Journal of Pharmaceutical Research International

33(60B): 722-734, 2021; Article no.JPRI.79546
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Prevalence of Single Umbilical Artery (Isolated and non-isolated) and Its Correlation with Birth Defects and Premature Death

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i60B34671

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/79546

Original Research Article

Received 15 October 2021
Accepted 19 December 2021
Published 22 December 2021

ABSTRACT

Background: The single umbilical artery (SUA) is linked to congenital abnormalities in almost every organ system, however published findings have been inconsistent. Although It has been proposed that inherited and long-term environmental factors do play a role, there is a need for further investigations on the same. The goal is to look into the possibility of a link between a single umbilical artery (SUA) in the incidence of chromosomal anomalies in the second trimester of pregnancy and their collective occurrence.
Methods: The exclusion of any one of the two umbilical artery and a present umbilical vein was considered as a single umbilical artery for the purpose of this research. A single umbilical artery was established by gross or histologic investigation of the placenta, neonatal evaluation, or autopsy. As a direct consequence, a newborn who did not have a single umbilical artery documented in these records was presumed to have an umbilical cord consisting of three vessels.
Results: SUA was identified in 0.46 percent of our population (4241/918 933). SUA risk factors included pregestational diabetes in the mother, consistently high blood pressure, prior Cesarean delivery. Some other factors include smoking, epilepsy, and conception via assisted reproductive

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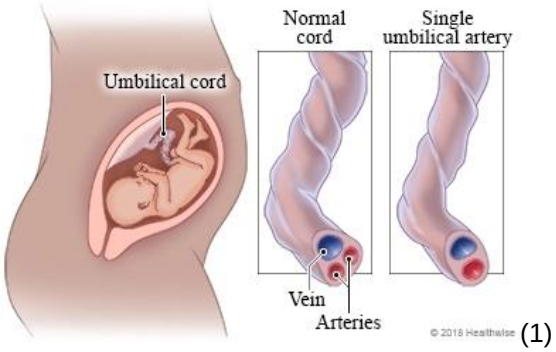
technology. SUA was associated with gastrointestinal atresia or stenosis in the neonate, esophageal and anorectal atresia or stenosis followed renal agenesis. SUA was linked to an elevated risk of congenital cardiac abnormalities by up to 7–8 times. There was a link between microcephaly, congenital hydrocephalus. There was a link established between other congenital brain and spinal cord anomalies as well. SUA displayed a lesser relationship with hernia associated with the diaphragm, limb reduction defect. It also showed a smaller relation to cleft lip or cleft palate. The risks of trisomy 13 and 21 were both increased, while the risk of trisomy 18 was maximum. Fetuses diagnosed with SUA, whether or not accompanied with a deformity, had two times the higher potential possibility of SUA in a future pregnancy.

Conclusion: Single Umbilical Artery is closely linked to gastrointestinal atresia or stenosis, implying the same developmental processes. The higher likelihood of reappearance of Single Umbilical Artery implies that inheritable and/or long-term environmental variables play a role. SUA was shown to have high correlations with trisomies 13 and 18.

Keywords: SUA; single umbilical artery; trisomy; malformations; congenital defects.

1. INTRODUCTION

A normal umbilical cord comprises three vessels, that is one vein and two arteries [1]. The umbilical vein is the means of transporting oxygenated blood from the placenta to the fetus during pregnancy. The arteries serve as a means of transport for the fetus's deoxygenated blood and unwanted byproducts to the placenta [2]. Sometimes, one of the arteries could further spontaneously agenitate or atrophy, having left only one umbilical artery.



(1)

Fig.1. Morphology of umbilical cord

The single umbilical artery (SUA) is significantly linked to inborn and chromosomal deformity in several bodily structures, however, evidence on the same ground is inadequate [3]. It has been hypothesized that hereditary and environmental variables have a role in the developmental stage of SUA, but it is still not known if there are higher stakes of reappearance in subsequent pregnancy for the same as well [3]. The researchers wanted to look at the occurrence of SUA and the stakes. Also to analyze its link to congenital abnormalities like cardiac defects, neural tube defects, orofacial deformities, and chromosomal anomalies like trisomy of chromosomes 13, 18, or 21, and the likelihood of SUA recurrence in subsequent pregnancies [3,4].

