Objectives In addition to breathing problems, patients with Robin sequence (RS) often encounter feeding difficulties (FD). Data regarding the occurrence of FD and possible influencing factors are scarce. The study aim was to elucidate these factors to improve treatment strategies.

Material and methods A retrospective comparative cohort study was conducted, consisting of 69 infants diagnosed with both RS and a cleft palate and 64 isolated cleft palate only (iCPO) infants. Data regarding FD, growth, and airway intervention were collected during the first 2 years of life. A systematic review of the literature was conducted to identify reported FD in RS patients.

Results RS patients had more FD (91%) than iCPO patients (72%; $p = 0.004$). Also, nasogastric (NG)-tube feeding was necessary more frequently and for a longer period (both $p < 0.001$). Growth was lower in RS than iCPO infants ($p = 0.008$) and was not affected by the kind of airway management (conservative/surgical; $p = 0.178$), cleft palate grade ($p = 0.308$), or associated disorders ($p = 0.785$). By contrast, surgical intervention subtype did significantly affect growth. Mean reported FD for RS in the literature is 80% (range = 47–100%), and 55% (range = 11–100%) of infants need NG-tube feeding.

Conclusions FD is present in a large proportion of infants with RS, which indicates the need for early recognition and proper treatment to ensure optimal growth. Growth during the first 2 years of life is significantly lower in RS patients than iCPO patients, which indicates the need for careful attention and long-term follow-up.

Clinical relevance This study indicates the need for early recognition and proper treatment of FD in RS to ensure optimal growth. In addition, growth needs careful attention and long-term follow-up.

Keywords (Pierre) Robin sequence · Cleft palate · Treatment · Feeding difficulties · Growth · Weight · Systematic review

Introduction

Although preceded by several earlier reports [1, 2], the French stomatologist Pierre Robin is credited as the first to draw attention to a symptom triad of breathing problems, glossoptosis, and micrognathia, known as Robin sequence (RS) [3, 4]. RS occurs in 1 in 8000 [5, 6] to 14,000 [7], depending on geography, ethnicity, and definition. Associated syndromes or anomalies coincide with RS in the majority of cases [8], and a concomitant cleft palate (CP) may exist but is not a required feature of RS [9–15].

Besides the varying degrees of respiratory problems, infants with RS frequently have feeding difficulties (FD) [16].
Swallowing difficulties directly related to the glossoptosis [16] and oroesophageal motor disorders caused by primary brainstem dysfunction [17] have been described as causes. FD is also a common feature in infants with a CP [18, 19]. These physiological abnormalities impede successful coordination of breathing, sucking, and swallowing. In infants with RS and a concomitant CP, these features can negatively affect the feeding process and there is a considerable risk of failure to thrive [20]. Consequently, these patients are often in need of nasogastric (NG)-tube feeding [21].

Although the majority of infants with RS and airway obstruction can be treated conservatively [22–26], surgical measures such as tongue lip adhesion (TLA) [27, 28], tracheotomy [29, 30], or mandibular distraction osteogenesis (MDO) [31–33] may be necessary. While the effect of these interventions on the obstructed airway has been frequently reported, information regarding the influence on FD is limited [16, 34].

To the best of our knowledge, this study is the first to identify factors that influence feeding and growth in RS and describe weight gain in the first 2 years of life. By obtaining a better understanding of all the facets of this condition, the treatment of these infants can be further optimized.

**Patients and methods**

**Retrospective cohort study**

**Baseline characteristics**

All infants diagnosed with RS (defined as the presence of micrognathia, glossoptosis, and signs of airway obstruction) and a concomitant CP treated at the Wilhelmina Children’s Hospital Utrecht, the Netherlands between 1996 and 2012 were included in the study group. All infants diagnosed with an isolated CP only (iCPO), without associated anomalies, were included in the control group. A retrospective analysis of the medical records during the first 2 years of life was conducted. Ethics committee approval was obtained to conduct this study (reference number WAG/th/14/020120).

The following variables were extracted from the medical files: gender, gestational age (GA), birth weight, grade of CP (grade 1–4) [35], and airway and nutritional treatment. In the study group, a subdivision was made between non-isolated RS infants (i.e., diagnosis of an additional syndrome, associated anomalies, or chromosomal defects) and isolated RS infants. Airway intervention was either conservative (i.e., prone/side positioning and possible use of supplemental oxygen, nasopharyngeal airway (NPA), oropharyngeal airway (mayotube), or continuous positive airway pressure) or surgical. The surgical intervention group was further divided into five subtypes: MDO, TLA, tracheotomy (Tr), TLA + Tr, and MDO + Tr.

