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2021-03

Syvanen , J , Raitio , A , Helenius , I , Löyttyniemi , E , Lahesmaa-Korpinen , A-M , Gissler , M & Nietosvaara , Y 2021 , ' Prevalence and risk factors of radial ray deficiencies: A population based case-control study ' , American Journal of Medical Genetics. Part A , vol. 185 , no. 3 , 33369153 , pp. 759-765 . https://doi.org/10.1002/ajmg.a.62033

http://hdl.handle.net/10138/353250
https://doi.org/10.1002/ajmg.a.62033

acceptedVersion

PREVALENCE AND RISK FACTORS OF RADIAL RAY DEFICIENCIES

A population-based case-control study

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Funding

Clinical Research Institute HUCH.

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Abstract

Radial ray deficiency (RRD) is the most common congenital deficiency of the upper limb. The aim of our study was to investigate maternal risk factors for radial ray deficiencies. We conducted a nationwide population-based case-control study using national registers. All cases with a radial ray deficiency born between 1996 and 2008 were included in the study and compared with five controls without a limb deficiency. In total, 115 children with radial ray deficiencies were identified and compared with 575 matched controls. The total prevalence in Finland was 1.22 per 10 000 births. Advanced maternal age (≥35 years) increased the risk of radial aplasia (aOR 2.32, 95% CI 1.38–3.89), and similar association was observed with multiple pregnancy (aOR 1.90, 1.22–2.94) and male sex (aOR 2.86, 1.19–6.85). Valproic acid was also risk factor for RRD (*P* = 0.002). In conclusion, novel associations of advanced maternal age and multiple pregnancy and increased risk of radial ray deficiencies were observed. Also, early reports on increased risk of RRD associated with valproate and male sex were supported by our results.

Keywords: Maternal Age; antiepileptic; Radial Ray Deficiency; Risk Factor

Introduction

Radial ray deficiency (RRD) refers to a spectrum of congenital anomalies that involve the radius, radial carpal bones, or thumb (Oberg et al., 2010). It is the most common congenital deficiency of the upper limb with reported prevalence ranging from 0.33 to 1.64 per 10 000 live births (Bednar et al., 2009; Ekblom et al., 2010; Froster and Baird, 1992; Goldfarb et al., 2006; Pakkasjarvi et al., 2013). Although both isolated and syndromic forms have been described, majority of cases are present with other major anomalies or syndromes, such as trisomy 18 (Pakkasjarvi et al., 2013; Stoll et al., 2013). Hence, infant mortality may be as high as 35% in bilateral RRD (Koskimies et al., 2011).

RRDs can be all included into the embryological class of formation defects, for which the primary event is a localized developmental failure due to genetic or non-genetic factors (Kozin, 2003). About half of radial disorders have a Mendelian cause and pattern of inheritance, whereas the remaining half appears sporadic with no known gene involvement. The genetics of radial deficiencies is complex, characterized by genetic heterogeneity and high inter and intra-familiar clinical variability (Elmakky et al., 2015)

Maternal use of valproic acid has been identified as a risk factor for RRDs and radial defects have been described as part of fetal valproate syndrome (Kikuchi et al., 2016; Langer et al., 1994; Rodriguez-Pinilla et al., 2000). Cases are often sporadic and due to rarity of RRD, only few studies have addressed the risk factors of this anomaly, and no population-based case-control studies on maternal risk factors of RRD exist.

Against this background, the aim of this study was to assess the national total prevalence and explore maternal and pregnancy related risk factors for RRD. We hypothesized that first trimester medication use would increase the risk of radial ray deficiencies.

Methods

All cases (n=115) with congenital RRD born in Finland between Jan 1, 1996 and Dec 31, 2008 were identified from the National Register of Congenital Malformations, the Medical Birth Register, and the Register on the Induced Abortions, all maintained by the Finnish Institute for Health and Welfare. Information on maternal prescription medicine use was obtained from the Register on Reimbursed Drug Purchases and the Register on Medical Special Reimbursements (Social Insurance Institution of Finland). These registers receive information based on a legally compulsory announcement request on and have been validated confirming accurate data with high coverage (Gissler et al., 1995; Leoncini et al., 2010; Pakkasjärvi et al., 2006).

