ala of sacrum, right lower limb (amelia), external genitalia and anus [Table/Fig-3a-c]. An"epidermoid cyst" was present at the perineum. Dissection revealed many internal anomalies. Trachea was completely absent, larynx was stenosed and Faro type C single broncho-oesophageal fistula [Table/Fig-4a,b] noted. The baby had truncus arteriosus [Table/Fig-4c] with pulmonary arteries arising from truncus, high VSD (ventricular septal defect) and absence of right common iliac artery. Bilateral kidneys were severely hypoplastic and cystic. Large intestine ended in cloaca. Ureters traced to open into cloaca [Table/Fig-5]. No urinary bladder seen. The baby was female with presence of ovaries and fallopian tubes in pelvis. Uterus was seen attached to cloaca anteriorly. Epidermoid cyst at perineum contained pultaceous material. Hepatobiliary system was normal. Endocrine organs including pituitary were normal. Brain was autolysed. Umbilical cord displayed single umbilical artery. Bilateral kidney sections displayed renal aplasia. Cloaca revealed denuded epithelium with prominent nerve bundles and sigmoid colon was in continuum with cloaca. Epidermoid cyst was lined by stratified squamous epithelium without associated adnexae. The case was concluded having VACTERL and caudal regression syndrome type V.

Case 2

A 37-year-old primigravida with 34 weeks of gestation with regular antenatal checkups had polyhydramnios. Ultrasound examination revealed gross polyhydramnios, Intrauterine Death (IUD) of fetus and mild distension of fetal left renal pelvis. The serology tests showed VDRL nonreactive and HBsAg negative. Glucose Screening Test (GST) was impaired. Labour was induced and fetus was delivered.

It was a male fetus weighing1650 grams, had peeling of skin and imperforate anus with empty right scrotum. Dissection revealed complete absence of trachea, stenosed larynx, bilateral broncho-oesophageal fistula (Faro type B) [Table/Fig-6] and high membranous VSD. The colon ended abruptly, blindly after sigmoid colon curvature. The blind end was attached to the base of the bladder between ureters by a cord. Rectum and anal canal were absent. Urinary bladder was filled with urine and showed only left ureteric opening. Right ureteric opening was absent. No vesico-colonic fistula noted. Right renal pelvis and left ureter found to be slightly distended. Both kidneys were normal sized and showed corticomedullary differentiation. Nephrogenic zone noted in microscopic examination. Right (undescended) testis was found near inguinal canal within abdominal cavity. Umbilical cord showed single umbilical artery. The case was diagnosed as VATER.

Case 3

A 23-year-old gravida 2 presented with 19 weeks of gestation with anomalous fetus. Serology tests for HIV, HBsAg were negative and VDRL nonreactive. Glucose tolerance test was normal. Ultrasonography revealed single live fetus with persistent flexion position. Lungs were grossly echogenic and overdistended with inversion of diaphragm. Heart was small. A dilated air column abruptly terminating towards lung base was noted in one of the lung fields. Fetal ascites, hypotelorism present. Pregnancy was terminated.

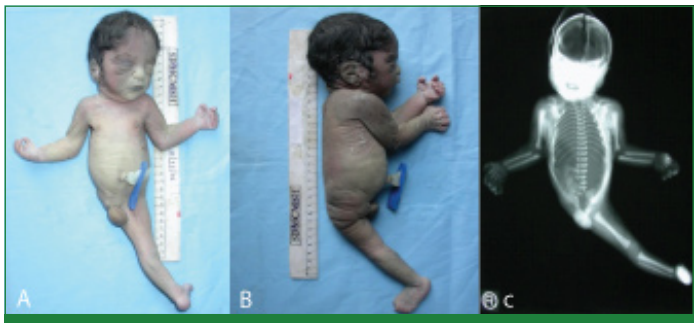
At autopsy, the male abortus weighed 53grams. No external anomalies noted. Dissection showed large whitish lungs, with rib impressions, compressing heart from side to side. The diaphragm was membranous thin. Larynx was stenosed. Proximal part of trachea was absent. A caudal stump representing lower part of trachea was present, ending blindly proximally. The right side of tip of the stump was connected to larynx by a cord. There was no trachea or broncho-ooesophageal fistula (Faro type F) [Table/Fig-7a,b]. Heart was compressed between large lungs and showed large foramen ovale. Cut section of lungs showed oozing of clear fluid on pressure. Other systems were normal. Umbilical cord showed three vessels. Microscopic sections of both lungs displayed dilated alveoli and bronchioles due to accumulation of fluid [Table/Fig-7c]. These features were conclusive of CHAOS.

