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Miscarriage is associated with cervical ribs in thoracic outlet syndrome patients

P.C. Schut^{a,*}, A.J. Eggink^a, T.E. Cohen-Overbeek^a, T.J.M. Van Dooren^{b,c}, G.J. de Borst^d, F. Galis^c

^a Department of Obstetrics and Gynecology, Division of Obstetrics and Fetal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

^b CNRS, Institute of Ecology and Environmental Sciences iEES Paris, Sorbonne University Paris, France

^c Naturalis Biodiversity Center, Leiden, the Netherlands

^d Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands

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ABSTRACT

The constancy of the number of cervical vertebrae in mammals is probably the result of selection against associated variations. A survey among patients with and without cervical ribs showed an association between miscarriage and the presence of cervical ribs. This supports the hypothesized selection against variations in cervical vertebral number.

1. Introduction

Like virtually all mammals, humans typically have seven cervical vertebrae [1,2]. Cervical ribs and other variations of the cervical vertebral pattern are rare in the general population. The exceptional constancy of the cervical vertebral pattern over the course of evolution seems to be the result of strong, indirect selection against changes in the number of cervical vertebrae [3–5]. This hypothesis is supported by studies showing that an abnormal number of cervical vertebrae is associated with congenital abnormalities [3,4] and stillbirth [3,6,7]. The presence of cervical ribs has also been associated with the occurrence of childhood cancers, like astrocytoma and leukemia [8,9]. It has been estimated that almost 90% of individuals with a variation in the number of cervical vertebrae die before reaching the reproductive age [3].

Although the presence of a cervical rib might not have direct life-threatening effects, it can be regarded as a marker of disturbed embryonic development. Somitogenesis takes place at the early stage of organogenesis, when the interactions between organ primordia throughout the entire body are very strong. Since somites emerge in a craniocaudal sequence, the interactivity is strongest when the cervical region is formed. Due to the strong interactions, the embryo is considered to be highly vulnerable to the induction of malformations and mortality at this stage, because any change is expected to induce multiple other changes [10].

In contrast to the low prevalence in the general population, cervical

ribs are present in approximately 30% of patients with thoracic outlet syndrome (TOS) [11]. An illustration of bilateral cervical ribs is shown in Fig. 1. Patients without cervical ribs can also have TOS symptoms, but the presence of cervical ribs increases the chance of compression of vessels or nerves within the thoracic outlet. As most of TOS patients with cervical ribs reach the reproductive age, they appear to have survived the hypothesized negative selection against cervical ribs. TOS symptoms can be rather incapacitating and particularly in prehistoric times when strength and agility were necessary for survival, TOS would have had a negative impact on survival.

The vast majority of studies concerning TOS patients and cervical ribs focus on the association between the presence of cervical ribs and the occurrence of TOS, or the outcome of surgical treatment. Considering the hypothesized negative selection against cervical ribs and the high prevalence in deceased fetuses, it is relevant to explore the possible association between the presence of cervical ribs and other health issues, including reproductive problems. This study aims to compare the prevalence of congenital structural abnormalities, malignancies and reproductive problems between TOS patients with and without cervical ribs.

2. Materials and methods

2.1. Subjects and study design

The study was approved by the institutional ethics committee (16-

* Corresponding author at: Erasmus MC, University Medical Center Rotterdam, Department of Obstetrics and Gynecology, Division of Obstetrics and Fetal Medicine, Room Na-1608, Postbus 2040, 3000 CA Rotterdam, the Netherlands.

E-mail address: p.schut@erasmusmc.nl (P.C. Schut).