A detailed description of the data collection for congenital limb deficiencies has been given in previous papers (Koskimies et al., 2011; Syvänen et al., 2014). All cases with ICD-9 codes 75XX and 65XX from 1996 to 2008 were identified and reviewed. Identified matches were checked by the principal investigators and all cases other than radial ray deficiencies were excluded. Live births, stillbirths, and

fetuses from spontaneous abortions and terminations of pregnancy due to fetal anomalies were included.

Five controls without limb deficiencies from the Medical Birth Register matched for residency, and time of conception (± 1 month) were randomly selected for each case. For the terminated fetuses, live-born controls without limb deficiencies were selected.

Maternal risk factors in the register were analyzed including maternal age, BMI, parity, smoking, documented long-term diseases (Diabetes Mellitus, Asthma, Psychotic Mental Conditions, Depression, Epilepsy, and Inflammatory Bowel Diseases based on information on right to get free medication), history of miscarriages, and infertility treatments including in vitro fertilization. Smoking was defined as active smoking during 1st trimester. Maternal weight was recorded at the first prenatal visit 8–10 weeks after conception. The initial analysis on maternal medication was done at the 4th level of the Anatomical Therapeutic Chemical (ATC) Classification System by WHO. Each drug group with at least five exposed mothers was studied in univariate logistic regression and significant risk factors in these analyses were included the multivariable model. Antiepileptic drugs were further analyzed independently as valproic acid (ATC-5: N03AG01) is reported to be associated with increased risk of RRD (Kikuchi et al., 2016; Langer et al., 1994; Rodriguez-Pinilla et al., 2000).

Conditional logistic regression was used to evaluate different risk factors. First, univariate models were programmed, and Fisher's exact test was executed to search potential risk factors. Subsequently, a multivariable model was created. Odds ratios (OR) along with adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated. The analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Ethical Considerations

The approval of the Institutional Review boards at the Finnish Institute of Health and Welfare and Turku University Hospital were obtained before conducting this study.

Results

There were 115 cases of congenital radial ray deficiencies including 11 (11/115, 9.6 %) stillbirths and 36 (36/115, 31.3 %) elective terminations of pregnancy. The total prevalence was 1.22 per 10 000 births and the live birth prevalence was 0.76 per 10 000 live births. Fourteen of the live born cases died during the first week of life and 13 cases died during the first year of life. The perinatal mortality rate was 316 per 1000 births. The infant mortality rate was 397 per 1000 live births.

In total, 115 cases with radial ray deficiencies were identified and compared with 575 matched controls. In univariate analyses, advanced maternal age (≥35 years) was identified as a significant risk factor for RRD, OR 2.48, 95% CI 1.52–4.04. Also, multiple pregnancy (OR 2.77, 95% CI 1.20–6.37) and male sex (OR 1.91, 95% CI 1.25–2.93) increased the risk of RRD. Other maternal risk factors were not significantly associated with increased risk (Table 1).

	Number of Events		Adjusted Odds ratio	95% CI
	Cases (n=115)	Controls (n=575)		
Maternal Age <25 years (ref 25 – 34)	21 (18.3%)	119 (20.7%)	1.11	0.64–1.90
Maternal Age ≥35 years (ref 25 – 34)	33 (28.7%)	81 (14.1%)	2.48	1.52–4.04
Nulliparity	48 (41.7%)	224 (39.0%)	1.13	0.74–1.72
Pregestational diabetes	2 (1.7%)	6 (1.0%)	0.60	0.12–2.99
Smoking	10 (8.7%)	85 (14.8%)	0.87	0.42–1.78
Multiple pregnancy	9 (7.8%)	17 (3.0%)	2.77	1.20–6.37
Invasive fetal investigation	6 (5.2%)	26 (4.5%)	1.47	0.57–3.77
Prematurity	68 (59.1%)	32 (0.2%)	17.4	9.62–31.4
Male sex	76 (66.1%)	301 (52.3%)	1.91	1.25–2.93

Table 1. Maternal risk factors for radial ray deficiencies.

Maternal use of progestogens (ATC code G03D) increased the risk of RRD in univariate analysis (OR 2.45, 95% CI 0.46–13.6). Similarly, valproic acid was significant risk factor (*P* = 0.002). OR is not reported and valproic acid is not included in the multivariable model due to zero exposures in the control group. No significant associations were found with other maternal medications (Table 2).