Case No.	Mother	Past history	Blood investigations	Present pregnancy USG	Management
1	21-year-old, Gravida 6, 28 wks gestation	4 abortions and 1 stillbirth	Serology – negative, GTT abnormal.	Oligohydramnios and IUGR	Caesarean section
2	37-year-old, Primi, 34 wks gestation	-	Serology – negative, GST raised.	Polyhydramnios with IUD	Induced labour
3	23-year-old, Gravida 2,19 wks gestation.	Previous LSCS, normal baby.	Serology – negative, GTT normal.	Hypotelorism,, large echogenic lungs with inversion of diaphragm, small heart, abruptly terminating air column in one lung, fetal ascites.	Termination of pregnancy
4	25-year-old, Gravida 2, 38wks gestation in labor	1st baby died due to neuroblastoma	Serology – negative, CRP normal	No details available	Emergency LSCS for fetal distress
5	22-year-old, Gravida 2, 28wks gestation	Previous LSCS for oligohydramnios, normal female baby	Serology – negative,	Severe oligohydramnios, bilateral* grossly enlarged polycystic kidneys	Termination of pregnancy

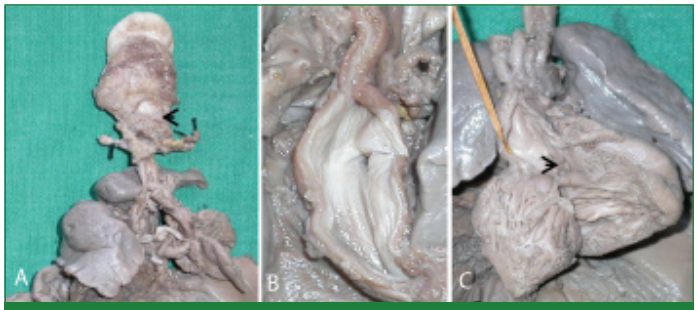
[Table/Fig-1]: The maternal details of five cases.
*USG reported as bilateral polycystic kidneys; Left kidney was absent in this case

Case No.	External features of fetus	Dissection	Faro Type	Final diagnosis
1	Female, 1060 grams. Absent right lower limb (amelia), external genitalia; imperforate anus, Perineal epidermoid cyst.	Truncus arteriosus, high VSD, absent right common iliac artery, stenosed larynx, tracheal complete agenesis, single B-E fistula, ureters and large intestine opening into cloaca, bilateral aplastic cystic kidneys, absence of right iliac artery, right partial sacral and right hip agenesis and single umbilical artery.	C	VACTERL association with caudal regression syndrome type V.
2	Male, 1650grams, imperforate anus, right undescended testis,	Stenosed larynx, complete tracheal agenesis, bilateral B-E fistula, high membranous VSD, abrupt termination of colon over base of bladder, absent right ureteric opening, single umbilical artery.	B	VATER
3	Male, 53 grams.	Large whitish lungs with rib markings, compressed heart, larynx stenosed, partial (proximal) agenesis of trachea, no T-E fistula, large foramen ovale.	F	Tracheal agenesis with CHAOS.
4	Male, 3186 grams.	Stenosed larynx, complete tracheal agenesis with single B-E fistula, single umbilical artery	C	Tracheal agenesis.
5	Male, 1003 grams, imperforate anus, undescended testis located intra-abdominally at inguinal canal.	1st tracheal ring stenosis, no T-E fistula, two lobes in right lung, distal colon ended blindly overbase of bladder, right dysplastic kidney, left renal agenesis, a cystic nodule over bladder near 0.3cm, near right ureteric opening (Uterus). Right testis showed torsion and left testis was normal.	-	Tracheal stenosis with CHAOS with VATER association and persistent mullerian duct syndrome.