**Feeding and growth**

FD were defined as (parentally) reported feeding problems, such as choking, regurgitation, gagging, distress, long-lasting feedings (≥30 min), impaired intake, and/or nasal regurgitation [36]. FD can lead to insufficient weight gain, failure to thrive, need for NG-tube feeding, and can potentiate airway or respiratory compromise [14]. Medical records and growth charts were thoroughly analyzed. In addition, parents received a phone call requesting participation in a short questionnaire about FD.

The following variables were collected: presence of FD, need and duration of NG-tube feeding, and weight at birth and at 1, 3, 6, 9, 11, 14, 17, and 24 months of age (if available). Growth was measured as a change between the consecutive measurements at these nine time points. In addition, normal weight standard deviation scores of healthy controls were collected [37]. In the surgical intervention subtypes, besides total NG-tube duration, the postoperative (i.e., after the airway intervention) NG-tube duration was also collected.

**Statistical analysis**

Data were analyzed using SPSS 20.0 (IBM SPSS, NY, USA). For interactions between nominal variables, chi-squared tests were used. To compare interactions between nominal and interval variables, t-tests and one-way ANOVA were computed. For two interval variables, two-way Pearson correlations were calculated. To compare growth, linear mixed model analysis was performed to model the repeated measurements data. In non-normally distributed data, non-parametric tests were used: Mann-Whitney U and Kruskal-Wallis H.

**Systematic literature review**

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to assess current data on the combination of RS and FD [38]. Electronic databases were searched using specific keywords (Table 1) for articles published between July 1967 and August 2014, according to the search and inclusion processes as illustrated in Fig. 1. All relevant level I to level IV articles [39] were included for further analysis (Table 2).

**Results**

**Baseline characteristics**

Sixty-nine RS patients (study group) and 64 consecutive iCPO patients (control group) were included. The study group included significantly more patients with a grade 3/4 CP than
the control group \((p < 0.001)\). The majority of the study group (54%; \(n = 37\)) was made up of non-isolated RS patients. Of these, more than half had an associated syndrome (51%, \(n = 19\)), Stickler syndrome (\(n = 9\)) being the most common (Table 3).

**FD and NG-tube feeding**

RS patients expressed FD (91%; \(n = 63\)) more than iCPO patients (72%; \(n = 38\), \(p = 0.004\)). In RS and iCPO patients with FD, a highly significant association was found in CP grade between the two groups \((p < 0.001)\); while a grade 3 and 4 CP was most common in RS patients with FD (grade 3 = 60%, \(n = 37\); grade 4 = 23%, \(n = 14\)), a grade 2 CP was most common in iCPO patients with FD (50%; \(n = 19\); Table 4). In a logistic regression analysis controlled for CP grade, presence of FD was still significantly associated with the RS patient group \((p = 0.005)\).

NG-tube feeding was more often necessary in RS patients (80%; \(n = 55\)) than iCPO patients (19%; \(n = 12\), \(p < 0.001\)). Furthermore, NG-tube feeding lasted longer in RS patients (median 59.0 days in study group vs. median 9.6 days in control group, \(p < 0.001\)). There was no significant association between the grade of CP (1–4) and the incidence of NG-tube feeding \((p = 0.23\); Table 4). NG-tube duration of the isolated (125 days; SD 203) and non-isolated (125 days; SD 171) RS patients did not differ significantly \((p = 0.996)\).

**Growth**

Birth weights of the two groups were comparable (iCPO group 3302 g vs. RS group 3217 g, \(p = 0.41\)). However, the iCPO group showed a significantly higher overall growth over the time points 1–9 (birth to 24 months of age) than the RS group \((p = 0.008)\). This increased growth in the iCPO group was also visible when separately analyzing time points 1–4 (birth to 6 months of age) and 5–9 (9–24 months of age; Table 5 and Fig. 2). When additionally controlling for grade of CP over time points 1–9, this difference remained significant \((p = 0.030)\).
Taken into consideration all nine time points, in the following analysis, both gender and group (iCPO vs. RS) were controlled for. Neither presence of FD nor the need for NG-tube feeding revealed significant effects on growth ($p = 0.893$ and $p = 0.467$, respectively). Furthermore, the grade of CP (1–4) did not significantly affect growth ($p = 0.308$; Table 5). Since a clinical interaction between the CP grade and group type could exist, this was also separately tested, showing that the interaction between the grade of CP (1–4) and group did not significantly affect growth ($p = 0.112$).

