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Single umbilical artery and risk of congenital malformation: population-based study in Norway

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KEYWORDS: intestinal atresia; malformations; recurrence; single umbilical artery; SUA; trisomy; umbilical cord

CONTRIBUTION

What are the novel findings of this work?
Single umbilical artery was associated with a congenital malformation in 11% of cases, and the strongest association was with gastrointestinal atresia or stenosis. There was an increased risk of recurrence, and associations with trisomy 18 and 13 were of equal magnitude. There was no difference in the occurrence of single umbilical artery between male and female fetuses.

What are the clinical implications of this work?
The results of this study should be useful for counseling pregnant women and their families in cases of single umbilical artery.

ABSTRACT

Objectives *Single umbilical artery (SUA) is associated with congenital malformations in most organ systems, but reported findings have not been consistent. While it has been suggested that genetic and persisting environmental factors influence the development of SUA, it is not known whether there is an increased risk of recurrence in a subsequent pregnancy of the same woman. The aims of this study were to investigate the occurrence of, and risk factors for, SUA in Norway, to assess its association with congenital malformations and trisomies 13, 18 and 21 and to study the risk of recurrence of SUA in subsequent pregnancies.*

Methods *This was a population-based study of all (*n *= 918 933) singleton pregnancies of > 16 weeks' gestation recorded in the Medical Birth Registry of Norway from 1999 to 2014. To identify risk factors and congenital malformations associated with SUA, generalized estimating equations and logistic regression were used to calculate odds ratios (OR) with 95% CIs. ORs were also calculated for the recurrence of SUA in subsequent pregnancy.*

Results *The occurrence of SUA in our population was 0.46% (4241/918 933). Parity ≥ 4, smoking, maternal pregestational diabetes, epilepsy, chronic hypertension, previous Cesarean delivery and conception by assisted reproductive technology increased the odds of having SUA. There was a particularly strong association between SUA and gastrointestinal atresia or stenosis in the neonate, with ORs of 25.8 (95% CI, 17.0–39.1) and 20.3 (95% CI, 13.4–30.9) for esophageal and anorectal atresia or stenosis, respectively, followed by an OR of 5.9 (95% CI, 1.9–18.5) for renal agenesis. SUA was associated with an up to 7–8 times increased risk of congenital heart defects. There was an association with microcephaly, congenital hydrocephalus and other congenital malformations of the brain and spinal cord. Diaphragmatic hernia, limb reductions and cleft lip or palate had a weaker association with SUA, with ORs ranging from 4.8 to 2.8. The associations with trisomy 18 and 13 were equally strong (OR 14.4 (95% CI, 9.3–22.4) and OR 13.6 (95% CI, 6.7–27.8), respectively), and the risk of trisomy 21 was doubled (OR 2.1 (95% CI, 1.2–3.6)). Pregnancies with SUA, with or without an associated malformation, had a 2-fold increased risk for SUA in a subsequent pregnancy.*

Conclusions *SUA is associated strongly with gastrointestinal atresia or stenosis, suggesting common developmental mechanisms. The increased risk of recurrence of SUA suggests that genetic and/or persisting environmental factors influence the risk. We found that SUA had equally strong associations with trisomies 13 and 18.* © *2019 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

The human umbilical cord normally develops with two arteries and one vein. The occurrence of single umbilical artery (SUA) depends on the type of population studied and the timing of examination, ranging from 0.55% in neonates to 5.9% in high-risk fetuses at 11–14 weeks' gestation[1–3].

It has been suggested that genetic and persisting environmental factors influence the development of SUA, since a possible increased risk has been seen in siblings and twins[4], and maternal risk factors, such as hypertension and smoking, have been identified[2,5]. It is unclear whether there is an effect of the sex of the fetus or paternal age on the risk of SUA, and if there is indeed an increased risk in siblings[5–7]. Some studies have reported differences in the occurrence of SUA based on ethnicity[5,8–10], but European studies are scarce[7]. Most studies of SUA are based on pathology reports or hospital series[5,11]. These studies may, however, be affected by selection bias, warranting carrying out population-based studies. One population study exists, but it used data from births more than 30 years ago[12].