The umbilical cord develops between 13 and 38 days after conception. The internal iliac artery inevitably leads to the umbilical artery, which is a paired vessel. It is indeed an essential element of fetal circulation throughout the whole of prenatal development [2]. The distal greater portion of the umbilical artery obliterates post safe delivery, and the medial umbilical ligament appears as its replacement. The part of the artery with greater proximity is still functional, providing blood supply to the upper portion of the urinary bladder. It functions in a similar fashion in relation to the ductus deferens in males. The inferior vesical, vaginal, and obturator arteries commonly often establish anastomoses with it [2]. The goal is to look into the possibility of a link between a single umbilical artery (SUA) in the second trimester of pregnancy and the occurrence as well as the risk of congenital deformities and chromosomal anomalies [5].

2. METHODOLOGY

The exclusion of any one of the two umbilical artery and a present umbilical vein was considered as a single umbilical artery for the purpose of this research. A single umbilical artery was established by gross or histologic investigation of the placenta, neonatal evaluation, or autopsy. As a direct consequence, a newborn who did not have a single umbilical artery documented in these records was

presumed to have an umbilical cord consisting of three vessels.

The total number of subjects was taken as those carried to full term. For multiples, twin categories were dichorionic and monochorionic. The later comprising monoamniotic and conjoined twins. In the event of twins and multiples, the frequency of single umbilical artery and results was evaluated autonomously for each fetus or neonate.

As potential risk factors, maternal variables such as age, obstetric history, maternal medical problems, along with treatments were investigated. Relevant prenatal risk factors number of babies carried to full term, sex of fetus, type of twin etc were considered.

The correlation between single umbilical artery and Maternal pregnancy concerns, fetal deformities, and genetic problems, placental disturbances, amniotic fluid abnormalities, intrauterine development constraint, and low for gestational age, labor, delivery, perinatal mortality, preterm, and neonatal outcomes were studied.

Complications during pregnancy studied comprised : Maternal age, parity, consumption of alcohol and drug abuse, CH, asthma, kidney disease, UTI, Rheumatoid arthritis, cardiac related health issues, epilepsy, Thyroidrelated health issues, pregestational diabetes, GDM, the requirement of Assisted Reproductive Technology (ART), cesarean delivery.

In this meta-analysis of 29 studies conducted on SUA and its correlation with congenital malformations from 1980 to 2020. This analysis includes data relating to isolated as well as non-isolated SUA with an extensive list of congenital malformation like trisomies, cardiac defects, neural tube defects, etc. This study on singleton pregnancies considered for the analysis comprises both prenatal complications i.e perinatal death, intrauterine death, etc., and post-delivery malformations and their respective association with the prevalence of Single umbilical artery (SUA).

2.1 Objective

Although the SUA has been linked to inborn defects related to several organ systems, although some published results are conflicting. Although genetic and long-term environmental variables have been hypothesized, It is not certain what aspects encourage the occurrance of SUA. The objective is to investigate if there is a relationship between a single umbilical artery (SUA) and the occurrance of chromosomal anomalies.

This analysis consists of a compilation of information from studies dated to as early as 1980s upto the year 2020.

2.2 Main Text

The two main categories of birth defects considered are:

1) Structural Birth Defects

Structural birth defects are congenital abnormalities that alter the structure of anatomical structures. These kinds of birth defects can include:[5]

- Cleft lip.[2,6].
- Cleft palate
- Heart defects:
  (For Example) missing or misshaped valves
- Abnormal limbs
  (For example) clubfoot [5].
- Neural tube defects
  (For example) Problems related to the development and growth of the spinal cord and the brain of the fetus, such a spina bifida [5].

2.3 Functional Birth Defects

This type of defect is caused by a flaw in how a biological component or system behaves or functions [6]. These issues may include:

- Problems with the nervous system or the brain.

Disabilities of cognition and development behavioral disorders, speech or language challenges, seizures, and movement difficulties are examples of these issues [6]. Examples of congenital abnormalities that impact the neurological system are Downs syndrome, Fragile X syndrome, and Prader-Willi syndrome [5].

- Problems associated with the sensory system.

Hearing impairment and vision problems, such as blindness or deafness, appear to be documented cases as well [7].

- Problems associated with the metabolic capabilities of our bodies.

