The missing umbilical artery

I. Prospective study based on a maternity unit

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Bryan, E. M., and Kohler, H. G. (1974). *Archives of Disease in Childhood*, **49**, 844. **The missing umbilical artery. I. Prospective study based on a maternity unit.** In a consecutive series of nearly 20,000 freshly delivered placentas, 2 vessels instead of the normal 3 were found in the umbilical cords of 143 (0.72%) infants, 83 females and 60 males. 4 infants were twins: in each instance the co-twin had 3 vessels. The incidence of single umbilical artery (SUA) in multiple pregnancies was slightly less than in singletons. 2 infants with SUA were sibs.

There was an increased incidence of major malformations (17.5%), of prematurity (16.5%), and of smallness for dates (34%) among infants with SUA. 25 (17.5%) infants, of whom 19 had a major malformation, died in the perinatal period; of these, 2 had a persistent vitelline artery. (A follow-up study has been carried out on the surviving infants—results to be published.)

This investigation into the incidence and significance of SUA is based on what is so far the largest prospective and unselected series collected in a single maternity unit. All placental examinations and necropsies were carried out by one pathologist, all follow-up examinations by one paediatrician.

The occasional absence of one umbilical artery has been observed since Renaissance times and both Gabriele Fallopio (1523–1562) and Caspar Bauhin (1560–1624) have been credited with the first description. In 1870, Josef Hyrtl, Professor of Anatomy at Vienna, published a monograph on the blood vessels of the human placenta in which a whole chapter is devoted to SUA. Hyrtl based his discussion on 14 specimens—all from male infants. This remarkable sex incidence has not been confirmed by any of the many subsequent investigators. Hyrtl emphasized that none of the infants was malformed, implying that such an association had previously been observed and considered significant.

It was this association with other congenital abnormalities that attracted attention to SUA. Weigert (1886), Ballantyne (1898), and Kampmeier (1927) considered the association of SUA with sirenomelia and other severe malformations as aetiologically significant. In 1955 Benirschke and Brown collected 55 cases from necropsy records and

found other developmental anomalies in 27 of these. In a similar retrospective study, Faierman (1960) reported 11 infants with SUA detected in 411 necropsy examinations; 9 were associated with other malformations. Molz (1965) found 28 instances of SUA in her records of 225 perinatal necropsies; 26 had other anatomical abnormalities, 22 multiple ones. (A further retrospective study has since been published by Molz, 1971). None of these studies permitted an estimate of the overall incidence of SUA.

In a prospective study Benirschke and Bourne (1960) of Boston, U.S.A., detected 15 cases of SUA in 1500 consecutive deliveries. A similar incidence was found by Cairns and McKee (1964) in Canada. Other prospective investigations from North America were reported by Little (1961), Peckham and Yerushalmy (1965), Hnat (1967), and Van Leeuwen, Behringer, and Glen (1967), and the largest series of all, utilizing the records of 12 different hospitals, by Froehlich and Fujikura (1966, 1973). Similar publications from Europe include those of Thomas (1961, Germany); Järvinen, Osterlund, and Van Numers (1961, Finland);

Gömöri and Koller (1964, Switzerland); Papadatos and Paschos (1965, Greece); Müller *et al.* (1969, France); Cederqvist (1970, Sweden); and Vlietinck *et al.* (1972, Belgium). The problem has also been studied in Israel by Lewenthal, Alexander, and Ben-Adereth (1967), who found an incidence of 0.97%. In this country the only published prospective investigation is that by Ainsworth and Davies (1969), who during 5 years found an incidence of 0.94% in over 12,000 births at the Radcliffe Infirmary, Oxford.

The problems discussed by other investigators are also the ones we have tried to answer in the present study: what is the incidence of SUA and how are the sexes affected? What associations, if any, exist with parity, maternal age, prematurity, etc? What is the perinatal mortality rate in affected infants and what association exists with severe developmental anomalies? Is there a connexion with retarded intrauterine growth? The foremost question of the clinician probably is whether the finding of SUA indicates the existence of other malformations not apparent at birth but which may give problems later in life. This will be dealt with in a future publication in which we shall also report on the post-neonatal development of these infants.