In 10–27% of cases of SUA, it is combined with other fetal malformations[1,2,13,14], and a strong association with trisomy 18 has been found[13]. SUA is associated with an increased risk of chromosomal aberrations and congenital malformations in the fetus[5,14–17]. These malformations have been reported to occur in most organ systems[5,12,14–16], but reported findings have not been consistent[2,5,8,12,16,18,19]. The association of SUA with malformations may point to its developmental origin, and, therefore, a study of SUA and associated congenital malformations is of interest. However, SUA and its associated malformations occur rarely, and current risk estimates carry a degree of uncertainty. This calls for population studies of a sufficient size[5,20].

The aims of the present study were to investigate the occurrence of, and risk factors for, SUA in Norway, to assess the association of SUA with different congenital malformations and trisomies 13, 18 and 21 and to ascertain if there is an increased risk of the recurrence of SUA in a subsequent pregnancy.

METHODS

This was a population-based study of all singleton pregnancies in Norway with a gestational age of more than 16 weeks and less than 45 weeks during the period 1999–2014 ($n = 918\,933$), using data from the Medical Birth Register of Norway (MBRN). In Norway, it has been compulsory to report the outcomes of all births and abortions after 16 weeks' gestation since 1967 and all those after 12 weeks since 2001. The attending midwife or physician examines the neonate or fetus and the umbilical cord, and enters the requested information into the registration form shortly after delivery.

Information regarding the umbilical cord has been specified since 1999 and reported as 'normal', 'marginal', 'velamentous' or 'vessel anomalies'. This was the rationale for the choice of starting time of the study period. If SUA was found, it was reported as a vessel anomaly. The category 'vessel anomaly' consists almost exclusively of SUA, but may also contain cases of supernumerary cord vessels, varices, aneurysms, thrombosis and hematomas, and cord cysts. Since cord-vessel abnormalities other than SUA constitute a very small proportion of cases[21–23], we considered 'vessel anomalies' to represent SUA in the analyses. Congenital malformations were recorded in the labor ward or in the neonatal department.

Gestational age was based on ultrasound dating in the first half of pregnancy when available (97% of cases) or the mother's last menstrual period. Parity was defined as the number of previous deliveries. Conception by assisted reproductive technology (ART) has been recorded in the register on a voluntary basis since 1988 and on a compulsory basis since 2001 ($n = 18\,638$). The report in the MBRN contains information about maternal health before and during pregnancy, and from delivery. In addition, demographic information, maternal medical conditions and medication, including the use of folic acid, smoking and complications during pregnancy and delivery are reported in the register. Furthermore, the report contains information about the neonatal condition at birth and transfer to the neonatal ward. Information on parental immigration status was provided by Statistics Norway; individuals were categorized as immigrants if both parents were born abroad.

We investigated specific major malformations registered in the MBRN, including: malformations of the central nervous system (anencephaly, encephalocele, microcephaly, hydrocephalus, other congenital malformations of the brain, spina bifida and other congenital malformations of the spinal cord and central nervous system, corresponding to ICD-10 diagnoses Q00–Q07), microtia, cleft lip and palate, gastrointestinal malformations (esophageal and anorectal atresia or stenosis), malformations of the abdominal wall (gastroschisis and omphalocele), diaphragmatic hernia, malformations of the heart and great vessels (hypoplastic left heart syndrome, transposition of the great arteries and other congenital heart malformations corresponding to ICD-10 diagnoses Q20–Q26), limb reductions and hypospadias. We also examined the association of SUA with trisomies 13, 18 and 21.

The study was approved by the Regional Committee for Medical and Health Research Ethics West (REK Vest).

Statistical analysis

Odds ratios (ORs) and 95% CIs for the association of risk factors and congenital malformations with SUA were estimated using generalized estimating equations in analyses including more than one birth from the same woman, otherwise logistic regression was used, with adjustments for possible confounding factors.

First, we studied SUA as an outcome in order to identify risk factors. Second, we studied SUA as the exposure in regression analysis, with congenital malformations

and trisomy as outcomes. The following variables were included in the regression models according to their potential influence on the risk estimates as determined in this study: parity, maternal age, cigarette smoking at the beginning of pregnancy, maternal medical conditions, conception by ART and sex of the neonate/fetus. In order to calculate the OR for the recurrence of SUA in a subsequent pregnancy, overall and according to the presence of an associated malformation in the previous pregnancy, the first and second birth or abortion of each woman were linked using the unique identification number. SPSS for Windows version 24 (SPSS, Chicago IL, USA) was used for statistical analysis.