Exposure (ATC code)	Number of Events		Odds ratio	95% CI
	Cases (n=115)	Controls (n=575)		
Valproic acid (N03AG01)	2 (1.7%)	- (0%)	N/A	N/A
Beta blockers (C07A)	1 (0.9%)	2 (0.4%)	0.40	0.04–4.43
Estrogens (G03C)	2 (1.7%)	4 (0.7%)	2.50	0.46–13.6
Progestogens (G03D)	8 (7.0%)	17 (3.0%)	2.45	1.03–5.81
Gonadotropins (G03G)	5 (4.4%)	21 (3.7%)	1.20	0.44–3.23
Muscle relaxants (M03B)	1 (0.9%)	6 (1.0%)	0.83	0.10–6.92

Table 2. Univariate analysis of prescription drugs for congenital radial ray deficiencies.

Significant risk factors in univariate analysis were entered into a multivariable model. Prematurity was not considered as a risk factor but rather a reflection of a pregnancy with an anomaly, and hence was not included in multivariable model. Pregestational diabetes was included as it is considered a significant risk factor for several birth defects including limb deficiencies. Multivariable analysis confirmed the increased risk associated with advanced maternal age (aOR 2.32, 95% CI 1.38–3.89). RRDs were also significantly associated with male sex (aOR 1.90, 95% CI 1.22–2.94) and multiple pregnancy (aOR 2.86, 95% CI 1.19–6.85) – Figure 1.