Material and methods

During the 7-year period beginning 1 January 1966, an attempt was made to subject every placenta delivered in this hospital to thorough naked-eye examination by one of us (H.G.K.). In addition to slicing of the placenta proper, the umbilical cord was cut across. If any of the blood vessels were not clearly visible, further cuts were made at various distances from the fetal end. If there was doubt, or if the number of vessels was obviously abnormal, a length of cord of approximately 10 cm was fixed in formalin for at least 24 hours and then again cut across. If the cross-section did not clearly reveal 3 vessels, at least one block was processed, embedded in wax, and examined histologically. Only specimens confirmed by microscopical examination were accepted as proven cases of SUA.

However, some of the 'negative' records, i.e. where a normal number of umbilical vessels was present, have been lost. The total number of births in the period covered by this investigation was 20,850. We estimated that our programme was approximately 95% successful and that the number of placentae examined was between 19,500 and 20,000, the latter being taken as an assumed total for convenience and also because we prefer to under-estimate the incidence of SUA.

In every case of stillbirth and neonatal death umbilical arteries were also examined at necropsy. One case in which there was a discrepancy between the abdominal umbilical vessels and those in the cord was excluded from this series. The total number of perinatal necropsies during this study was 680.

Weights, measurements, and clinical observations of infants are based on hospital records, and in the necropsy cases both weight and length were checked as part of the post-mortem examination. All live-born infants were routinely examined by a paediatric resident on at least one occasion during the first week of life. The fact that an umbilical vessel was missing was not necessarily known to the examining doctor, particularly in the earlier years of the study. Infants in whom no major developmental abnormality was detected will hereafter be referred to as 'normal'.

Results

Among the 20,000 umbilical cords examined, we found 143 examples of SUA, an incidence of 0.72%. No arterial anastomoses were seen. Of these cases, 83 (58%) were in female infants and 60 (42%) in males, a female: male ratio of 1.4:1. 4 babies were twins and in each case the co-twin had normal umbilical vessels. The overall hospital incidence of twin births during this period was 1/33.6 births and in infants with SUA 1/35.7 births.

Congenital malformations. 25 infants (17.5%) had major congenital malformations apparent in the perinatal period. These are listed in Table I. 20 of these were stillborn or died within the first week of life. One died at the age of 3 weeks and 4 survived beyond the neonatal period.

We detected no major abnormalities in the perinatal period in 118 infants of whom 6 were stillborn. The overall perinatal mortality associated with SUA was 17.5%. Of the 6 stillborn infants with no apparent malformations, 3 were small-for-dates. One was the first-born infant of a mother suffering from an unspecified collagen disease who has since had another baby whose umbilical vessels were normal; this infant had dysplasia epiphysealis punctata and died in the perinatal period. The mother was receiving corticosteroid therapy in the second pregnancy only.

Maternal age and gravidity. Fig. 1 shows the distribution of cases of SUA according to the age and gravidity of the mother. These are compared with a current hospital control series (criteria for hospital booking have not changed substantially during the period of study). There is no significant difference between the two series, though, as has been generally found with congenital malformations, there is a higher proportion of this group among primigravid and 5+ gravid mothers.

Gestation and birthweight. 24 (16.5%) infants were preterm (gestation <37 completed weeks), of whom 15 were either malformed or

Case no.	Sex	Gestational age (wk)	Age at death	Weight (g)
<i>(a) Perinatal necropsy cases</i>				
1	F	Uncertain ? 32	3½ hr	2423
2	M	35	Stillbirth	1017
3	F	35	60 hr	2180
4	F	28½	Stillbirth	910
5	F	43	2 hr	2574
6	M	35	Stillbirth	1300
7	M	34	Stillbirth	1825
8	M	40	Stillbirth	2595
9	F	38	15 hr	2767
10	M	32	Stillbirth	1985
11	F	33	2 hr	1320
12	F	35	Stillbirth	955
13	F	36	Stillbirth	860
14	F	36	Stillbirth	1408
15	F	39	Few minutes	3380
16	M	38	Stillbirth	2355
17	F	37½	Stillbirth	1160
18	F	40	Stillbirth	1810
19	F	41	Stillbirth	1280
<i>(b) Infants surviving the perinatal period</i>				
20	F	41	Alive at time of survey	3230
21	M	35½	9 dy	3285
22	M	35½	Alive at time of survey	2050
23	F	42	Alive at time of survey	4020
24	M	41½	3 mth	3760
25	M	Unknown	3 wk	3710