RESULTS

The occurrence of SUA in our population of singletons was 4241/918 933 (0.46%). Parity ≥ 4, conception by ART, daily smoking and previous Cesarean delivery were associated with a slightly increased risk of SUA, while neither maternal nor paternal age influenced the risk (Table 1). Including parity or maternal age in the model assessing the association between a previous Cesarean delivery and SUA did not significantly change the results (adjusted OR, 1.16 and 1.12, respectively). Fetuses of immigrant parents had a reduced risk of SUA. Maternal, paternal and pregnancy risk factors were similar for isolated SUA, except that pregnancies conceived by ART were not at increased risk for isolated SUA (OR 1.18 (95% CI, 0.96–1.46)).

We found no difference in the risk of SUA between male and female neonates (Table 1). Maternal chronic hypertension, epilepsy and pregestational diabetes mellitus were

Table 1 Odds ratios (OR) for association of pregnancy characteristics with single umbilical artery (SUA) in population of 918 933 singleton pregnancies > 16 weeks in Norway (1999 to 2014)

Characteristic	*SUA (n/N) (%)*	*OR (95% CI)*
Maternal age		
< 20 years	98/20 097 (0.49)	1.00
20–24 years	574/134 960 (0.43)	0.87 (0.70–1.08)
25–29 years	1246/298 270 (0.42)	0.86 (0.70–1.05)
30–34 years	1484/303 639 (0.49)	1.00 (0.82–1.23)
35–39 years	708/136 836 (0.52)	1.06 (0.86–1.31)
≥ 40 years	131/25 046 (0.52)	1.07 (0.83–1.39)
Not recorded	85	
Paternal age		
< 20 years	30/5536 (0.54)	1.00
20–24 years	266/64 293 (0.41)	0.76 (0.52–1.11)
25–29 years	887/214 086 (0.41)	0.76 (0.53–1.10)
30–34 years	1458/306 678(0.48)	0.88 (0.61–1.26)
35–39 years	966/200 615 (0.48)	0.89 (0.62–1.28)
40–44 years	419/78 644 (0.53)	0.98 (0.68–1.43)
45–49 years	116/23 857 (0.49)	0.90 (0.60–1.34)
≥ 50 years	47/10 559 (0.45)	0.82 (0.52–1.30)
Not recorded	14 665	
Parity		
0	1747/381 086 (0.46)	1.00
1	1499/329 235 (0.46)	0.99 (0.93–1.06)
2	677/147 170 (0.46)	1.00 (0.92–1.10)
3	202/41 564 (0.49)	1.06 (0.92–1.23)
≥ 4	116/19 878 (0.58)	1.27 (1.06–1.54)
Smoker*		
No	2973/650 488 (0.46)	1.00
Sometimes	71/14 686 (0.48)	1.06 (0.84–1.34)
Daily	613/106 574 (0.58)	1.26 (1.15–1.37)
Not disclosed	584/147 185 (0.40)	0.87 (0.79–0.95)
ART		
No	4129/900 295 (0.46)	1.00
Yes	112/18 638 (0.60)	1.31 (1.09–1.58)
Immigrant status		
No	3841/818 670 (0.47)	1.00
Yes	400/100 263 (0.40)	0.86 (0.77–0.95)
Folate consumption		
No	3410/735 888 (0.46)	1.00
Yes	831/183 045 (0.45)	0.98 (0.91–1.06)
Previous CD†		
No	2062/455 873 (0.45)	1.00
Yes	432/81 974 (0.53)	1.17 (1.05–1.29)
Neonatal gender		
Male	2163/470 340 (0.46)	1.00
Female	2069/445 474 (0.46)	1.01 (0.95–1.07)
Undetermined	8/428 (1.87)	4.12 (2.05–8.31)
Not recorded	2691	
Maternal medical conditions		
Asthma		
No	4048/878 877 (0.46)	1.00
Yes	193/40 056 (0.48)	1.05 (0.91–1.21)
CH		
No	4205/913 773 (0.46)	1.00
Yes	36/5160 (0.70)	1.52 (1.09–2.11)
Kidney disease		
No	4216/913 287 (0.46)	1.00
Yes	25/5646 (0.44)	0.96 (0.65–1.42)
UTI		
No	4104/887 430 (0.46)	1.00
Yes	137/31 503 (0.43)	0.94 (0.79–1.11)
Rheumatoid arthritis		
No	4231/915 998 (0.46)	1.00
Yes	10/2935 (0.34)	0.74 (0.40–1.37)
Maternal cardiac disease		
No	4209/912 450 (0.46)	1.00
Yes	32/6483 (0.49)	1.07 (0.76–1.52)
Epilepsy		
No	4196/912 292 (0.46)	1.00
Yes	45/6641 (0.68)	1.48 (1.10–1.98)
Thyroid disease		
No	4167/902 298 (0.46)	1.00
Yes	74/16 635 (0.44)	0.96 (0.76–1.21)
Pregestational diabetes		
No	4193/912 590 (0.46)	1.00
Yes	48/6343 (0.76)	1.65 (1.24–2.20)
GDM		
No	4134/898 274 (0.46)	1.00
Yes	56/13 641 (0.41)	0.89 (0.68–1.16)
Not reported	7078	