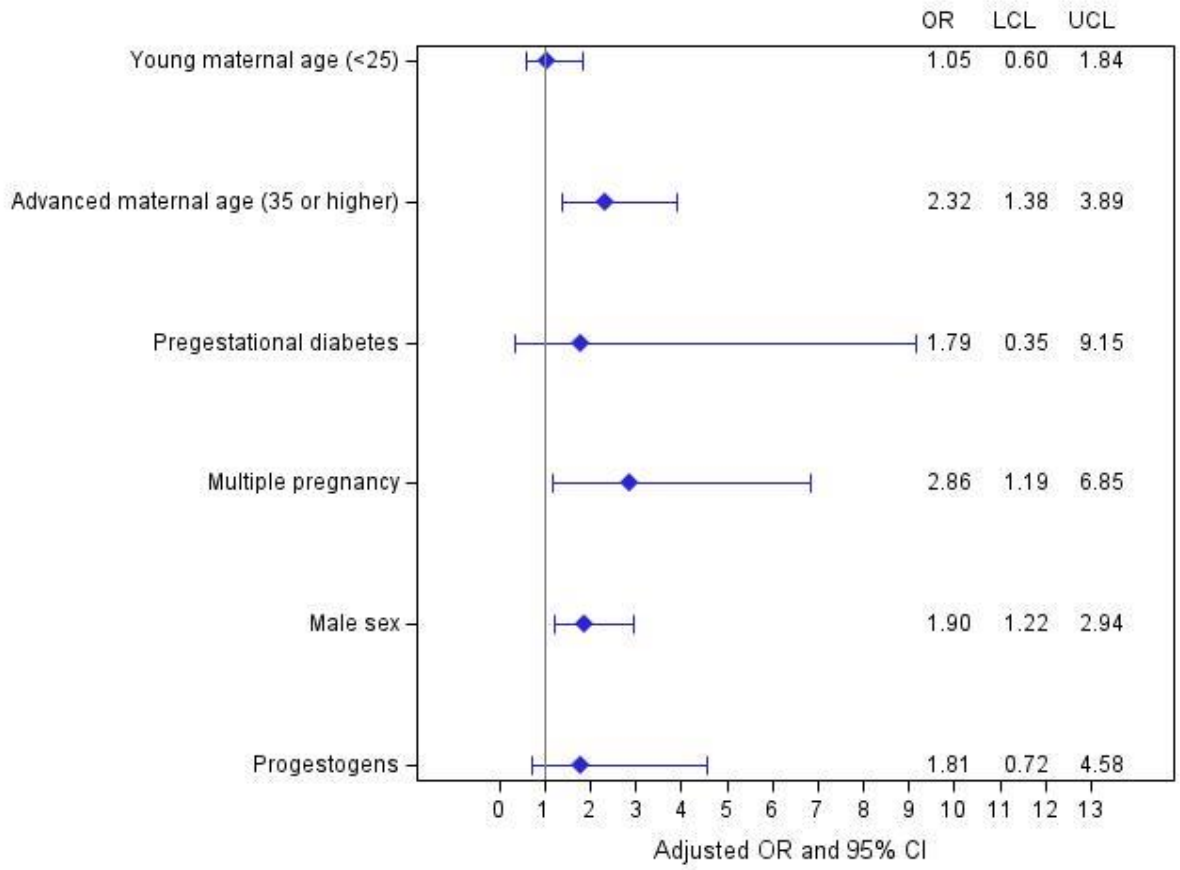

Figure 1. Multivariable analysis of the risk factors for RRD.

Discussion

In this large population-based case-control study we have demonstrated that advanced maternal age is a significant risk factor for RRD. Similarly, male sex and multiple pregnancy were associated with increased risk. Valproic acid used during the first trimester of pregnancy was also a significant risk factor for RRD.

Our data on exposures and outcomes were prospectively collected by the universally accessible healthcare system of our country. The registers used in this study were complete with accurate and validated data and the coverage during the study years is high (Gissler et al., 1995; KELA; Koskimies et al., 2011; Leoncini et al., 2010; Pakkasjärvi et al., 2006; Syvänen et al., 2014). The diagnosis of each RRD was confirmed by the principal investigators and the controversial cases were discussed by two experienced pediatric orthopedic surgeons. The case-control design was selected to identify risk factors for very rare clinical conditions.

Our study also supports previous few findings of associations between valproic acid and RRD. However, no association was observed between maternal special reimbursements for epilepsy and radial ray deficiencies. Similarly, a Norwegian study (Klungsøyr et al., 2019) also reported no significant

association between epilepsy and congenital limb deficiencies. In keeping with our results, valproic acid therapy has been previously associated with limb deficiencies and RRD has been described as a part of valproate syndrome (Langer et al., 1994; Rodriguez-Pinilla et al., 2000).

Advanced maternal age was significantly associated with increased risk of RRD in our study. To the best of our knowledge, the association between advanced maternal age and increased risk of RRD is a novel finding. However, advanced maternal age is a known risk factor for chromosomal abnormalities (Harris et al., 2017; Zhang et al., 2017) as well as non-chromosomal birth defects (Harris et al., 2017). According to previous studies, only 8–30% of RRD cases are isolated (Goldfarb et al., 2006; Koskimies et al., 2011) and half the cases are associated with known syndromes or chromosomal anomalies (Pakkasjarvi et al., 2013). Hence it is logical that advanced maternal age is also a risk factor for RRD.

Live birth prevalence was 0.76 per 10,000 live births, and in keeping with previous reports (Aro et al., 1982; Bednar et al., 2009; Froster and Baird, 1992; Kallen et al., 1984; Pakkasjarvi et al., 2013). Also, male preponderance of RRD cases has been similarly reported in previous studies (Froster and Baird, 1992; James et al., 1999). We found no previous reports on the association of multiple pregnancy and the risk of RRD. However, multiple pregnancy is a well-established risk factor for several other birth defects (Layde et al., 1980; Li et al., 2003; Mastroiacovo et al., 1999; Tang et al., 2006)

There are early reports on the association of maternal use of exogenous sex hormones and various congenital malformations including limb deficiencies (Czeizel et al., 1983; Heinonen et al., 1977; Janerich et al., 1974). As progestogens are often used in assisted reproductive technology, previous studies have failed to demonstrate, whether the increased risk of anomalies is associated with the hormone itself, the technology used, or the maternal and paternal factors related to subfertility (Berntsen et al., 2019). Our data suggest that progestogens would be associated with increased risk of RRD. However, the association was not significant in the multivariable model.

In conclusion, early reports on the increased risk of RRD associated with valproic acid were supported by our results. Also, increased risk of RRD appears to be associated with advanced maternal age, male sex, and multiple pregnancy.

Acknowledgements

Dr Raitio, Dr Helenius and Dr Syvänen report grants from Clinical Research Institute HUCH, and Dr Helenius reports grants and personal fees from Medtronic, grants from K2M, outside the submitted work. Also, we would like to thank Drugs and Pregnancy project for their co-operation with this study.