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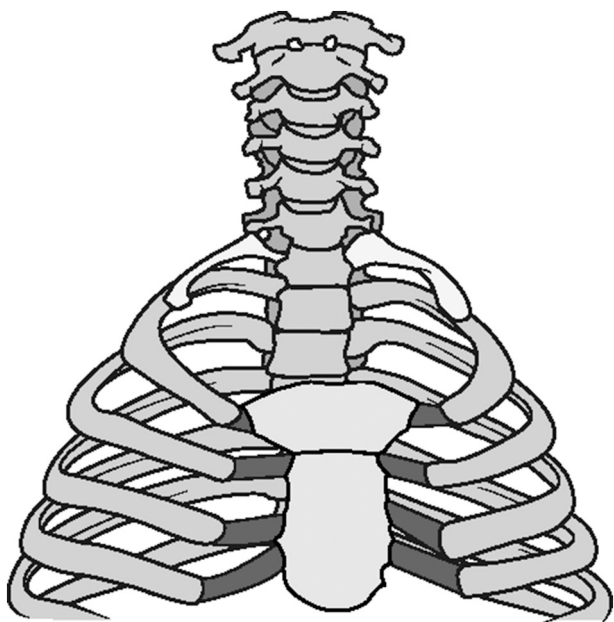


Fig. 1. The upper part of the vertebral column and sternum. The seventh cervical vertebra has bilateral rudimentary cervical ribs. Drawing by Erik-Jan Bosch (Naturalis Biodiversity Center), based on Fischel, 1906 [24].

559/C). Sample size was calculated to detect a difference between the prevalence of congenital structural abnormalities between two groups, assuming that the true proportions were 1% and 10%. Fisher exact test was chosen as a tool for statistical analysis. Based on the simulations we calculated that a sample of 97 persons per group was required to detect a significant difference between the prevalence of congenital structural anomalies with a power of 80%. Patients with TOS symptoms, referred to the department of Vascular Surgery at the University Medical Center Utrecht between July 2003 and July 2016, were contacted by a letter to participate in a survey. Patients were only included if a radiograph of the cervical vertebral column was present. After informed consent, a questionnaire was sent by letter or email, or a telephone interview was conducted, according to the participants' preference. Patients not responding or not returning the questionnaire were contacted by telephone on several occasions, and received a reminder by letter if they were not reached by telephone. When mandatory, relevant medical information was requested from other physicians after patients' consent.

2.2. Radiographic assessment

Radiographs of the cervical vertebral column in an anterior-posterior view were present (Philips DigitalDiagnost release 1, Philips Medical Systems, Eindhoven, the Netherlands). If the length of the transverse processes of the seventh cervical vertebra was more than the transverse process of the first thoracic vertebra, it was considered a rudimentary cervical rib. If the rib was longer than half of the first thoracic rib, it was considered a (complete) cervical rib [4].

2.3. Statistical analysis

SPSS (IBM Corp released 2013. IBM SPSS statistics for windows, version 24.0. Armonk, NY: IBM Corp) was used for descriptive analyses to evaluate the prevalence of cervical ribs, congenital anomalies, malignancies and reproductive problems. We studied the association between the presence of cervical ribs and the presence of congenital anomalies, miscarriages, fertility treatment, involuntary childlessness and the gender of the responder, using log-linear modelling analysis in

R [12,13]. We fitted a model with associations between these variables and simplified it until only interactions that were significant at 5% for a likelihood-ratio test remained. Simplification started with an automated stepwise removal of associations using function stepAIC [14], followed by likelihood ratio tests on the remaining interactions. In each round of simplification the association with the largest tail probability was removed.

3. Results

Ninety-nine (40.6%) of the 244 eligible patients completed the questionnaire. The results are summarized in Table 1. The responders were significantly more often female (67/99 (67.7%) vs 74/145 (51.0%) female non-responders, $p = 0.01$). Neurogenic TOS was the most common form of TOS (44/99, 44.4%), followed by arterial and venous TOS (23/99, 23.2% and 21/99, 21.2% respectively). In the remaining 11 patients (11.1%), the type of TOS could not be extracted from the medical file. Cervical ribs were present in 33/99 responders (33.3%) and were mainly rudimentary and bilateral (15, 45.5%). Most participants with cervical ribs were female (29/33) and significantly more patients with cervical ribs had undergone surgery compared with patients without cervical ribs (72.7% vs 48.5%, $p = 0.02$).