These include issues with the body's chemical reactions, for example, disorders that impair the capacity of the human body to eliminate unwanted or dangerous compounds. Phenylketonuria and hypothyroidism are two prevalent metabolic diseases [5,7,8].

- Degenerative disorders.

This type of disorder may not be visible when the fetus is born but gradually deteriorate one or more aspects of one's physical and mental wellbeing. Examples of some degenerative disorders are X-linked adrenoleukodystrophy, muscular dystrophy that affects the nervous system, and suprarenal glands [6].

Several birth abnormalities impact a variety of body components or functions, causing morphological and functional issues.

Normally, the funiculus umbilicalis consists of three vessels, two arteries, and one vein. The prevalence of SUA varies from population to population examined and the timeline of testing, which is found to be from 0.2 percent in newborns to 11% in high-risk fetuses at 11–14 weeks of gestation. [9,6,10,11].

Scientists and researchers have proposed that hereditary and long-term environmental variables impact the development of SUA since a potentially elevated risk is reported in siblings and children [11]. Twins, as well as maternal risk factors including multiple births, gestational diabetes, ethnicity, greater maternal age, multiparity, smoking, and the existence of maternal medical and behavioral problems, preexisting diabetes, hypertension, preeclampsia, and epilepsy, are examples of pregnancy problems [11]. Connections with maternal drug usage have been documented (for example, levothyroxine, vitamin A and phenytoin,) [11,12]. Substance misuse, seasonal changes in conception are all factors to consider, and placental anomalies have been documented [11,12,13,14,15,16].

Ultrasonography may readily be used to make a prenatal diagnosis of SUA, and guidance by a professional for the use of ultrasound in pregnancy advocate assessing the number of vessels in the umbilical cord.

Even though the prognostication for babies with a SUA is mostly determined by concomitant fetal structural or chromosomal abnormalities, findings show an increased incidence of fetal mortality either intrauterine or intrapartum among fetuses with SUA. (Heifetz 1984) It has been observed that the frequency of occurrences of (IUGR) intrauterine growth restriction is higher in fetuses with a SUA and can occur even when other congenital abnormalities are absent.

SUA is linked to many more fetal abnormalities in 10–27% of cases1,2,13,14, and there is a substantial connection with trisomy 18, 21.

3. RESULTS

3.1 Risk Factors

Several factors regarding the health of the mother and baby have been linked to a single umbilical artery, namely, sex, multiple births, racial background, old aged, multiple pregnancies. Chronic smokers are at high risk as well. The occurrence of SUA becomes more frequent when the mothers considered for the study suffer from medical and pregnancy complications. Such maternal health problems include preexisting diabetes, high blood pressure, placental abnormalities, and epileptic episodes [2,17,18] .If the mother undergoes frequent administration of levothyroxine or phenytoin, is dependent on other drugs, has an irregular pattern of conception that may be seasonal, etc also puts the fetus at risk for SUA [10,11,12,19].

In the univariable risk factor assessment for isolated single umbilical artery, smoking, drug use, the presence of maternal antibodies, neurological illness, respiratory illness, preexisting diabetes, and chronically hypertensive individuals were related with an elevated risk for single umbilical artery. If prenatal risk factors are considered, then twins and higher-order, their chances of having an SUA is greater than those who are single birthed [19].

The prevalence of SUA has been investigated as an objective in this review to determine risk variables with inborn abnormalities as well as trisomy as outcomes [3]. The following factors were included in the study based on their possible effect on the risk estimations:

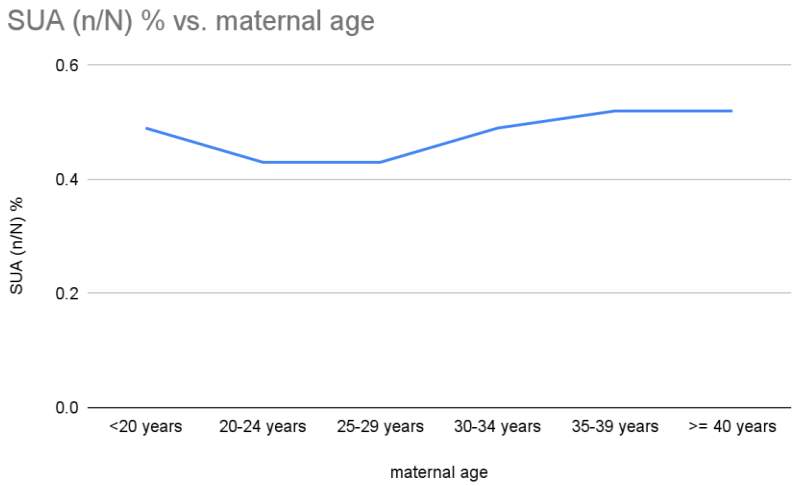


Fig. 2. Maternal age:[2,20,21] [2]