I

in infants with SUA

Length (crown-heel) (cm)	Malformations	Remarks
47	Bilateral polycystic kidneys ('grape-like'); aplasia of ureters; atresia of bladder	Oligohydramnios; breech delivery; Potter's facies
38	Complex cardiovascular anomaly: dual outlet R ventricle; large VSD; R aortic arch with L innominate artery; exomphalos; club hands	Hydramnios; macerated; exomphalos contained viscera, including spleen
46.5	Hydrocephaly; occipital meningocele; absence of corpus callosum; dysraphic lesion of cervical cord; high arched palate; transverse facial cleft	Hydramnios
29	Iniencephaly; large thoracolumbar myelocele; absence of corpus callosum; small cerebellum; persistent Meckel's diverticulum	Hydramnios
50.5	Anencephaly	Mild hydramnios
36	Anencephaly; spina bifida anterior and posterior; congenitally short oesophagus; persistent Meckel's diverticulum	Hydramnios; recurrent malformation
47	Hydrocephaly (no spina bifida); Arnold-Chiari lesion; R diaphragmatic hernia; L renal agenesis	Hydramnios; hypertrophied right kidney
41	Exomphalos (short umbilical cord); severe scoliosis of spine and deformity of thoracic cage	Hydramnios; breech delivery; bilateral tentorial lacerations
46	Choanal atresia; pulmonary dysplasia (bilateral single lobes); 'hypoplastic L heart'; retro-oesophageal R subclavian artery; syndactyly and polydactyly	Hydramnios; recurrent malformation
40	Bilateral polycystic kidneys (urethral obstruction type); male pseudohermaphrodite	Oligohydramnios; amnion nodosum; multiple serous effusions
45	Pericardial defect; bilateral diaphragmatic defects; exomphalos; absence of external genitalia; absence of urethra; imperforate anus	Vitelline artery
33.5	Anencephaly with extensive spina bifida	Acute hydramnios
	Atypical incomplete anencephaly with spina bifida; ectopia cordis; coarctation of aorta; diaphragmatic hernia; exomphalos; kyphosis and lordosis of spine	Hydramnios; cranial abnormality suggested an intermediate stage between anencephaly and iniencephaly
40	Anencephaly	Hydramnios; recurrent malformation; (1 hydrocephalic infant, 1 anencephalic abortion)
46.5	Brevicollis; deformity of spine; L-sided diaphragmatic defect; severe pulmonary hypoplasia; single kidney; persistent cloaca; hypoplasia of abdominal muscles	Transient hydramnios
42	Hydrocephaly; Arnold-Chiari lesion; thoracolumbar myelomeningocele; L-sided diaphragmatic hernia; scoliosis of spine; horse-shoe kidney	Hydramnios
41	L-sided diaphragmatic hernia	Placental hypoplasia; long-standing intrauterine death
29 (crown-rump)	Sireniform fetus: complete absence of urinary tract and of genital and anal orifices; abnormality of bony pelvis; complete absence of L lower extremity; stunting of R lower extremity; hypoplastic pulmonary artery; persistent L superior vena cava	Vitelline artery; oligohydramnios
35.5	Anencephaly with extensive spina bifida	Hydramnios
Not recorded	Ventricular septal defect; subaortic stenosis; ectopic anus	
55.5	Malrotation of intestines	Cause of death: volvulus; recurrent malformation; placenta praevia posterior type III; history of hydramnios
42	Trigonocephaly; mental retardation; bilateral inguinal hernia	
53.5	Hydrocephaly; lumbosacral myelomeningocele	
Not recorded	Ventricular septal defect; pulmonary atresia; persistent ductus arteriosus	
54	Hydrocephaly; oesophageal atresia; imperforate anus; agenesis of L kidney; R hydroureter	Possibly a case of the 'Vater' syndrome.