Two patients reported a history of malignancy; one TOS patient without cervical ribs had a carcinoma of the uterine cervix at the age of 30 and one patient with cervical ribs had been treated for a congenital melanoma. The medical history among patients with and without cervical ribs did not reveal any distinct differences. Familial occurrence of cervical ribs was mentioned by three patients with cervical ribs.

One TOS patient without cervical ribs decided to terminate pregnancy because of fetal hydrops. Three patients with cervical ribs reported congenital anomalies in their offspring (a cyst of the tongue, femur fibula ulna syndrome and Ehlers Danlos syndrome). After model selection, we found a direct association between the presence of miscarriages and cervical ribs in the selected log-linear model ($\text{chisq}(1) = 5.22$, $p = 0.022$). This was confirmed by a Chi-squared test for the association between cervical ribs and miscarriages when not accounting for any other association ($\text{chisq}(1) = 6.03$, $p = 0.014$). One third of patients with cervical ribs reported having had one or more miscarriages (11/33, 33.3%), which was more than in patients without cervical ribs (7/66, 10.6%). When we calculated the parameter estimating the association, it was found positive and significantly different from zero (1.64 (s.e. 0.74), $z = 2.21$, $p = 0.027$). Among patients without cervical ribs one miscarriage at 15 weeks occurred in a patient with hyperhomocysteinemia and one miscarriage occurred in a twin pregnancy at 16 weeks.

In none of the other cases a clear cause for the miscarriage was known by the patients. Parental karyotyping in a couple with 6 miscarriages showed a normal result. None of the other patients with recurrent miscarriages reported karyotype had been tested.

4. Discussion

We found an association between cervical ribs in TOS patients and miscarriages. TOS patients with cervical ribs more often have miscarriages than those without cervical ribs. No significant differences in the occurrence of malignancies, involuntary childlessness, the use of assisted reproduction, or specific other health problems were found between patients with and without cervical ribs within this cohort. In view of the hypothesized indirect selection against the occurrence of cervical patterning abnormalities, the association between cervical ribs and miscarriages is an intriguing finding that warrants further evaluation. Interestingly, according to the literature, the prevalence of cervical ribs in deceased fetuses and neonates with and without congenital anomalies, including miscarriages, has been shown to be strikingly high compared with healthy individuals [4,5,7].

The presence of cervical ribs and the occurrence of congenital

Table 1
Characteristics of the included patients with thoracic outlet syndrome, and differences between patients with and without cervical ribs.

	Total (N = 99)	Cervical ribs (N = 33)	No cervical ribs (N = 66)	p-Value
Current age (years)	51 (19–88)	49 (20–70)	51 (19–88)	0.98 ^a
Gender				0.002^b
Male	32 (32.3%)	4 (12.1%)	28 (42.4%)	
Female	67 (67.7%)	29 (87.9%)	38 (57.6%)	
Surgery	56 (56.6%)	24 (72.7%)	32 (48.5%)	0.022^b
Congenital abnormality	4 (4.0%)	2 [†] (6.1%)	2 [‡] (3.0%)	0.60 ^d
Involuntarily childlessness	12 (12.1%)	5 (15.2%)	7 (10.6%)	0.53 ^d
Pregnancy after assisted reproduction	5/98 (5.1%)	2/32 (6.3%)	3/66 (4.5%)	0.66 ^d
1 unknown		1		
Miscarriage	18 (18.2%)	11 (33.3)	7 (10.6)	0.006^b
Number of miscarriages				0.23 ^c
1	10	4	6	
2	4	4	0	
3	1	1	0	
4	0	0	0	
5	1	1	0	
6	1	0	1*	
Unknown	1	1	0	
Offspring				0.11 ^d
No	58 (58.6%)	17 (51.5%)	41 (62.1%)	
Yes	39 (39.4%)	14 (42.4%)	25 (37.9%)	
Unknown	2 (2.0%)	2 (6.1%)	0	
Offspring with congenital anomalies	4/37 (10.8%)	3/13 (23.1%)**	1/24 [‡] (4.2%)	0.12 ^d
Unknown	2	1	1	
Deceased offspring	3/39 (7.7%)	0	3/25 [§] (12.0%)	0.55 ^d

P-values marked with bold indicate statistically significant p-values.

