# Special Article

# Birth Prevalence of Goldenhar Syndrome (Severe Oculo-Auriculo-Vertebral Spectrum): A Systematic Review of Prospective Studies

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***Background:*** *Reported birth prevalence of Goldenhar syndrome and Oculo-Auriculo-Vertebral Spectrum (OAVS) vary, however, a systematic review of prospective studies has not been done.*
***Objective:*** *To review the birth prevalence of Goldenhar syndrome and OAVS systematically in documented prospective reports.*
***Material and Method:*** *A systematic literature search was conducted through PubMed and Scopus between 1952 and April 2017, using the search terms "Goldenhar syndrome" or "oculoauriculovertebral spectrum [Oculo-Auriculo-Vertebral spectrum]" and "prevalence".*
***Results:*** *Among the 4 prospective, register-based studies, there were 295 patients with either Goldenhar syndrome (134 cases) or the severe form of OAVS (161 cases) found in a study population of 8,104,255 births. Despite the lack of a well-accepted definition of these conditions, the current study calculated the pooled-average, birth prevalence of Goldenhar syndrome or the severe form of OAVS to be 1 case per 27,472 births (0.36 [95% confidence interval, 0.32 to 0.41] cases per 10,000 births).*
***Conclusion:*** *The differences in the birth prevalence may be due to (a) the lack of a well-accepted case definition, (b) differences in case ascertainment methods, (c) data processing, (d) true differences in the risk for Goldenhar syndrome and OAVS among population groups, and/or (e) other unidentified factors.*

***Keywords:*** *Goldenhar syndrome, Oculoauriculovertebral dysplasia, Oculoauriculovertebral spectrum, Prevalence, Birth, Branchial arches, Hemifacial microsomia*

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Oculo-Auriculo-Vertebral Spectrum (OAVS) is a complex developmental disorder that mainly affects the craniofacial structures derived from the first and second branchial arches and their derivatives[1-3]. It has a wide range of organ anomalies and variable severity[1-3]. It is characterized by malformations of the facial structures (including hemifacial microsomia), and sometimes with malformations of the spine, heart, kidney, bone, or other anomalies[2,4]. Sporadic and genetic transmissions are found in 1% to 2% of cases[1-4].

Goldenhar syndrome was initially described in 1952 by the ophthalmologist, Dr. Maurice Goldenhar, who described patients with epibulbar dermoids, pre-auricular skin tags, and mandibular asymmetry[1]. This group of anomalies was subsequently called Goldenhar syndrome. Later, Gorlin et al suggested the use of the term oculo-auriculo-vertebral dysplasia to describe the syndrome characterized by malformations of the eyes (microphthalmia, missing eyelids, or epibulbar dermoids), the ears (microtia, missing ears, ear tags, ear pits, or hearing loss), and the spine (hemivertebrae, or fused or missing vertebrae)[2]. Although there are no precise diagnostic criteria, patients with Goldenhar syndrome typically present with varying degrees of eye anomalies, ear malformations and diverse vertebral anomalies[1,2]. Goldenhar syndrome is considered to be a subset or a severe form of OAVS[1,2,5].

The birth prevalence of OAVS has been estimated to be between 1 in 44,907[6] and 1 in 5,642[3] live births[3,6-11]. The purpose herein is to provide an up-to-date systematic review of the birth prevalence of Goldenhar syndrome and severe OAVS among the

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prospective studies reported; in order to improve awareness of Goldenhar syndrome and OAVS.

## Material and Method

### *Data sources*

A systematic literature search was conducted of electronic databases using PubMed and Scopus with the medical subject heading (MESH) "Goldenhar syndrome" or "Oculoauriculovertebral spectrum [Oculo-Auriculo-Vertebral spectrum]" and "prevalence" between 1952 and April 2017. The eligible papers in all languages were included and screened. The titles and abstracts of the 59 relevant articles were assessed independently by two authors (KW and MP) to identify potentially relevant articles for which the respective full text was retrieved. Duplicate papers were removed. Reference lists of included papers were examined for additional relevant papers that may have been missed in the database search.

### *Definitions*

The birth prevalence in this review was expressed by dividing the number of cases (numerator) by the number of births (denominator) multiplied by 10,000. Diagnosis of Goldenhar syndrome was according to the author of each report[9-11] and diagnosis of severe OAVS included an ear anomaly and at least one major craniofacial anomaly and/or vertebral anomaly[8].