Conflict of Interest

None

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Aro T, Heinonen OP, Saxen L. 1982. Incidence and secular trends of congenital limb defects in Finland. Int J Epidemiol 11(3):239-244. doi: 10.1093/ije/11.3.239

Bednar MS, James MA, Light TR. 2009. Congenital longitudinal deficiency. J Hand Surg Am 34(9):1739-1747. doi: 10.1016/j.jhsa.2009.09.002

Berntsen S, Söderström-Anttila V, Wennerholm U-B, Laivuori H, Loft A, Oldereid NB, Romundstad LB, Bergh C, Pinborg A. 2019. The health of children conceived by ART: 'the chicken or the egg?'. Human Reproduction Update 25(2):137-158. doi: 10.1093/humupd/dmz001

Czeizel A, Keller S, Bod M. 1983. An aetiological evaluation of increased occurrence of congenital limb reduction abnormalities in Hungary, 1975-1978. International Journal of Epidemiology 12(4):445-449. doi: 10.1093/ije/12.4.445

Ekblom AG, Laurell T, Arner M. 2010. Epidemiology of congenital upper limb anomalies in 562 children born in 1997 to 2007: a total population study from stockholm, sweden. J Hand Surg Am 35(11):1742-1754. doi: 10.1016/j.jhsa.2010.07.007

Elmakky A, Stanghellini I, Landi A, Percesepe A. 2015. Role of Genetic Factors in the Pathogenesis of Radial Deficiencies in Humans. Curr Genomics 16(4):264-278. doi: 10.2174/1389202916666150528000412

Froster UG, Baird PA. 1992. Upper limb deficiencies and associated malformations: a population-based study. Am J Med Genet 44(6):767-781. doi: 10.1002/ajmg.1320440611

Gissler M, Teperi J, Hemminki E, Merilainen J. 1995. Data quality after restructuring a national medical registry. Scand J Soc Med 23(1):75-80. doi: 10.1177/140349489502300113

Goldfarb CA, Wall L, Manske PR. 2006. Radial longitudinal deficiency: the incidence of associated medical and musculoskeletal conditions. J Hand Surg Am 31(7):1176-1182. doi: 10.1016/j.jhsa.2006.05.012

Harris BS, Bishop KC, Kemeny HR, Walker JS, Rhee E, Kuller JA. 2017. Risk Factors for Birth Defects. Obstet Gynecol Surv 72(2):123-135. doi: 10.1097/OGX.0000000000000405

Heinonen OP, Slone D, Monson RR, Hook EB, Shapiro S. 1977. Cardiovascular birth defects and antenatal exposure to female sex hormones. The New England Journal of Medicine 296(2):67-70. doi: 10.1056/NEJM197701132960202

James MA, McCarroll HR, Jr., Manske PR. 1999. The spectrum of radial longitudinal deficiency: a modified classification. J Hand Surg Am 24(6):1145-1155. doi: 10.1053/jhsu.1999.1145

Janerich DT, Piper JM, Glebatis DM. 1974. Oral contraceptives and congenital limb-reduction defects. The New England Journal of Medicine 291(14):697-700. doi: 10.1056/NEJM197410032911403

Kallen B, Rahmani TM, Winberg J. 1984. Infants with congenital limb reduction registered in the Swedish Register of Congenital Malformations. Teratology 29(1):73-85. doi: 10.1002/tera.1420290109

KELA. The Social Insurance Institution of Finland. doi:

Kikuchi N, Ohira S, Asaka R, Tanaka K, Takatsu A, Shiozawa T. 2016. Prenatal sonographic diagnosis of fetal valproate syndrome: a case report. J Med Case Rep 10(1):312. doi: 10.1186/s13256-016-1094-1

Klungsøyr K, Nordtveit TI, Kaastad TS, Solberg S, Sletten IN, Vik A-K. 2019. Epidemiology of limb reduction defects as registered in the Medical Birth Registry of Norway, 1970-2016: Population based study. PloS One 14(7):e0219930. doi: 10.1371/journal.pone.0219930

Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. 2011. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. The Journal of Hand Surgery 36(6):1058-1065. doi: 10.1016/j.jhsa.2011.03.015

Kozin SH. 2003. Upper-extremity congenital anomalies. J Bone Joint Surg Am 85(8):1564-1576. doi: 10.2106/00004623-200308000-00021