Data presented as median and range or number and percentage. [†]Patient 1: Aortic stenosis. Patient 2: Hypoplasia right outer ear, cochlea and meatus. [‡]Patient 1: Mild pulmonary stenosis. Patient 2: Cervical block vertebra. *Patient and partner have a normal karyotype. **Patient 1: Cyst of the tongue. Patient 2: Femur fibula ulna syndrome. Patient 3: Ehlers Danlos syndrome. [‡]Fetal hydrops; termination of pregnancy. [§]Patient 1 died because of cardiomyopathy at the age of 27. Patient 2 died because of lung hypoplasia due to premature delivery. Patient 3 died at the age of 20; the cause of death was not reported.

^a Independent t-test.

^b Chi-Square test.

^c Mann-Whitney test.

^d Fisher Exact test.

anomalies and miscarriages have been shown to be associated with abnormal Homeobox (HOX) gene expression. HOX genes are a highly conserved family of genes that play an essential role in the determination of the anteroposterior patterning early in embryonic development [15]. Because abnormalities of the cervicothoracic region of the vertebral column co-occur with abnormalities of the pattern of more caudal vertebral regions in slightly more than half of the cases [4], the association between the occurrence of a miscarriage and the presence of cervical patterning abnormalities may be explained by disturbance of the expression of multiple genes, including HOX genes. The changes in expression patterns are probably caused by mutations in regulatory genes upstream of HOX, or by teratological disturbances of early embryogenesis [4]. So far, only a limited number of HOX disorders has been reported in humans [16], possibly because of early lethality of most HOX gene mutations. This study has some limitations. Miscarriages can have different causes and the most common risk factors are advanced maternal age, chromosomal abnormalities, uterine abnormalities and periconceptional environmental and nutritional factors, such as alcohol intake [17–19]. Detailed information concerning these risk factors at the time of miscarriage was not known for the included patients. The calculated sample size was not reached, which resulted in a very low prevalence of rare outcomes, such as congenital malformations. Yet, despite the small sample size, miscarriages and cervical ribs were found to be associated. The possibility of respondent error and non-response bias is a disadvantage of the use of questionnaires. Limited information regarding the characteristics of the non-responders was available, so non-response bias could not be entirely ruled out. Finally, due to the retrospective nature of the study, the causes of the miscarriages could not be further studied, nor were gene mutations studied in the patients with cervical ribs. Despite these limitations, the

hypothesis of selection against variations of the cervical vertebral pattern warrants further attention, in particular in light of the high percentage of unexplained stillbirths in the general population (17–66%) [20–23] and the current strong ambition to lower perinatal mortality [21,23]. The association between miscarriages and cervical ribs in TOS patients can be seen as support for the hypothesis of selection against variations of the cervical vertebral pattern. Prospective studies are indicated to confirm the association between the presence of cervical ribs and miscarriages to determine whether and how cervical ribs may be related to health problems with a negative influence on survival or reproduction.

CRedit authorship contribution statement

P.C. Schut:Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft.**A.J. Eggink:**Conceptualization, Writing - review & editing, Supervision.**T.E. Cohen-Overbeek:**Conceptualization, Writing - review & editing, Supervision.**T.J.M. Van Dooren:**Methodology, Formal analysis, Writing - review & editing.**G.J. de Borst:**Conceptualization, Methodology, Resources, Writing - review & editing.**F. Galis:**Conceptualization, Writing - review & editing.

Declaration of competing interest

None to declare.

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