### *Study selection*

The current study included prospective reports on the birth prevalence of Goldenhar syndrome and of OAVS. The authors excluded studies limited to clinical features without mention of the prevalence rates and studies that did not include data for the respective calculation of prevalence rates. Two authors (KW and MP) performed the search independently using these study selection criteria. Disagreements were resolved through discussion until consensus was reached. When a study was eligible for inclusion, the two authors independently verified the numerator and denominator to check for accuracy.

### *Data extraction*

Data were extracted regarding diagnosis, types of study, number of cases, and number of birth infants.

### *Quality assessment*

Studies were assessed on the completeness of the data and its sources.

### *Statistical analysis*

The birth prevalence of Goldenhar syndrome and OAVS were presented as the number of cases per 10,000 births, and calculated 95% confidence intervals (CI) for the prevalence rates.

## Results

The search combination in the databases identified 59 relevant articles. After thorough evaluations of these articles by using the study selection criteria, the authors excluded 56 articles, so only 3 articles met the study selection criteria. Of the 3 remaining articles, after critical review of the full text, one article was excluded due to incomplete data. Of the remaining 2 papers, two additional studies were found after reference checking. These two additional studies were not initially retrieved by the original search because they were not indexed in the databases. Thus, 4 reports were eligible for inclusion into the systematic review (Fig. 1).

From the 4 prospective, register-based studies, 295 patients with either Goldenhar syndrome or severe form of OAVS were found in a study population of 8,104,255 births. The current study calculated the birth prevalence of Goldenhar syndrome and the severe form of OAVS to be 1 case per 27,472 births (i.e., 0.36 [95% CI, 0.32 to 0.41] cases per 10,000 births) (Table 1).

## Discussion

Despite the wide ranges of birth prevalence of Goldenhar syndrome and OAVS previously reported, the current study is the first systematic review of the prospective studies on birth prevalence rates of these conditions. By pooling data from the 4 prospective studies[8-11], the current study examined the birth prevalence of Goldenhar syndrome and the severe form of OAVS to be 1 case per 27,472 births, which is 0.36 (95% CI, 0.32 to 0.41) cases per 10,000 births (Table 1). These figures are within the range of the previous estimated birth prevalence of OAVS (i.e., between 1 per 5,642[3] and 1 per 44,907[6] births).

The definition for Goldenhar syndrome varied. Three prospective reports did not provide either a clinical description or a definition for the diagnosis of Goldenhar syndrome[9-11]. The other study (the EUROCAT) included cases with OAVS in patients with ear anomalies and at least one major craniofacial anomaly and/or vertebral anomaly[8]. As a consequence, the prevalence reported in the EUROCAT registries of

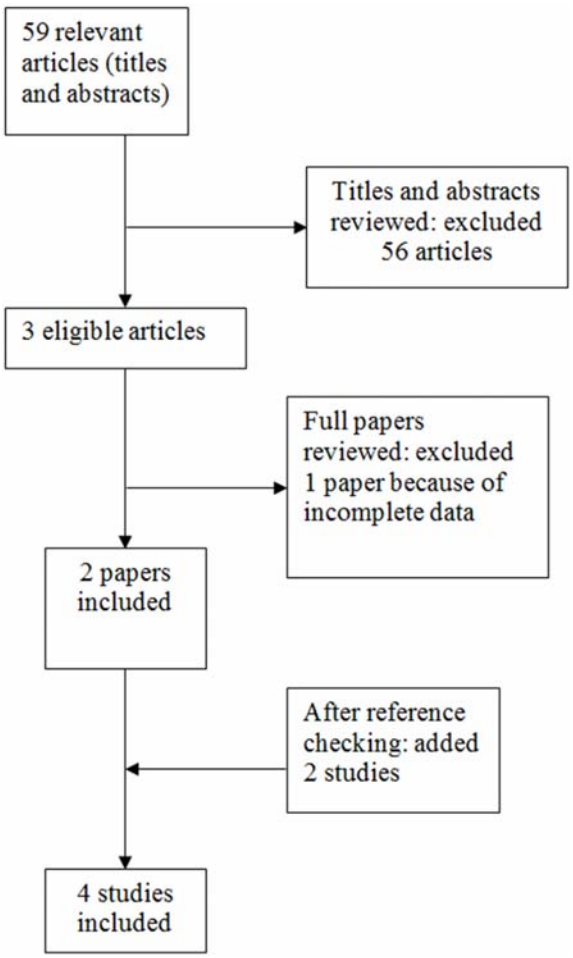


**Fig. 1** Flow diagram of articles searched and studies included in the systematic review.

1 per 26,370 represents a clinically serious (severe) group of patients with OAVS. These prospective registry-based studies indicate that the birth prevalence of Goldenhar syndrome (3 studies)[9-11] and of the severe group of OAVS (1 study)[8] are comparable-i.e., 1 per 28,797 births (0.35 [95% CI, 0.29 to 0.41] case per 10,000 births) vs. 1 per 26,370 births (0.38 [95% CI, 0.32 to 0.44] case per 10,000 births), respectively.