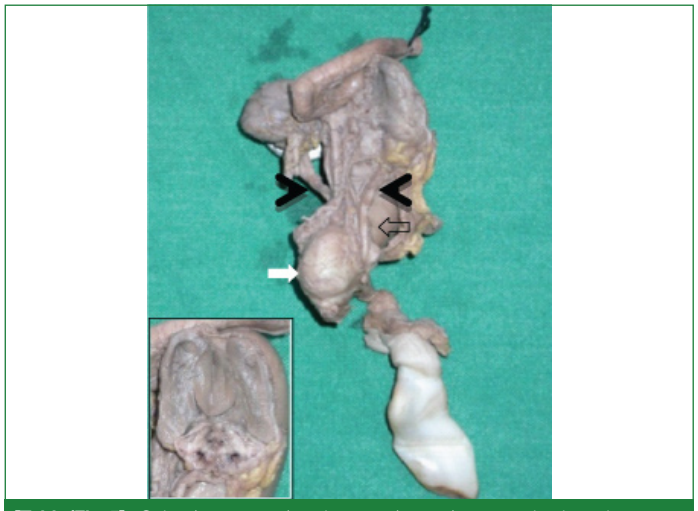
[Table/Fig-2]: The fetal details of five cases.



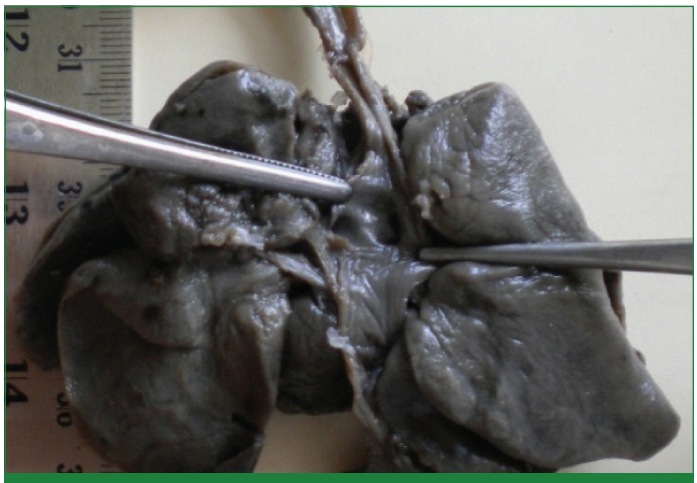
[Table/Fig-3]: A, B. Absence of right lower limb, genitalia and anus. Perineal epidermoid cyst, contractures at elbow are seen, C. The radiograph was taken after dissection. However, it shows the absence of right ala of the sacrum and hip. Both radii are present. (Case 1)



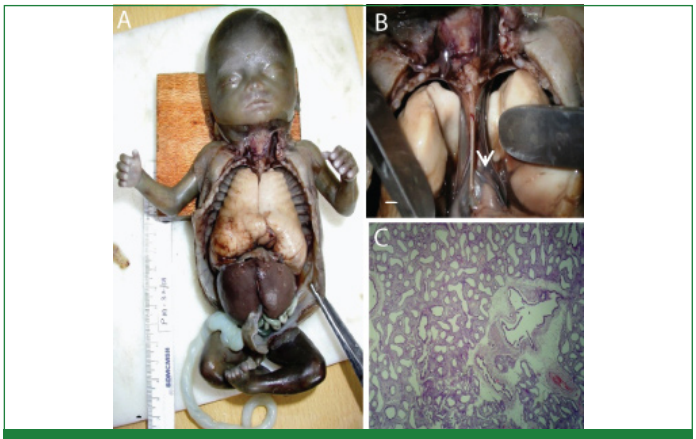
[Table/Fig-4]: A. Stenosed larynx (arrow) and absence of trachea, B. Bronchoesophageal fistula (Faro type C), C. Opened right ventricle showing truncus arteriosus and VSD (arrow). (Case 1)



[Table/Fig-5]: Colon (open arrow) and ureters (arrows) are opening into cloaca (white arrow). (Inset- Bisected right aplastic kidney below adrenal. (Case 1)



[Table/Fig-6]: Shows Faro type B broncho-esophageal fistula. (Case 2)

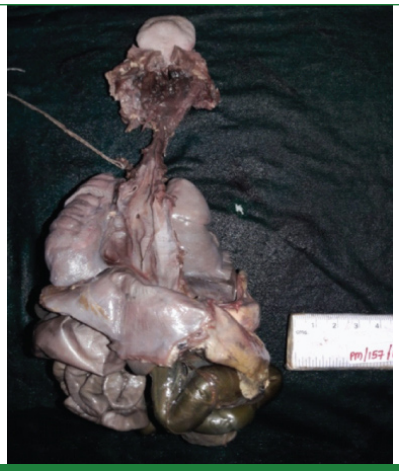


[Table/Fig-7]: A. Enlarged lungs with rib markings, B. Proximal tracheal agenesis with caudal tracheal stump (arrow) connected to larynx by a cord arising from right side, C. Dilated alveoli and bronchioles of lung (CHAOS) (10x, H&E). (Case 3)