Within the RS group, neither the presence of associated disorders (isolated/non-isolated) nor intervention type (surgical/conservative) had a significant effect on growth ($p = 0.517$ and $p = 0.052$, respectively; Table 5).

**Interventions in the study group**

While 40 (60 %) RS patients could be treated with conservative measures, in 27 infants (40 %), a surgical intervention was performed because of severe respiratory distress. MDO was pursued at a mean age of 36 days (SD 32) in 14 (52 %) of these cases, TLA (mean age = 77 days, SD 49) in 3 cases (11 %), and a tracheotomy was performed (mean age = 45, SD 27) in 7 cases (26 %). Finally, in one case after TLA, a tracheotomy was performed due to an unstable airway. In two other cases, MDO was performed after tracheotomy (Table 6). Background information on the decisional process can be found in earlier work [55].

FD showed a significant association with intervention (surgical/conservative; $p = 0.04$); while all surgically treated patients had FD (100 %), in the conservatively treated group 85 % expressed FD. Since 100 % of the surgically treated patients showed FD, further investigation of presence of FD within the type of surgical treatment was not possible (Table 6).

Surgically treated RS patients were significantly more often in need of NG-tube feeding than conservatively treated patients (93 vs. 63 %, $p = 0.03$). NG-tube feeding lasted significantly longer in surgically treated RS patients (median = 72.0 days; mean rank 29.4; $p = 0.011$) compared to conservatively treated patients (median = 21.0 days; mean rank 19.2). Surgical intervention subtype had a significant effect on postoperative duration of NG-tube feeding ($p = 0.003$), with a median of 36.5 days for MDO, 183.0 days for TLA, 461.5 days for Tr, and 38.0 days for MDO + Tr. A post hoc test revealed significant differences between all these group interactions ($p < 0.05$), except for TLA vs. Tr ($p = 0.302$), TLA vs. MDO + Tr ($p = 0.083$), and MDO vs. MDO + Tr ($p = 0.874$; Table 6).

The subtype of surgical intervention (MDO, TLA, Tr, TLA + Tr, or MDO + Tr) also demonstrated a significant effect on growth from birth to 24 months of age ($p = 0.007$); a post hoc test showed significant differences between MDO vs. Tr ($p = 0.008$), TLA vs. Tr ($p = 0.012$), Tr vs. TLA + Tr ($p = 0.004$), TLA + Tr vs. MDO ($p = 0.05$), and TLA + Tr vs. MDO + Tr ($p = 0.029$; Table 5).
| Article                  | Population                  | Reported FD |
|-------------------------|-----------------------------|-------------|
| Abadie et al. [40]      | N = 66                      |             |
|                         | GI, RG, CP                  |             |
|                         | - IRS                       |             |
| Anderson et al. [35]    | N = 12                      |             |
|                         | GI, MG, CP, ORD             |             |
|                         | - IRS, sRS                  |             |
| Baujat et al. [17]      | N = 35                      |             |
|                         | GI, RG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Butow et al. [24]       | N = 143                     |             |
|                         | GI, MGRG, CP                |             |
|                         | - IRS, sRS                  |             |
| Cruz et al. [41]        | N = 43                      |             |
|                         | GI, MG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Daniel et al. [42]      | N = 39                      |             |
|                         | GI, MG, ORD                 |             |
|                         | - IRS, sRS                  |             |
| Evans et al. [43]       | N = 115                     |             |
|                         | GI, RG/MG, CP, ORD          |             |
|                         | - IRS, sRS                  |             |
| Glyn et al. [30]        | N = 69                      |             |
|                         | GI, MG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Gozu et al. [44]        | N = 20                      |             |
|                         | GI, MG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Hamdi et al. [45]       | N = 30                      |             |
|                         | CP, ORD, FD                 |             |
|                         | - IRS, sRS                  |             |
| Li et al. [46]          | N = 82                      |             |
|                         | GI, MG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Lidsky et al. [47]      | N = 82                      |             |
|                         | GI, MG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Maas et al. [48]        | N = 151                     |             |
|                         | MG/RG and ORD/GI/FSnoring/  |             |
|                         | hypoxemia/failure to       |             |
|                         | thrive/syndrome or CP       |             |
|                         | - IRS, sRS                  |             |
| Meyer et al. [49]       | N = 74                      |             |
|                         | GI, MG, CP                  |             |
|                         | - IRS, sRS                  |             |
| Smith et al. [50]       | N = 60                      |             |
|                         | GI, MGRG, CP and/or ORD     |             |
|                         | IRS, sRS                    |             |
| Stubenitsky et al. [51] | N = 44                      |             |
|                         | GI, MGRG, CP, ORD           |             |
|                         | IRS                         |             |
| van den Elen et al. [52]| N = 74                      |             |
|                         | MG, CP, and/or Gl           |             |