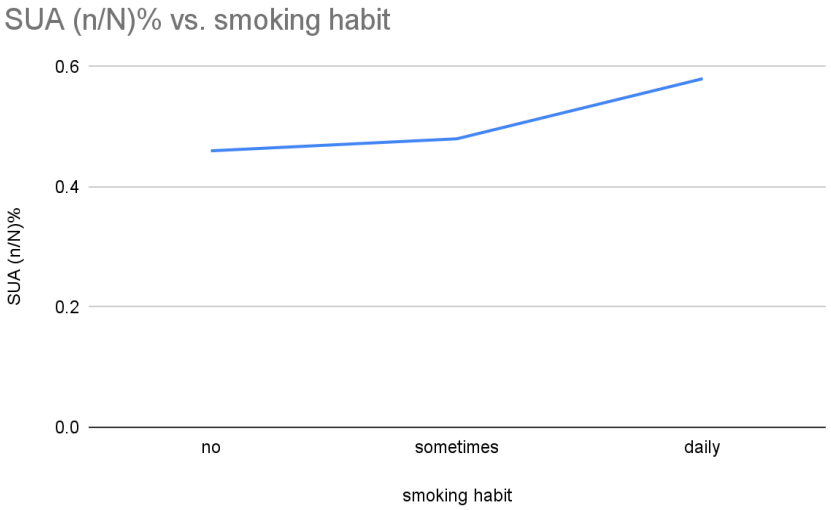


Fig. 3. Cigarette smoking at the start of pregnancy [22]

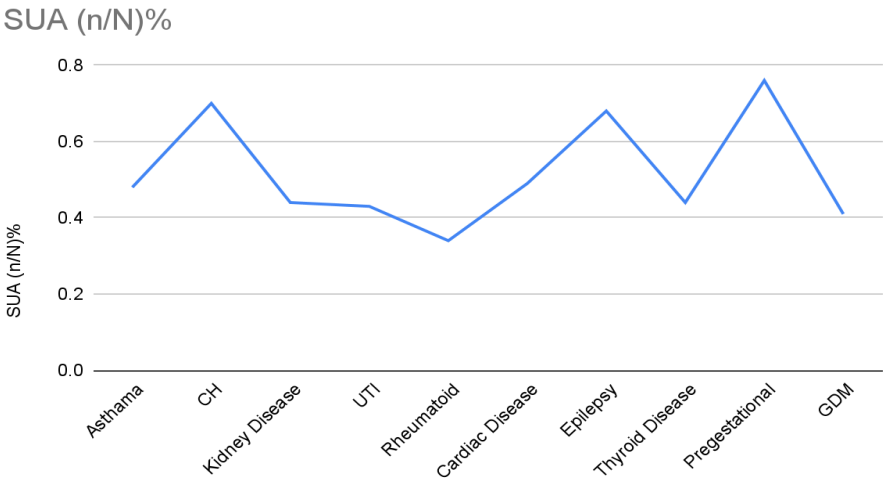


Fig.4. maternal medical problems [2,11,23]