Case 4

A 25-year-old gravida 2 lost her 1st baby boy due to Neuroblastoma and died at 8 months of age. Regular antenatal checkups were done for the present pregnancy. Serology tests for HIV, HBsAg were negative and VDRL nonreactive. At 38 weeks of gestation, she presented with polyhydramnios, in labour. Since there was variable deceleration of fetal heart sounds, fetal distress was suspected and emergency caesarean section was performed.Liquor was clear. The male baby did not cry after birth.

At autopsy, baby weighed 3186grams, had no external anomalies. Internal examination revealed 1.5 cm long larynx which was stenosed at the lower end. No trachea was present. Single broncho-oesophageal fistula noted which was connecting to carina (Faro type C) [Table/Fig-8]. No urinary, hepatobiliary, cardiovascular and skeletal anomalies noted. Sections of umbilical cord showed 2 vessels. Both lungs showed dilated alveoli due to accumulation of fluid in airspaces and some alveoli were collapsed.

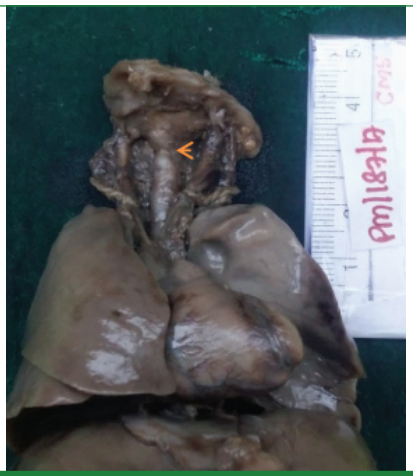


[Table/Fig-8]: Bronchoesophageal fistula of Faro type C. Left lung shows rib markings. (Case 4)

Case 5

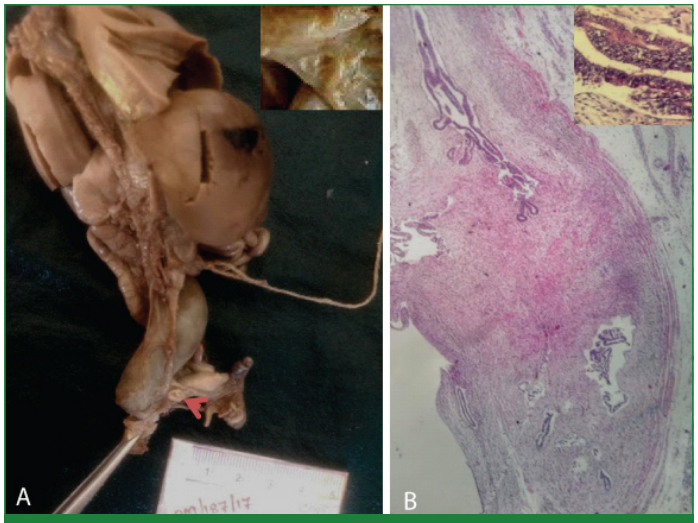
A 22-year-old gravida 2, was referred for severe oligohydramnios at 7 months of amenorrhea. Only growth scan was done elsewhere and reported to have single live fetus of 27 weeks, 3±10 days gestation, in variable presentation with severe oligohydramnios. Fetus showed normal body movements and normal heart rate. She had regular ANC visits and serologies for HIV and HBsAg were negative. Ultrasonography revealed bilateral grossly enlarged polycystic kidneys with severe oligohydramnios. Pregnancy was terminated stillborn baby was delivered with club foot anomaly at birth.

The male baby weighed 1003 grams. External examination revealed imperforate anus with undescended testis.Dissection revealed tracheal stenosis at 1st tracheal ring [Table/Fig-9] with no evidence of tracheo-oesophageal fistula. Trachea was mildly distended beyond stenosis. Right lung had two lobes. Right kidney was small (1.4x0.7x0.3 cm) and had multiple variable sized cysts throughout the parenchyma (dysplastic). Left kidney was absent. A small nodule was seen at the junction of right ureter to bladder measuring 3 mm in diameter [Table/Fig-10a]. Cut section showed uniloculate cyst and drained clear fluid. Distal colon was distended at recto-sigmoid part and rectum was ending blindly over urinary bladder near prostate. Both testis were abdominal and at inguinal canal. Brain and other visceral organs appeared normal. Placenta weighed 211grams and cut sections were normal.