| Treatment n (%) | NG-tube | Gastrostomy | Other |
|----------------|---------|-------------|-------|
| 98 %           | 34 (52 %) | - | - |
| 100 %          | 12 (100 %) | - | - |
| 100 %          | 30 (86 %) | - | - |
| 52 %           | 27 (19 %) | 2 (6 %) | Suction and drinking plate (n = 134, 94 %) |
| 82 %           | 32 (82 %) | - | - |
| 95 %           | 27 (23 %) | 49 (43 %) | Nipple (n = 40, 35 %) |
| 70 %           | 48 (70 %) | 2 (3 %) | 3 months (3 weeks–6 months) |
| 60 %           | 12 (60 %) | - | - |
| 100 %          | 30 (100 %) | - | - |
| Nm             | 46 (42 %) | - | Obturator plate/CP bottles (n = 36, 44 %) |
| Nm             | - | 17 (25 %) | - |
| 89 %           | 76 (55 %); data only provided at time of discharge, after a mean of 19 (11–38) days | - | Feeding plate (n = 56, 37 %) |
| 50 %           | 19 (26 %) | 18 (24 %) | - |
| 62 %           | 17 (28 %) | 20 (33 %) | - |
| 100 %          | 30 (68 %) | 1 (2 %) | Reflux therapy (n = 27, 61 %) |
| 68 %           | 30 (41 %) | 2 (3 %) | Central venous line (n = 1, 1 %) |

| Duration        | Growth/weight gain | Intervention | Effect on FD |
|-----------------|--------------------|--------------|--------------|
| 3 months        | Normal in 97 %     | Tr           | 26 % (n = 5) bottle feeding after Tr |
| nm              | Mean of 28 g/day   | NPA          | nm           |
| 8.6 months      | nm                 | nm           | nm           |
| 26 % (n = 35)   | NG-tube feeding    | 26 % (n = 35) NG-tube feeding or gastrostomy needed |
| nm              | Suction and drinking plate | nm     |
| 8.6 months      | nm                 | nm           | nm           |
| 8900 ± 1290 g   | NPA, Tr, TLA      | nm           |
| 3 months        | NPA, Tr, TLA      | nm           |
| 12 months       | Tr, removable palatal appliance | nm     |
| 57 days (1–120 days) | Tr            | nm           |
| 26 % (n = 35)   | NG-tube feeding    | 26 % (n = 35) NG-tube feeding or gastrostomy needed |
| nm              | NPA, Tr, TLA      | nm           |
| Tr              | Reduction of need for feeding intervention in IRS | nm     |
| Tr or MDO       | Orthodontic plate therapy, CPAP, Tr, TLA, mandibular traction, functional therapy (e.g., Castillo Morales) | |
| Infants with pre-epiglottic baton plate demonstrated better weight gain during admission | nm     |
Systematic literature review

The literature search resulted in 347 unique titles. After initial screening, the full text of 80 potentially relevant articles was retrieved. References of these were checked, which provided three additional papers. These 83 texts were then analyzed by selection criteria and validity, yielding 20 articles (Table 2) [5, 17, 24, 30, 35, 40–54].

The selected reports included a mean of 65 patients (range = 22 [54]–151 [48]) with mixed isolated and non-isolated RS cases. In the majority, RS was defined as infants expressing micrognathia, glossoptosis, and a CP, while in the others, obstructive respiratory distress or FD were (optionally) included in the features of RS. An average of 80 % of cases expressed FD (range = 47 [53]–100 [17, 35, 45, 51] %). On average, NG-tube feeding was given to 55 % of the infants (range = 11 [41]–100 [35, 45, 54] %), and a gastrostomy in 17 % (range = 2 [24]–43 [43] %). Other feeding interventions described were special oral plates [24, 46, 48] or functional therapy (such as Castillo Morales) [5]. When mentioned, mean duration of NG-tube feeding varied between several weeks [30, 54] and 18 months [50].