*At start of pregnancy. †Only women with parity > 0 included. ART, assisted reproductive technology; CD, Cesarean delivery; CH, chronic hypertension; GDM, gestational diabetes mellitus; UTI, urinary tract infection.

risk factors for developing SUA (Table 1) but not for isolated SUA (data not shown).

Overall, 0.65% ($n = 5949$) of the population had at least one malformation compared with 10.9% ($n = 464$) of cases with SUA. Table 2 shows the association of SUA with specific malformations. A particularly strong association was seen between SUA and upper or lower gastrointestinal atresia or stenosis (OR, 20–26), followed by renal agenesis, diaphragmatic hernia and limb reductions. There was an association between SUA and microcephaly, congenital hydrocephalus and other congenital malformations of the brain and spinal cord. The risks for different congenital heart defects were more than doubled to almost eight times increased in pregnancies with SUA. There were strong associations between SUA and trisomies 13 and 18, and a weaker association with trisomy 21 (Table 2). Forty-eight percent of fetuses with trisomy 18 and 53% of those with trisomy 13 were aborted before 22 weeks' gestation.

In the study population, 282 989 women had two or more births. We found an increased risk of recurrence of SUA, and the association was stronger, with a four-fold increased risk, if SUA was combined with malformations in the first pregnancy (Table 3). Malformations without SUA in the first pregnancy did not increase the risk of SUA in the subsequent pregnancy. These results did not change when we included maternal age and parity in the equation.

DISCUSSION

This large population-based study found that pregnancies with SUA had a strong association with congenital malformations in the upper and lower gastrointestinal

Table 2 Odds ratios (ORs) for association of single umbilical artery with congenital malformations and trisomies 13, 18 and 21 in 918 933 singleton pregnancies > 16 weeks in Norway (1999 to 2014)