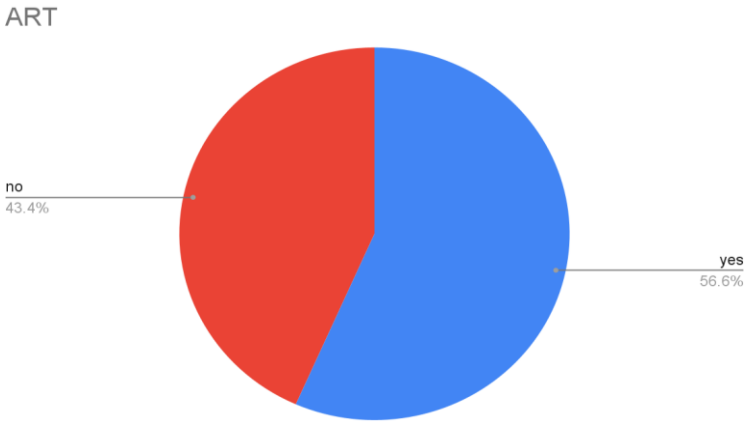


Fig. 5. ART conception

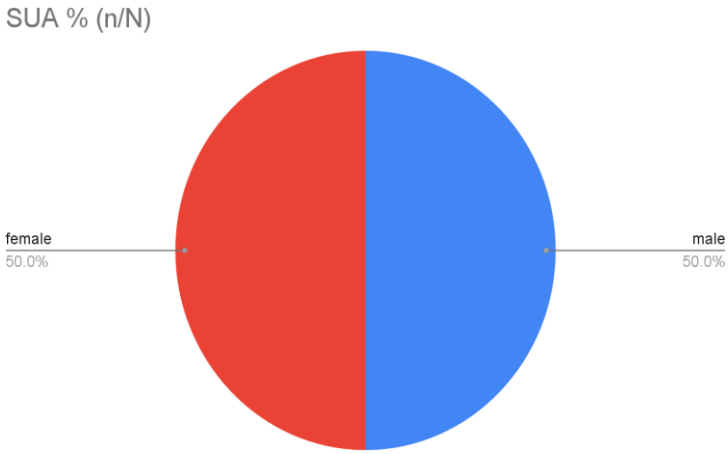


Fig. 6. Neonate/fetus sex

Table 1. Malformations in the first pregnancy

Diagnoses in 1st pregnancy	Diagnosis of SUA in further conceptions (n/N)%	OR (95%CI)
SUA (Malformation +/-)		
No	0.48	1
Yes	1.07	2.26
No SUA, no Malformation	0.48	1
SUA, no Malformation	0.95	2
No SUA, Malformation	0.47	0.99
SUA, Malformation	1.94	4.12

+/-, with or without

Conception through Assistive Reproductive Technology (ART), daily smoking, also including prior Cesarean section was linked with a slightly elevated risk of Single Umbilical Artery, but in the case of maternal age and paternal age. Even after including maternal age and parity in the model for evaluation, there was no significant increase in the risk of SUA prior to cesarean delivery [22,23]. Maternal, paternal, and gestational risk variables are seen to be identical for isolated Single Umbilical Artery, with the exception that ART-conceived pregnancies were not at higher risk for isolated SUA [2].

Neonatal/fetal sex did not seem to affect the occurrence of SUA and appears to have a similar

magnitude of occurrence in males and females [3].

3.2 Ethnicity

SUA data by ethnic groupings were supplied by two researchers. An incidence rate of 1.2% was reported for SUA in caucasian infants and an rate of 0.5% was reported in black infants [12,24,25].

3.3 Malformations in the First Pregnancy

Risk of single umbilical artery reappearance odds ratios (study in Norway 1999-2014) and its relation with abnormalities in the first pregnancy: (2)

3.4 Obesity

Obesity impacted 10% of the people surveyed. Morbid obesity (BMI greater than 40) negatively affected 0.7 percent of the population. Congenital abnormalities were discovered in 4.7 percent of the infants in this investigation, while rather serious problems were found in 3.2 percent.Mothers who were morbidly obese had a higher chance of conceiving a fetus, that would further in life develope orofacial clefts neural tube defects and/or heart problems.

Maternal obesity (BMI greater than 30) raised the chance of:

- Hydrocephalus. [4]
- anal atresia. [20]
- pars equinovarus [8]
- cystic kidney. [26]
- hypospadias.[27]
- omphalocele. [4]
- diaphragmatic hernia considerably [28].

In conclusion, this large register research found that maternal morbid obesity before pregnancy was linked to neural tube abnormalities [7], cardiac disease [29], and orofacial malformations [26], clefts with women having the greatest risk estimate possessing a BMI of 40 [20]. Obesity in mothers increases the incidence of several severe congenital birth abnormalities, including hydrocephaly, anal atresia, hypospadias, cystic kidney, pes equinovarus, and other conditions like omphalocele, as well as a diaphragmatic hernia [27]. The danger considering a single individual pregnant woman is relatively minimal, but these findings are significant in view of the growing obesity pandemic, a problem on a population-wide scale [28].