FIG. 1.—Maternal age and gravidity.

stillborn. The remaining 9 represented 7.9% of the 113 'normal' infants. 33 of the total 143 were of low birthweight (2.5 kg and under), an incidence of 13.3% (15/113) in 'normal' infants and 60% (18/30) in those malformed or stillborn. 25 'normal' infants (16 female and 9 male) and 17 malformed or stillborn ones were small-for-dates, their weights being below the 10th centile for gestational age (National Birthday Trust Fund, 1969) (Fig. 2).

Fig. 3 compares the birthweights of infants with SUA with those of their sibs. In both groups babies known to have major congenital malformations are excluded. The birthweights of the sibs are in most cases taken from obstetric records but where these were not available the information was obtained from the mother.

Family history. Only one mother in this series is known to have had 2 infants with SUA, and neither of these had malformations. The familial incidence might possibly have been higher as many of the sibs were either born elsewhere or before 1966. Conversely, in 3 families in which there was a recurrence of malformations, 3 umbilical vessels were present in the other malformed sib. Table II presents the familial incidence of malformation associated with SUA.

In addition to the 143 index cases of SUA, the 142 mothers had 202 pregnancies. The outcome of these pregnancies is shown in Table III. There

FIG. 2.—Birthweight and gestational age of 'normal' infants with SUA.

FIG. 3.—Comparison of birthweights of infants with SUA and their sibs.

was a significant increase in malformations among the sibs of malformed index cases. There were 4 cases (2.4%) of major malformations among sibs of 'normal' index cases.

Smoking. On specific inquiry of 78 mothers of 'normal' infants, 41 (52%) admitted to smoking cigarettes during the SUA pregnancy. This incidence is higher than that found in a more recent random sample in this hospital—110/300 (36.7%).

Discussion

Comparison of incidence. In prospective and nonselective studies in published reports the

TABLE II
Familial incidence of malformations associated with SUA

Case no. and sex	SUA	Sib(s)
1 M	Normal	Congenital heart disease (died)
2 M	Normal	Diaphragmatic hernia
3 M	Volvulus	(1) Acephaly (1)
4 F	Anencephaly	(2) Intestinal obstruction
5 F	Multiple anomalies	(1) Anencephaly
6 M	Anencephaly	(2) Hydrocephaly
7 F	Stillborn (no anomalies)	Pseudohermaphrodite and multiple anomalies
8 F	Normal	Spina bifida
		Skeletal defects
		Congenital heart disease (died)

TABLE III
Outcome of previous and subsequent pregnancies

	Index case malformed (25)	Index case normal (118)	Total
Abortion	9 (22.5%)	28 (16.7%)	37
Malformed	6 (15%)	4 (2.4%)	10
Normal	25 (62.5%)	136 (80.9%)	161
Total pregnancies	40	168	208

incidence of SUA varies widely, but if investigations based on fewer than 4000 infants (Table IV) are excluded, the range extends only from 0.27% (Cederqvist, 1970, Sweden) to 0.97% (Lewenthal *et*

al., 1967, Israel). Our finding of 0.72% agrees with that of 0.76% reported by Froehlich and Fujikura (1966, U.S.A.) in their collaborative study of 26,539 singleton births.

Apart from the size of the series, other factors which may affect the reported incidence are the selection of mothers for hospital confinement, the enthusiasm and thoroughness of the examiner, and the proportion of different racial and socioeconomic groups. Froehlich and Fujikura (1966) found a lower incidence of SUA among Negro infants, as did Peckham and Yerushalmy (1965) among both Negroes and Orientals. The number of non-Caucasian infants born in the Leeds Maternity Hospital is not large enough to make an effective comparison. The incidence of SUA in series of 4000 and over is shown in Table IV.

Rather than confirming the male preponderance which Hyrtl (1870) encountered, we have found a distinct female predominance (1.4:1) which accords well with that reported by Froehlich and Fujikura of 1.2:1.