	SUA		
Malformation	*Yes* (n = *4241*)	*No* (n = *914 692*)	*OR (95% CI)*
CNS (ICD-10*)			
Anencephaly	1 (0.02)	279 (0.03)	0.77 (0.11–5.51)
Encephalocele	0 (0.00)	79 (0.01)	0
Microcephaly	2 (0.05)	48 (0.005)	8.89 (2.16–36.59)
Congenital hydrocephalus	8 (0.19)	459 (0.05)	4.10 (2.02–8.19)
Other CM of brain	8 (0.19)	425 (0.05)	4.54 (2.34–8.78)
Spina bifida	4 (0.09)	415 (0.05)	2.08 (0.78–5.57)
Other CM of spinal cord	2 (0.05)	28 (0.003)	15.24 (3.63–64.01)
Other CM of nervous system	0 (0.00)	177 (0.02)	0
CHD			
ICD-10†			
Chambers and connections	18 (0.42)	682 (0.07)	5.65 (3.53–9.03)
Cardiac septa	106 (2.50)	5902 (0.65)	3.98 (3.28–4.83)
Pulmonary and tricuspid valve	13 (0.31)	516 (0.06)	5.81 (3.42–9.90)
Aortic and mitral valves	12 (0.28)	548 (0.06)	4.68 (2.64–8.30)
Other	20 (0.47)	562 (0.06)	7.62 (4.88–11.92)
Great arteries	61 (1.44)	3748 (0.41)	3.57 (2.77–4.59)
Great veins	4 (0.09)	133 (0.01)	6.42 (2.37–17.37)
Transposition of the great vessels	5 (0.12)	377 (0.04)	2.86 (1.18–6.92)
Hypoplastic left heart syndrome	5 (0.12)	296 (0.03)	3.65 (1.51–8.83)
Gastrointestinal			
Esophageal atresia or stenosis	25 (0.59)	210 (0.02)	25.82 (17.04–39.14)
Anorectal atresia or stenosis	24 (0.57)	256 (0.03)	20.33 (13.36–30.92)
Genitourinary			
Hypospadias	15 (0.35)	1237 (0.14)	2.62 (1.57–4.40)
Renal agenesis	3 (0.07)	109 (0.01)	5.94 (1.90–18.54)
Abdominal wall			
Omphalocele	2 (0.05)	209 (0.02)	2.06 (0.51–8.31)
Gastroschisis	1 (0.02)	270 (0.03)	0.80 (0.11–5.69)
Other			
Microtia	1 (0.02)	44 (0.005)	4.90 (0.68–35.59)
Cleft palate (without cleft lip)	8 (0.19)	621 (0.07)	2.78 (1.38–5.59)
Cleft lip (with or without cleft palate)	21 (0.50)	1106 (0.12)	4.11 (2.67–6.34)
Limb reduction defects	8 (0.19)	375 (0.04)	4.61 (2.29–9.29)
Diaphragmatic hernia	5 (0.12)	226 (0.02)	4.78 (1.97–11.59)
Trisomy			
21	14 (0.33)	1435 (0.16)	2.11 (1.24–3.57)
18	21 (0.50)	337 (0.04)	14.40 (9.25–22.42)
13	8 (0.19)	135 (0.01)	13.61 (6.66–27.82)

Data are given as *n* (%). *ICD-10 diagnoses Q00–Q07. †ICD-10 diagnoses Q20–Q26. CHD, congenital heart defect; CM, congenital malformation; CNS, central nervous system.

Table 3 Odds ratios (ORs) for risk of recurrence of single umbilical artery (SUA) in 918 933 singleton pregnancies > 16 weeks in Norway (1999 to 2014), overall and according to presence of associated malformations (malf) in first pregnancy

Diagnosis in first pregnancy	*SUA in second pregnancy* n/N *(%)*	*OR (95% CI)*
SUA (+/− malf)		
No	1341/281 584 (0.48)	1.00
Yes	15/1405 (1.07)	2.26 (1.35–3.76)
No SUA, no malf	1274/267 392 (0.48)	1.00
SUA, no malf	12/1266 (0.95)	2.00 (1.13–3.54)
No SUA, malf	67/14 176 (0.47)	0.99 (0.78–1.27)
SUA, malf	3/155 (1.94)	4.12 (1.31–12.94)

+/−, with or without.

tract (atresia or stenosis), renal agenesis and congenital heart defects. However, we could not demonstrate an association between SUA and spina bifida, encephalocele or anencephaly. Secondly, we found an increased risk of recurrence of SUA, particularly if it was combined with malformations in the first pregnancy. Paternal age or sex of the fetus did not influence the risk of SUA. The associations of trisomies 18 and 13 with SUA were of equal magnitude, while the risk of trisomy 21 in SUA pregnancies was weaker, with a 2-fold increased risk.