3.5 Occurrence of Congenital Malformations with Increasing Maternal BMI

Neural tube and cardiac disorders; pulmonary, gastrointestinal, musculoskeletal, and genitourinary anomalies; and acardiac twinning are all congenital deformities associated with a single umbilical artery. Some of these are discussed below with a correlation to BMI.

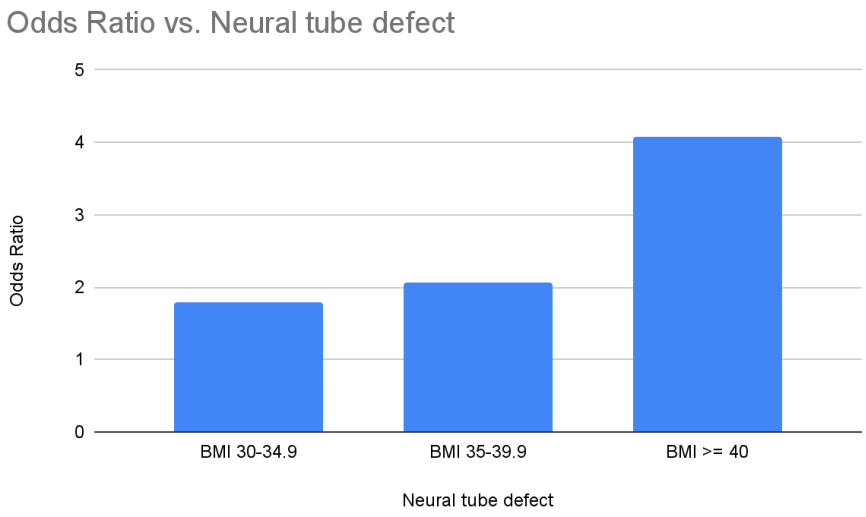


Fig. 7. Neural tube defects

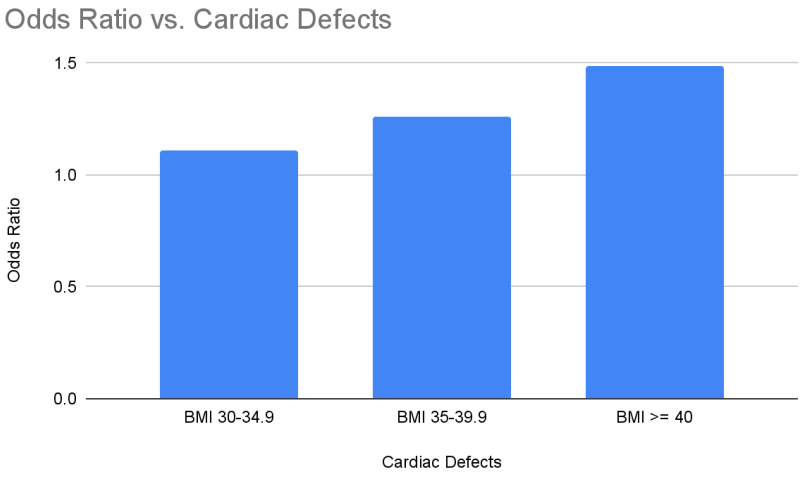


Fig. 8. Heart Defects

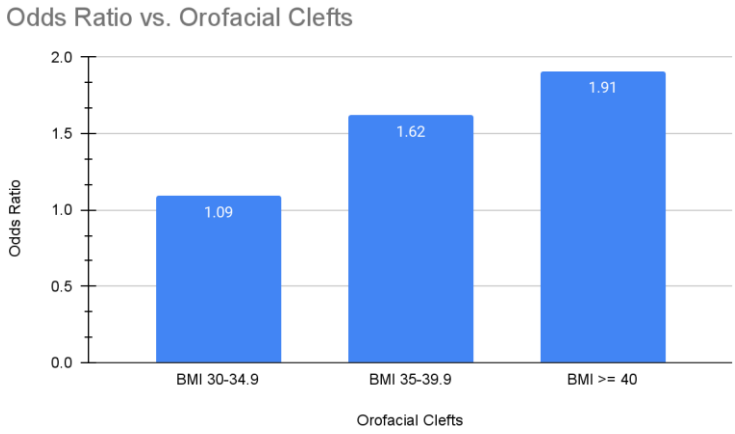


Fig. 9. Orofacial clefts

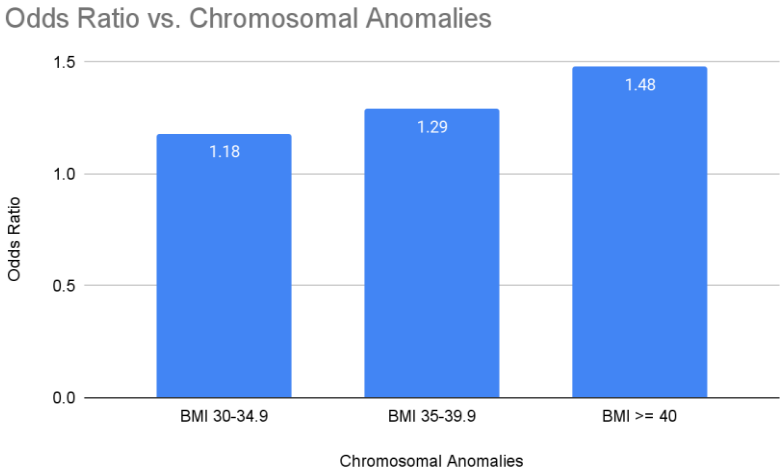


Fig. 10. Chromosomal anomalies

Chromosomal disorders and congenital deformities were more common in fetuses presenting with SUA.

3.6 Association of SUA with Malformations

SUA presented in fetuses and newborns had an approximately 15-fold increased chance relating to congenital anomalies and a 6-7-fold increased risk of one to two severe chromosomal anomalies, with an additional 18-19 fold increased risk of having two or more errors. The majority of congenital anomalies in single umbilical artery fetuses were Genitourinary malformations. These malformations were followed by cardiovascular and musculoskeletal defects in terms of chances of occurence [19].