Low birthweight and small-for-dates babies. Fischer (1957) first reported the association between SUA and small-for-dates infants. Our findings agreed with those of many other authors (Benirschke and Brown, 1955; Thomas, 1961; Froehlich and Fujikura, 1966; Carrier *et al.*, 1966) with respect to the higher incidence of SUA among infants of low birthweight. Unlike Seki and Strauss (1964), we found that the mean birthweight of infants with

TABLE IV
Survey of prospective investigations of SUA based on 4000 or more births

Year	Author(s)	Country	Total no.	SUA (%)	Sex ratio F/M	No. of cases with major malformations (% of SUA)
1961	Thomas	Germany	6970	27 (0.39)	Not stated	5 (18)
1964	Fujikura	U.S.A.	5972	38 (0.64)	" "	7 (18)
1964	Feingold, Fine, and Ingall	U.S.A.	6080	32 (0.52)	" "	15 (46)
1965	Papadatos and Paschos	Greece	7886	32 (0.41)	14/18	10 (31)
1965	Peckham and Yerushalmy	U.S.A.	5848	51 (0.87)	NS	10/49 (20)
1966	Froehlich and Fujikura	U.S.A.	26,539	203 (0.76)	110/93	20 (10)
1966	Carrier, Matteau, and Jean	Canada	4138	33 (0.8)	13/19*	5 (15)
1967	Hnat	U.S.A.	4590	38 (0.83)	NS	6 (16)
1967	Leissner	France (Strasbourg)	4000	26 (0.65)	19/7	6 (23)
1967	Lewenthal <i>et al.</i>	Israel	5135	50 (0.97)	31†/19	12 (24)
1969	Müller <i>et al.</i>	France (Strasbourg)	4600	27 (0.59)	17/10	2 (7.4)
1969	Ainsworth and Davies	England (Oxford)	12,078	113 (0.94)	'Equal'	38 (33.6)
1970	Cederqvist	Sweden	19,422	53 (0.27)	21/32	17 (32)
1974	Present study	England (Leeds)	20,000	143 (0.72)	80/63	25 (17.5)

*Sex not recorded in one case.

†Includes one male pseudohermaphrodite.

SUA (3.06 kg) was significantly lower ($P = 0.0185$) than that of the control series (3.23 kg), even when infants with major malformations had been excluded from the study.

In discussing the causes of intrauterine growth retardation, Naeye (1965) suggested that there are two entirely different types. First, that which results from some harmful influence inhibiting mitotic division at a vital time in embryological development, and secondly, that due to malnutrition where the actual rate of cell division is comparatively unaffected but cytoplasmic mass is reduced.

It seems likely that small-for-dates infants with SUA can be similarly divided into these two groups of (1) those who may have associated malformations caused by an insult during the development of both the umbilical artery and other organs, which subsequently turn out to be malformed and (2) those in whom poor intrauterine growth is due to malnutrition. Supporting this theory is the finding that in most reports of SUA in twins it is the lighter of the two that is affected (Benirschke and Brown, 1955; Seki and Strauss, 1964; Kristofferson, 1969). In our series it was the lighter twin in 3 out of 4 cases who had SUA. When we reviewed 16 of the small-for-dates infants in our series, at ages ranging from 6 months to 6½ years, we found that 14 had gained weight satisfactorily, and their weights were all above the 10th centile for their age. The two remaining children showed stigmata suggestive of additional congenital abnormalities (results to be published).

Recurrence of SUA, multiple pregnancy.

There have been two previous reports of familial recurrence (Papadatos and Paschos, 1965; Lewenthal *et al.*, 1967). In all 4 affected infants there was no record of associated malformations. Similarly, the sibs reported here, a boy and a girl, were free from associated malformations. Fujikura (1964) reported a case of dizygous twins, both of whom had SUA. A case of concordant SUA in monozygous twins was reported by Fasolis and Okely (1961). Several authors, but especially Benirschke and Bourne (1960) and Bourne and Benirschke (1960), have emphasized a substantially greater frequency of SUA in multiple pregnancy. It was surprising to find that in our series the incidence of SUA in twins was no greater and even marginally less than in singletons. No bias existed against examination of multiple pregnancy placentae, and thus, we regard this point as still undecided.