[Table/Fig-9]: Tracheal stenosis (arrow). (Case 5)

Microscopy revealed dysplastic right kidney having cystic tubules, glomeruli, immature mesenchyme and interstitial haematopoiesis. The cyst showed endometrial glands [Table/Fig-10b], stromal cells and myometrial smooth muscle fibres. Right testis shows features of torsion with interstial haemorrhage. Left testis was normal. Placenta, cord and membranes were normal. Due to tracheal, anal and renal anomalies with presence of uterus, VATER anomaly with persistent mullerian duct syndrome and CHAOS diagnosis was considered.



[Table/Fig-10]: A. Cut section of cystic nodule (arrow) at junction of right ureter and bladder (Inset: Cystic nodule closure view), B. Cyst is lined by endometrium (Inset: Endometrial lining) (Case 5).

DISCUSSION

The incidence of tracheal agenesis is very rare with few case reports in the literature after the first case was reported by Payne in 1900. Tracheal agenesis is characterised by the congenital absence of almost complete trachea. Tracheal stenosis indicates the narrowing or absence of lumen in a limited part of trachea. Isolated such anomalies are uncommon. Nearly 84% of these cases are associated with other congenital anomalies [1]. Since this is a very rare and lethal anomaly, we undertook this study to know the hospital based incidence and to carry out a detailed autopsy study to look for type of tracheal agenesis using Faro's classification and any other associated abnormalities.

The clinical suspicion arises with the presentation of polyhydramnios or oligohydramnios. Isolated tracheal anomalies have polyhydramnios whereas those in combination with renal dysplasia or agenesis present with oligohydramnios. The new borns exhibit aphonic cry and present with rapidly increasing respiratory distress after cord is disconnected. The tracheal intubation fails as endotracheal tube does not advance beyond larynx.Tracheal rings may not be palpable [2]. The realization of tracheal agenesis occurs at the attempt of tracheostomy if not previously suspected on radiologic investigations [2-9]. To maintain ventilation,oesophageal intubation will be helpful in cases where lower airway-oesophageal fistula is present and is also helpful in introducing bovine surfactant [3,10]. The intentional ventilation through oesophagus is life saving and also gives valuable time to plan and undertake surgical correction [4]. Rarely a laryngo-oesophageal fistula can be present with partial tracheal agenesis [11].

Floyd classified the tracheal agenesis into I, II, III types depending on whether distal trachea/carina/bronchioles communicate with oesophagus respectively in a case of partial or complete tracheal agenesis. In many instances certain tracheal anomalies couldn't be accommodated into Floyd classification. The third fetus encountered in our study did not have tracheo-oesophageal fistula. Faro classification describes other types of tracheal agenesis (cf. no fistula) and is more preferable [6].

CHAOS is a clinicopathologic designation used for those cases where tracheal agenesis/stenosis is not associated with trachea/broncho/carina-oesophageal fistula. In these cases, the lungs become echogenic on sonography or highly intense on T2 weighted MRI because of fluid accumulation in lungs [2,12]. It is incompatible with life and can be suspected if amniotic fluid contains low levels of phospholipids since these are secreted by lungs [13]. Two of the fetuses in our study had CHAOS. One with no other anomalies apart from partial proximal tracheal agenesis similar to the features described by De Luca D et al., but the distance between larynx and

blind end of trachea was more in our case. The other fetus had the tracheal stenosis of 1st tracheal ring similar to the one described by Zhang P et al., but additionally our case had VATER association [4,12]. A successful surgical airway in partial or complete tracheal agenesis by EXIT (Ex-utero intrapartum treatment) procedure can save the CHAOS baby and give precious time for planning definitive surgery [14-16].

VATER is a nonrandom association of anomalies of vertebrae (V), anal canal (A), renal (R) with Tracheo-Oesophageal fistula (TE). Radial dysplasia, cardiac anomalies and nonradial limb anomalies were later added to make it VACTERL.Furthermore, the vascular anomalies, auricular defects, rib anomalies and single umbilical artery were added [17,18]. To diagnose VATER/VACTERL association requires the presence of at least three of the core component features-vertebral defects, anorectal malformations, cardiac defects, trachea-oesophageal fistula with or without oesophageal atresia, renal malformations, and limb defects. Tracheal agenesis and tracheal stenosis may be considered as part of VACTERL association [19-21].