Among the two, large population-based registries, the New York State registry reported a birth prevalence rate of Goldenhar syndrome of 1 per 28,949 births, which is somewhat lower than the rate for the EUROCAT registry, which reported 1 per 26,370 births for a severe form of OAVS. Although the two registries represent prospective data, there are differences in the respective diagnostic criteria and follow-up duration. Moreover, one represented a single center (New York

**Table 1.** Birth prevalence of Goldenhar syndrome and the severe form of OAVS

| Authors/Years | Number of cases | Total number of births | Rate in number of births per case | Rate in number of cases per 10,000 births (95% CI) | Follow-up duration after birth |
|---|---|---|---|---|---|
| Barisic, et al[8]/2014[a] | 161[c] | 4,245,519[e] | 26,370[e] | 0.38 (0.32-0.44)[e] | 1 month |
| NY State, Health[9]/2008[b] | 132[d] | 3,821,264[f] | 28,949[f] | 0.35 (0.29-0.41)[f] | 2 years |
| Higurashi et al[10]/1990 | 1[d] | 27,472[f] | 27,472[f] | 0.36 (0.009-2.03)[f] | NA |
| Van Regemorter, et al[11]/1984 | 1[d] | 10,000[f] | 10,000[f] | 1.00 (0.03-5.60)[f] | NA |
| Total | 295 | 8,104,255 | 27,472 | 0.36 (0.32-0.41) | 1 month-2 years |

OAVS = Oculo-Auriculo-Vertebral Spectrum; NY = New York; CI = Confidence Interval; NA = not available
[a] EUROCAT congenital anomaly registries from 1990 to 2009; [b] New York State Department of Health registry from 1994 to 2008; [c] cases with severe OAVS; [d] cases with Goldenhar syndrome; [e] total births; [f] live births

State registry) and the other a multi-center (EUROCAT registry). In addition, the birth prevalence rate of Goldenhar syndrome reported by the New York State registry was apparently lower than that for OAVS reported by the EUROCAT registry, possibly because Goldenhar syndrome is a severe form of OAVS.

Previous available data provide wide ranges of birth prevalence figures of between 1 in 44,907[6] and 1 in 5,642[3] births[3,6-11]. Morrison et al[6] retrospectively ascertained all known clinical cases of OAVS in tertiary centers located in Northern Ireland and calculated a birth prevalence of 1 in 44,907 births[6]. Mild cases that did not come to the attention of their tertiary centers would not have been identified. These low prevalence figures are likely to come from studies which include only severe cases. Van Regemorter et al[11] reported one case of Goldenhar syndrome in a series of 10,000 births. Van Regemoter's report also stated that further three cases of facial asymmetry were observed. If these 3 cases had been included as cases of OAVS, the birth prevalence of OAVS could have been increased to 1 case per 2,500 births, a rate nearer that reported by Grabb[3] (1 in 5,642 births). These high prevalence figures suggest the studies included mild cases.

***Study limitations***

Despite reviewing the birth prevalence of prospective population-based studies, variability persists because there (a) was lack of a widely-accepted definition, (b) were differences in case ascertainment methods and (c) was variability in the competency of physicians involved.

**Conclusion**

The current study reviewed existing data on the birth prevalence of Goldenhar syndrome and the severe form of OAVS. Despite the lack of a well-accepted definition for these conditions, the pooled average the birth prevalence of Goldenhar syndrome or severe OAVS was 1 case per 27,472 births, or 0.36 (95% CI, 0.32 to 0.41) cases per 10,000 births. Differences in the birth prevalence may be due to (a) the lack of a well-accepted case definition, (b) differences in case ascertainment methods, (c) data processing practices, (d) true differences in the risk for Goldenhar syndrome and OAVS among population groups, and/or (e) other unidentified factors.

**What is already known on this topic?**

The birth prevalence of OAVS had been estimated to be between 1 in 44,907 and 1 in 5,642 births.

**What this study adds?**

This study examines the birth prevalence of Goldenhar syndrome (or the severe form of OAVS) to be 1 case per 27,472 births (0.36 [95% CI, 0.32 to 0.41] case per 10,000 births).

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**Potential conflicts of interest**

None.