Associated malformations. 25 infants (17.5%) with SUA showed major malformations

which either materially contributed to perinatal death or were likely to be prejudicial to extrauterine life if not surgically corrected. Of 25 malformed infants, 19 were either stillborn or died soon after birth. All were examined post mortem by one of us (H.G.K.). The principal findings are tabulated (Table I). A total of 148 infants with major malformations had necropsy examinations during the period of investigation; the SUA cases form 11.5%. Detailed analysis of malformations encountered, with or without SUA, is outside the scope of this paper, but it seems that there is no marked bias towards a particular organ or organ system being malformed in the SUA cases as compared with infants who have two umbilical arteries. The high percentage of CNS defects in the SUA series corresponds to a similar frequency in the total group. Though SUA is associated with exomphalos relatively frequently, the figures are too small for any definite conclusions. We believe that there is no known type of malformation or syndrome which is invariably associated with SUA*. Even in sirenomelia, classically associated with SUA, both umbilical arteries may be present occasionally, as seen in one of mono-amniotic twins in this series and reported elsewhere (Kohler, 1972).

In the smaller series of fewer than 4000 umbilical cords the influence of uncontrolled factors may be so great as to render useless conclusions on the incidence of malformations, as indicated by Lemtis (1968) who found no significant malformation in 17 infants with SUA. In Froehlich and Fujikura's (1966) series of 203 SUA infants (out of 26,539 single births) 20 had major malformations, i.e. 10%. Cederqvist (1970) reported 17 out of 53 SUA cases, i.e. 32%. However, the overall incidence of SUA was only 0.27% and the incidence of major malformations in his total material would be only approximately 0.9/1000 compared with ours of 1.25/1000. In the series of Ainsworth and Davies (1969) from Oxford, there was not only a higher incidence of SUA (0.9%), but a significantly larger percentage of malformations, as high as 33.6%. We know of no apparent explanation for the discrepancy, but the possibility of geographical and socioeconomic influences should be considered.

Persistent vitelline artery. Occasionally both umbilical arteries are missing and the one arterial vessel found in the umbilical cord is, in fact, a persistent vitelline artery, which branches off the abdominal aorta. We have encountered 2 such cases, one in a sireniform fetus, the other in an infant

*Acardiac fetuses are a possible exception.

suffering from exomphalos, bilateral diaphragmatic hernia, and other lesions. A persistent vitelline artery can be identified only at necropsy and appears to be associated with serious developmental defects. There is, however, at least one case on record (Gisel, 1938) in which a persistent vitelline artery was associated with minor abnormalities only, death being due to unrelated causes. Little attention has so far been given to this variant of the missing umbilical artery in most of the published studies.

Thalidomide and SUA. As thalidomide-containing drugs were withdrawn from sale at the end of 1961 no malformations caused by this drug should have occurred during our study. Benirschke and Driscoll (1967) implied that an increased incidence of SUA occurs as a result of thalidomide medication during pregnancy and they quoted reports by Dunn, Fisher, and Kohler (1962) and Kajii *et al.* (1963). These two references have since appeared in a number of subsequent publications. While the paper by Kajii *et al.* indeed supports Benirschke and Driscoll's contention, this is questionable in the case of Dunn *et al.* (1962) who detected SUA in one of 4 cases of phocomelia (namely, in one of dizygous twins who were concordant in respect of the extremity abnormality). However, in that case the mother as far as is known had taken thalidomide for only a few days late in the third trimester, well past the period of teratogenic determination.

The exact incidence of SUA in thalidomide-injured infants is not known and there is no evidence that it is more common in thalidomide babies than in any other group of malformed infants.

Karyotype anomalies and SUA. Chromosome analyses were done in only a few cases, either at necropsy or during clinical investigation in the neonatal period. No abnormality was found. During our follow-up study (to be published), however, we found a mosaic XO karyotype in a 5-year-old girl. A case of Turner's syndrome associated with SUA was reported by Richart and Benirschke (1958). A remarkable incidence of SUA in trisomy anomalies has been reported in other series (Lenoski and Medovy, 1962; Lewis, 1962; Gustavson, 1964; Seki and Strauss, 1964; Van Leeuwen *et al.*, 1967).

Perinatal mortality of nonmalformed infants. 6 out of 118 'normal' infants (4.2%) died in the perinatal period, compared with an overall perinatal mortality in this hospital of nonmalformed infants of 2.66%.

During the period of investigation a total of 532 nonmalformed stillbirths and neonatal deaths were examined post mortem. The 6 cases with SUA represent 1.1% compared with 0.72% in the total newborn population. Our results suggest an increased perinatal mortality in infants with SUA without associated major anomaly, but the figures are too small for a more definite statement.

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