These polytopic anomalies are thought to result from mutations during blastogenesis period leading to field defect in multiple organ systems. However, small proportion of cases has familial clustering indicating inherited defects in genes of morphogenesis. During 3-7th week of gestation, incomplete separation of the trachea and oesophagus, pulmonary trunk and aorta, urogenital sinus and hindgut will lead to formation of tracheal agenesis, truncus arteriosus and cloaca formation respectively [18,22].

Lower limb amelia and sacral agenesis in VACTERL has been described in few studies [23-25]. Our case shared similarities with the one reported by Ijaz L et al., [24]. Amniotic bands can cause lower limb amelia, which was not seen in our case [26,27]. The caudal regression, like sirenomelia is associated with aberrant umbilical artery arising from aorta instead of internal iliac arteries [25].

To the best of our knowledge, persistent mullerian duct syndrome with tracheal stenosis, CHAOS and VACTERL association is the first of its kind and no such case has been reported in the literature. Persistent mullerian duct syndrome has been associated with various syndromes such as Urioste syndrome, Hirschsprung's disease, renal anomalies [28]. However, its association with VACTERL and tracheal stenosis has not been documented.The comparison of findings in our study with similar other studies have been summarised in [Table/Fig-11] [2-5,7,8,12,14,15,22,24,29].

The strength of this study is that, this is the first of its kind to tracheal stenosis/agenesis. Detailed morphologic study into their associated anomalies revealed a new combination of VACTERL association, persistent mullerian duct syndrome, tracheal stenosis with CHAOS, which is published for the first time in the literature to the best of our knowledge.

Tracheal anomaly	Present study	Other studies	Anomalies in other studies
Tracheal agenesis Faro type- B	VATER association (Case 2)	1. Pratap A et al., [2] 2. Ahmed R et al., [7]	1. Tracheal agenesis, Faro type- B. 2.VACTERL
Tracheal agenesis Faro type- C	VACTERL association with CRS type V (Case 1)	Ijaz L et al., [24]	VACTERL with CRS and (with no TA or TE fistula).
	Tracheal agenesis, single umbilical artery. (Case 4)	a) Ergun S et al., [8] b) Haben CM et al., [29] c) Bertholdt C et al., [3] d) Xu GQ et al., [22] e) Densmore JC et al., [5]	a) Tracheal agenesis (Floyd Type II) b) Tracheal agenesis (Floyd type II) with left ventricular and aortic hypoplasia. c) Tracheal agenesis (Floyd type II). d) Tracheal agenesis (Floyd type II) with VACTERL and TACARD association. e)Tracheal agenesis (Floyd type II)
Tracheal agenesis Faro type- F	Tracheal agenesis with CHAOS. (Case 3)	1) Gonzales SK et al., [15] 2) De Luca D et al., [4]	MRI findings suggestive of tracheal agenesis Faro type F. Tracheal agenesis with CHAOS.
Tracheal stenosis	Right renal dysplasia. 1st tracheal ring stenosis with CHAOS, VATER association and persistent mullerian duct syndrome. (Case 5)	1) Zhang P et al., [12] 2) Crombleholme TM et al., [14]	Stenotic trachea at the level of larynx with CHAOS, small cystic hygroma of neck. CHAOS

[Table/Fig-11]: Comparison of tracheal anomalies in our study with other studies [2,3,4,5,7,8,12,14,15,22,24,29].

LIMITATION

One of the limitations of our study is the smaller sample size. We encountered five cases over a 13-year period. This is because tracheal agenesis/stenosis is a very rare anomaly with very few case reports and autopsy based studies being published thus far in the literature.

CONCLUSION

This study highlights the significance of poly or oligohydramnios during routine anomaly scan. When present, the fetuses should be examined for anomalies in trachea and other organs by radiologic investigations especially with MRI. The anomalies of trachea (agenesis and stenosis) carry high mortality and, if the baby survives for having fistula, require immediate surgical correction, the results of which are not very promising. Early diagnosis with regular antenatal check-up and anomaly scans can identify these anomalies and EXIT procedure can be planned before hand.

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