**References**

1. Goldenhar M. Associations malformatives de l'oeil et de l'oreille, en particulier, le syndrome dermoide epibulbaire-appendices auriculaires-fistula auris congenita et ses relations avecla dysostose mandibulo-faciale. J Genet Hum 1952; 1: 243-82. [in French]
2. Gorlin RJ, Jue KL, Jacobsen U, Goldschmidt E. Oculoauriculovertebral dysplasia. J Pediatr 1963; 63: 991-9.
3. Grabb WC. The first and second branchial arch syndrome. Plast Reconstr Surg 1965; 36: 485-508.
4. Cohen MMJr, Rollnick BR, Kaye CI. Oculoauriculovertebral spectrum: an updated critique. Cleft Palate J 1989; 26: 276-86.
5. Rollnick BR, Kaye CI, Nagatoshi K, Hauck W, Martin AO. Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet 1987; 26: 361-75.
6. Morrison PJ, Mulholland HC, Craig BG, Nevin NC. Cardiovascular abnormalities in the oculo-auriculo-vertebral spectrum (Goldenhar syndrome). Am J Med Genet 1992; 44: 425-8.
7. Gabbett MT. The oculoauriculovertebral spectrum: Refining the estimate of birth prevalence. J Pediatr Genet 2012; 1: 71-7.
8. Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, et al. Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe. Eur J Hum Genet 2014; 22: 1026-33.
9. New York State Department of Health. Statistical summary of children born in 1994-2008 [Internet]. 2008 [cited 2017 Mar 31]. Available from: http://

www.health.ny.gov/.
10. Higurashi M, Oda M, Iijima K, Iijima S, Takeshita T, Watanabe N, et al. Livebirth prevalence and follow-up of malformation syndromes in 27,472 newborns. Brain Dev 1990; 12: 770-3.
11. Van Regemorter N, Dodion J, Druart C, Hayez F, Vamos E, Flament-Durand J, et al. Congenital malformations in 10,000 consecutive births in a university hospital: need for genetic counseling and prenatal diagnosis. J Pediatr 1984; 104: 386-90.

## *ความชุกแต่กำเนิดของกลุ่มอาการ Goldenhar (Oculo-Auriculo-Vertebral Spectrum ที่รุนแรง): ทบทวนอย่างเป็นระบบในวิจัยที่ศึกษาไปข้างหน้า*

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***ภูมิหลัง:*** *รายงานความชุกแต่กำเนิดของกลุ่มอาการ Goldenhar และ Oculo-Auriculo-Vertebral Spectrum (OAVS) มีความแตกต่างกันอย่างมาก แต่ยังไม่มีทบทวนอย่างเป็นระบบในวิจัยที่ศึกษาไปข้างหน้า*

***วัตถุประสงค์:*** *เพื่อศึกษาความชุกแต่กำเนิดของกลุ่มอาการ Goldenhar และ OAVS ที่รุนแรงโดยทบทวนอย่างเป็นระบบในวิจัยที่ศึกษาไปข้างหน้า*

***วัสดุและวิธีการ:*** *ค้นหาอย่างเป็นระบบในฐานข้อมูล PubMed and Scopus ช่วงระหว่าง พ.ศ. 2495 ถึง เมษายน พ.ศ. 2560 โดยใช้คำค้นว่า "Goldenhar syndrome" or "oculoauriculovertebral spectrum [Oculo-Auriculo-Vertebral spectrum]" and "prevalence"*

***ผลการศึกษา:*** *ใน 4 งานวิจัยที่ศึกษาไปข้างหน้ามีเด็กเกิดใหม่จำนวน 8,104,255 ราย พบว่ามีผู้ป่วยทั้งหมด 295 ราย เป็น Goldenhar syndrome จำนวน 134 รายและ OAVS ที่รุนแรงจำนวน 161 ราย ในการศึกษานี้พบว่าค่าเฉลี่ยของความชุกแต่กำเนิดของกลุ่มอาการ Goldenhar และ OAVS ที่รุนแรง เท่ากับ 1 รายต่อเด็กเกิด 27,472 ราย หรือคิดเป็น 0.36 (95% confidence interval, 0.32 ถึง 0.41) รายต่อเด็กเกิด 10,000 ราย*

***สรุป:*** *ความชุกแต่กำเนิดของกลุ่มอาการ Goldenhar และ OAVS อาจมีความแตกต่างกันได้เนื่องจากยังไม่มีคำจำกัดความของกลุ่มอาการที่ชัดเจน ความแตกต่างในวิธีการศึกษาและวิธีการรวบรวมข้อมูล ความแตกต่างจริงในความชุกของแต่ละกลุ่มประชากรหรือจากปัจจัยอื่น ๆ ที่ยังค้นไม่พบ*