The incidence of SUA and the factors identified as associated with SUA (parity, conception by ART, smoking, maternal chronic hypertension, epilepsy, pregestational diabetes mellitus and previous Cesarean delivery) in the present study are in line with the data of previous reports[1,2,5,12]. However, in contrast to previous studies[6,7], we found no difference between male and female neonates in the occurrence of SUA. A few cases of familial recurrence of SUA have been reported[6], but our finding of an increased risk of recurrence in the subsequent pregnancy of an affected woman is novel. Another new finding is that SUA, when combined with a malformation, is associated with an increased risk for SUA in the subsequent pregnancy, suggesting that genetic or persisting environmental factors may cause congenital malformations and SUA through a common pathway. A study in mice showed a tight connection between the endoderm and placenta, and that Hedgehog genes play a key role in the development of the fetoplacental interface (arteries) and the visceral endoderm/hindgut[24]. This is consistent with the spectrum of malformations in the gastrointestinal tract found to be associated with vessel anomalies in the umbilical cord in our study. In experimental studies, a number of genes that are involved in umbilical cord patterning have been identified. The HOX genes have also been found to play a critical role in vertebrates during the early development of the cardiovascular system involving the great vessels and of other midline structures, and in axial misalignment[25]. The increased risk of recurrence of SUA following a pregnancy with SUA associated with a malformation lends support to the hypothesis that cord development and midline malformations share persisting environmental and/or genetic etiology.

We found that, in 10.9% of cases, SUA was associated with at least one malformation. This percentage was, as expected, lower than in selected institution or autopsy series[1] and in line with a previous population study[12]. In our population, immigrants had a significantly lower risk for SUA than did native-born Norwegians, which is in line with data from previous studies[5,10]. This may suggest that there are genetic factors in the development of SUA, but may also indicate an environmental origin, as immigrants may differ from the majority population in a range of lifestyle factors. This difference may also be due to a 'healthy-immigrant effect', in which immigrants are, on average, healthier than the native born. The associations between SUA and trisomies 13 and 18 were equally strong, which is in contrast to the findings of previous studies that have reported a stronger association with trisomy 18 than 13[3,26].

The prenatal diagnosis of SUA can be made easily by ultrasound, and assessment of the number of vessels in the umbilical cord is recommended in clinical guidelines for the use of ultrasound in pregnancy[27]. The detection rate in the second trimester is high, but it is somewhat lower during the first trimester[28]. Although the absolute risk of gastrointestinal atresia in pregnancies with SUA is low, it may be beneficial to diagnose gastrointestinal malformations before birth in order to plan delivery according to the need for neonatal intervention. Knowledge of the different congenital malformations associated with SUA may be of value in counseling the mother and her partner.

A strength of this study is that it was population based, thus minimizing the risk of selection bias. The large size gave us the opportunity to study rare exposures and outcomes such as SUA and associated malformations, and allowed for the analysis of subgroups. All data in the MBRN are collected prospectively, which eliminates recall bias. Many variables in the MBRN have been validated[29–32], including data on measurement and classification of the placenta and umbilical cord[33], and good validity and reliability were found regarding the data reported in the MBRN on the characteristics of the umbilical cord. Malformations may be evident immediately after birth or later on. If the neonate is not hospitalized at the time of diagnosis, the malformation may not be registered, which may lead to under-ascertainment of these malformations. Validity of the registration of trisomy 21 in the MBRN has been found to be satisfactory[34]. Another strength was that it provided the opportunity to study longitudinally each woman from one pregnancy to the next, making it possible to determine the risk of recurrence.

A limitation of this study is that prenatal diagnosis of SUA was not registered, nor was the side on which the umbilical artery was missing[18]. Thus, assessing whether the associated malformations and other outcomes were influenced by the laterality (right or left) of the missing artery was not possible. In epidemiological and registry studies, there is always a possibility of misclassification of both exposures and outcomes. However, this would probably diminish rather that strengthen the observed associations. In this large study, we can probably rule out

the possibility that vessel anomalies other than SUA (that may be registered in the vessel-anomaly category and anticipated in our population to be < 100 cases according to the literature[23,35]) had any significant influence on the observed effects. In addition, it is reassuring that the rate of occurrence of SUA in our population was similar to that in other studies. Spontaneous hematomas of the umbilical cord have been reported with an incidence of 1:5500 in the literature[22,23,36]. It was beyond the scope of our study to examine the relationship of SUA and associated malformations with other genetic syndromes.

To summarize, we found that SUA had a strong association with gastrointestinal atresia or stenosis, and there was no associated risk of omphalocele or gastroschisis in pregnancies with SUA. Equally strong associations were seen with trisomies 13 and 18. The increased risk of recurrence suggests that genetic and/or persisting environmental factors influence the development of SUA.

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