- Fetuses and newborns with a SUA or iSUA were morer likely to have adverse outcomes. (23) Diagnosis of congenital abnormalities and aneuploidy before birth focuses on the identification of a SUA. Improved monitoring of a single umbilical artery may help to enhance pregnancy prospects [19].
- Prematurity, growth limitation, and poor neonatal outcomes were all higher in neonates with a SUA or an iSUA [29].
- Postnatally identified congenital abnormalities are more common in newborns with iSUA than the general public [23].

Table 2. Association of Single Umbilical Artery with some common malformations [3]

Malformation	Yes	No
Total subjects= 919,033	n=4341	n=914692
CNS		
Anencephaly	1	279
Encephalocele	0	79
Microcephaly	2	48
Congenital Hydrocephalus	8	458
Other CM of brain	8	425
Spina Bifida	4	415
Other CM of spinal cord	2	28
Other CM of the nervous system	0	177
CHD		
Chambers and connections	18	628
Cardiac septa	106	5902
Pulmonary and tricuspid valve	13	516
Aortic and mitral valves	12	548
Gastrointestinal		
oesophageal atresia or stenosis	25	210
Anorectal atresia or stenosis	24	256
Genitourinary		
Hypospadias	15	1237
Renal agenesis	3	107
Abdominal wall		
Omphalocele	2	209
Gastroschisis	1	270
Other		
Microtia	1	44
Cleft palate (w/o) cleft lip	8	621
Cleft lip	21	1106
limb reduction defects	8	375
Diaphragmatic hernia	5	226