Langer B, Haddad J, Gasser B, Maubert M, Schlaeder G. 1994. Isolated fetal bilateral radial ray reduction associated with valproic acid usage. Fetal Diagn Ther 9(3):155-158. doi: 10.1159/000263924

Layde PM, Erickson JD, Falek A, McCarthy BJ. 1980. Congenital malformation in twins. Am J Hum Genet 32(1):69-78. doi:

Leoncini E, Botto LD, Cocchi G, Annerén G, Bower C, Halliday J, Amar E, Bakker MK, Bianca S, Canessa Tapia MA, Castilla EE, Csáky-Szunyogh M, Dastgiri S, Feldkamp ML, Gatt M, Hirahara F, Landau D, Lowry RB, Marengo L, McDonnell R, Mathew TM, Morgan M, Mutchinick OM, Pierini A, Poetzsch S, Ritvanen A, Scarano G, Siffel C, Sípek A, Szabova E, Tagliabue G, Vollset SE, Wertelecki W, Zhuchenko L, Mastroiacovo P. 2010. How valid are the rates of Down syndrome internationally? Findings from the International Clearinghouse for Birth Defects Surveillance and Research. American Journal of Medical Genetics Part A 152A(7):1670-1680. doi: 10.1002/ajmg.a.33493

Li SJ, Ford N, Meister K, Bodurtha J. 2003. Increased risk of birth defects among children from multiple births. Birth Defects Res A Clin Mol Teratol 67(10):879-885. doi: 10.1002/bdra.10093

Mastroiacovo P, Castilla EE, Arpino C, Botting B, Cocchi G, Goujard J, Marinacci C, Merlob P, Metneki J, Mutchinick O, Ritvanen A, Rosano A. 1999. Congenital malformations in twins: an international study. Am J Med Genet 83(2):117-124. doi: 10.1002/(sici)1096-8628(19990312)83:2<117::aid-ajmg7>3.0.co;2-4

Oberg KC, Feenstra JM, Manske PR, Tonkin MA. 2010. Developmental biology and classification of congenital anomalies of the hand and upper extremity. J Hand Surg Am 35(12):2066-2076. doi: 10.1016/j.jhsa.2010.09.031

Pakkasjarvi N, Koskimies E, Ritvanen A, Nietosvaara Y, Makitie O. 2013. Characteristics and associated anomalies in radial ray deficiencies in Finland--a population-based study. Am J Med Genet A 161A(2):261-267. doi: 10.1002/ajmg.a.35707

Pakkasjärvi N, Ritvanen A, Herva R, Peltonen L, Kestilä M, Ignatius J. 2006. Lethal congenital contracture syndrome (LCCS) and other lethal arthrogryposes in Finland--an epidemiological study. American Journal of Medical Genetics Part A 140A(17):1834-1839. doi: 10.1002/ajmg.a.31381

Rodriguez-Pinilla E, Arroyo I, Fondevilla J, Garcia MJ, Martinez-Frias ML. 2000. Prenatal exposure to valproic acid during pregnancy and limb deficiencies: a case-control study. Am J Med Genet 90(5):376-381. doi: 10.1002/(SICI)1096-8628(20000228)90:5<376::AID-AJMG6>3.0.CO;2-V

Stoll C, Dott B, Alembik Y, Roth MP. 2013. Associated malformations among infants with radial ray deficiency. Genet Couns 24(2):223-234. doi:

Syvänen J, Nietosvaara Y, Ritvanen A, Koskimies E, Kauko T, Helenius I. 2014. High risk for major nonlimb anomalies associated with lower-limb deficiency: a population-based study. The Journal of bone and joint surgeryAmerican volume 96(22):1898-1904. doi: 10.2106/JBJS.N.00155

Tang Y, Ma CX, Cui W, Chang V, Ariet M, Morse SB, Resnick MB, Roth J. 2006. The risk of birth defects in multiple births: a population-based study. Matern Child Health J 10(1):75-81. doi: 10.1007/s10995-005-0031-5

Zhang XH, Qiu LQ, Ye YH, Xu J. 2017. Chromosomal abnormalities: subgroup analysis by maternal age and perinatal features in zhejiang province of China, 2011-2015. Ital J Pediatr 43(1):47. doi: 10.1186/s13052-017-0363-y