Discussion

Feeding difficulties and growth

FD are an important and common symptom in RS, possibly leading to failure to thrive and developmental problems, if not recognized and treated in time [40]. Up to 73 % of infants with a CP have been reported to suffer FD [56]. The current study demonstrated that more FD were seen in infants with RS (91 %) than iCPO (72 %), also after controlling for CP grade (p = 0.005). All RS patients demonstrated a significantly lower growth than iCPO patients during the first 2 years of life irrespective of the treatment regime (p = 0.030) yet remained within the 0 SD (P50) and −1 SD (P16) line (Fig. 2). This finding is in line with other studies that have also demonstrated a lower birth weight in RS patients, compared to healthy individuals and iCPO patients [48, 52, 57, 58]. A hypothesis for the lower growth in RS infants is the presence of morphological characteristics as primary predisposing factors, which is supported by the finding that infants with CP have a tendency towards smaller cranial circumference [55]. Also genetic factors are of interest, especially the role of growth factors that might influence growth retardation in RS [57]. In addition, airway infections during 0–3 months of age negatively affect growth [59]. Finally, arguments for other origins of feeding disorders and subsequent growth retardation in patients with RS exist, such as primary brainstem dysfunction, or neuromotor disabilities, which might be more prevalent in
RS than iCPO patients [17, 40]. Although CP patients have a lower weight than healthy controls [57], they tend to “catch-up” later in childhood [57, 59]. To date, no studies exist that describe growth patterns in patients with RS during a longer period. There is sparse evidence that severe functional feeding and respiratory disorders do not affect long-term developmental outcomes in infants with isolated RS of Stickler [21]. Still, longer follow-up studies of both isolated and non-isolated RS infant are needed to evaluate the cause, a possible catch-up in growth, and the effect of the lower weight on further (cognitive) development.

### Airway interventions

Growth was not affected by the type of airway intervention (conservative vs. surgical, \( p = 0.178 \)); therefore, we hypothesize that adequate relief of airway obstruction is important to maintain adequate growth [60]. This finding is substantiated by similar findings of Daniel et al. [42], in which the degree of adequately treated OSA did not influence growth infants with RS. In the majority (58%) of RS cases of our cohort, airway problems could be managed conservatively. Surgical options were only considered after NPA treatment failed [61]. Until 2006, either TLA or tracheotomy was performed. MDO has become our surgical procedure of preference in a supraglottic airway obstruction since 2006 [31, 61]. NG-tube feeding duration was significantly reduced after MDO treatment compared to the other surgical interventions, which corresponds with the results of others [34]. Lidksy and co-authors [47] show that also timing of surgery (i.e., MDO within 3 months) dramatically reduces the need for feeding interventions in isolated RS patients. Moreover, disappearance of gastroesophageal reflux has been demonstrated after MDO [16]. The positive effect of MDO on feeding capacity and growth has also been confirmed by others [44, 47, 62–64]. Interestingly, the RS infants of our cohort that received a tracheotomy had a significantly higher weight than the MDO or TLA group. This growth difference might result from a disproportionate presence

### Table 3: Baseline characteristics of the patients in the study and control groups treated in the Wilhelmina Children’s Hospital between 1996 and 2012