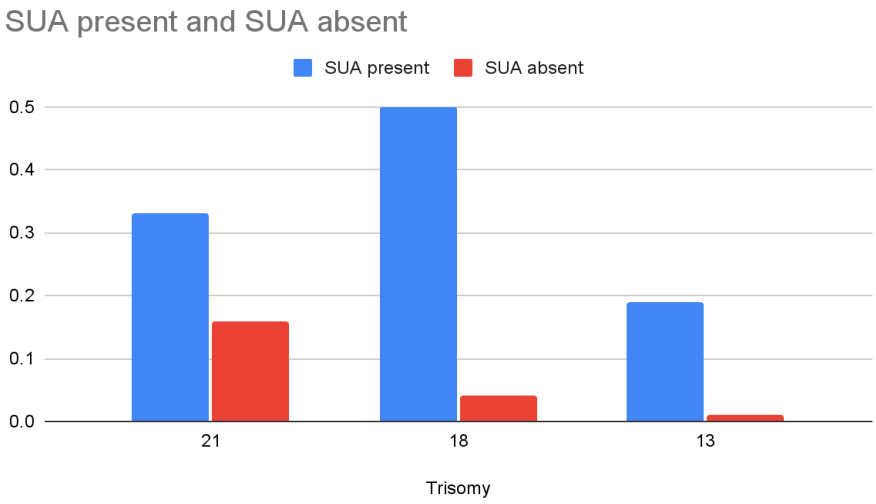


Fig. 11. Correlation of SUA with Trisomy [13,18,21]

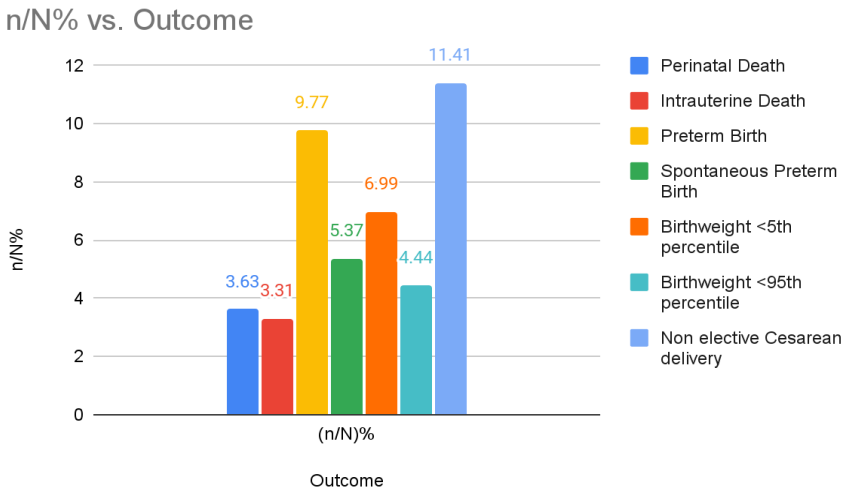


Fig. 12. SUA and adverse perinatal outcome [26]

- Although the presumptive diagnosis regarding babies with iSUA is mostly determined by concomitant fetal morphological or chromosomal abnormalities, fetuses with iSUA show a higher rate of preterm or postpartum fetal fatalities [23,24,30].
- Prematurity, low birth weight, and associated fetal abnormalities make up a substantial amount of infant mortality rate. The mortality for newborns with iSUA also may present anomalies in relation to the placneta [31]. An increased overall mortality for new borns with SUA is seen in the presence of placental abnormalities, as compared to new borns with a normal 3 vessel cord [32,33].
- When the comparison to those fetuses and newborns with normal umbilical cords with three vessels was equated, higher rates of stillborns, intrauterine growth retardation, preterm labor, and intrauterine death were documented, along with findings that cannot be satisfactorily justified and understood by aneuploidy or chromosomal anomalies [34-39].
- The mode of birth may be influenced by the presence of a single umbilical artery. The risk of cesarean delivery is two times greater in fetuses having a single umbical

artery as compared to those who didn't [40-42].

4. CONCLUSION

In this large collaborative study, In young life, the majority of infants with an iSUA turned out to be healthy and fit and developing properly, indicating thatmost of the children presenting with a iSUA develop normally cognitively and physically. There appears to be a strong relationship of SUA with Cardiac septa, and a weaker but persistent correlation with gastrointestinal atresias, and cleft lip. There was no substantial link between omphalocele or gastroschisis in SUA pregnancies.

In pregnant mothers with a fetus diagnosed with SUA, the risk of various congenital cardiac abnormalities ranged from an increase of twice to almost eight times as compared to normal pregnancies. SUA was shown to have a high relationship with trisomies 18 and 21 a much less association with trisomy [13]. The higher likelihood of recurrence during 2nd pregnancy implies that hereditary factors are to blame and/or long-term environmental variables have an impact on SUA advancement. The repercussion of iSUA has not been studied extensively in a long-run scenario, although there are some studies that there might be a few long term problems as a result of this condition. Further investigation is needed in this particular section.

CONSENT

As per international standard or university standard, respondents' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/79546