| Variable                          | Study group (RS) n (%) | Control group (iCPO) n (%) | \( p \) value* |
|-----------------------------------|------------------------|----------------------------|---------------|
| Total number of patients          | 69                     | 64                         |               |
| Sex                               |                        |                            |               |
| Male                              | 32 (46 %)              | 23 (36 %)                  | 0.22          |
| Female                            | 37 (54 %)              | 41 (64 %)                  |               |
| Gestational age                   |                        |                            |               |
| <37 weeks                         | 8 (12 %)               | 7 (11 %)                   | 0.91          |
| \( \geq 37 \) weeks               | 61 (88 %)              | 57 (89 %)                  |               |
| Birth weight (g)                  | Mean = 3217 SD = 669   | Mean = 3302 SD = 556       | 0.44          |
| Grade of CP\(^a\)                |                        |                            |               |
| 1. Submucous cleft or bifid uvula| 3 (4 %)                | 9 (14 %)                   | <0.001        |
| 2. Soft palate only               | 10 (15 %)              | 27 (42 %)                  |               |
| 3. Soft palate and segment of hard palate | 38 (56 %)   | 18 (28 %)                  |               |
| 4. Total palate up to incisive foramen | 17 (25 %)    | 10 (16 %)                  |               |
| Associated disorders              |                        |                            | 0.06          |
| Isolated RS 32 (46 %)             |                        |                            |               |
| Non-isolated RS 37 (54 %)         |                        |                            |               |
| Stickler syndrome                 | 9                      |                            |               |
| Treacher Collins syndrome         | 2                      |                            |               |
| Spondyloepiphyseal dysplasia      | 1                      |                            |               |
| 4q deletion syndrome              | 1                      |                            |               |
| Van der Woude syndrome            | 1                      |                            |               |
| Osteopathia striata with cranial sclerosis | 1              |                            |               |
| Goldberg–Shprintzen syndrome      | 1                      |                            |               |
| Yunis–Varon syndrome              | 1                      |                            |               |
| Auriculo-condylar syndrome        | 1                      |                            |               |
| Hemifacial microsomia             | 1                      |                            |               |
| Other                             | 18                     |                            |               |

\( RS \) Robin sequence, \( iCPO \) isolated cleft palate only, SD standard deviation, CP cleft palate

*\( p \) value < 0.05 was considered statistically significant

*Modified from Jensen et al. cleft palate classification (1988) [34], according to the division made in the Dutch Cleft Registry database
of comorbidities or syndromes in the various surgical subtype groups, differing ages at surgery, or longer NG-tube durations in infants treated with tracheotomy. Also the radical resolution of their obstruction might add to a longer stay under medical control and nutritional support. Data of a recent German review demonstrates that improvement of weight is also possible by the appliance of a pre-epiglottic baton plate (PEBP) in RS infants with severe upper airway obstruction [48, 65]. Treatment with this orthodontic appliance was associated with a higher increase of weight than infants treated with prone positioning or tracheotomy [48]. Moreover, at discharge, a decrease in the proportion of infants requiring NG-tube feeding from 66 to 8 % was seen after PEBP treatment [65]. Although we have no experience with this conservative treatment method, the results of others are very promising and could be considered in an institutional algorithm.

### Associated anomalies

Infants with syndromes, such as in non-isolated RS, often express FD [66]. In the current study, a higher, although nonsignificant, presence of FD and NG-tube feeding frequency was seen in the non-isolated RS patients, compared with the isolated RS group. No significant effect of the presence of an associated disorder or syndrome was illustrated on growth, a finding that is in agreement with

#### Table 4  Association of feeding difficulties and NG-tube feeding between the study and the control groups

| Variable                              | Study group (RS) | Control group (iCPO) | p value* |
|---------------------------------------|------------------|----------------------|----------|
| Total number of patients              | 69               | 64                   |          |
| With feeding difficulties             |                  |                      |          |
| Sex                                   |                  |                      |          |
| Male                                  | 27 (43 %)        | 15 (40 %)            | 0.74     |
| Female                                | 36 (57 %)        | 23 (61 %)            |          |
| Gestational age                       |                  |                      |          |
| <37 weeks                              | 7 (11 %)         | 5 (13 %)             | 0.76     |
| ≥37 weeks                             | 56 (89 %)        | 33 (87 %)            |          |
| Birth weight (g)                      |                  |                      |          |
| Mean                                  | 3237             | 3289                 | 0.68     |
| SD                                    | 644              | 586                  |          |
| Grade of CP                           |                  |                      |          |
| 1. Submucous cleft or bifid uvula    | 2 (3 %)          | 3 (8 %)              | <0.001   |
| 2. Soft palate only                   | 9 (15 %)         | 19 (50 %)            |          |
| 3. Soft palate and segment of hard palate | 37 (60 %)    | 10 (26 %)            |          |
| 4. Total palate up to incisive foramen | 14 (23 %)    | 6 (16 %)             |          |
| Associated disorders                  |                  |                      |          |
| Non-isolated RS                       | 36 (57 %)        | NA                   | NA       |
| Isolated RS                           | 27 (43 %)        |                      |          |
| With NG-tube feeding                  |                  |                      |          |
| NG-tube feeding duration (days)        |                  |                      |          |
| Mean                                  | 59.00            | 9.56                 | <0.001   |
| SD                                    | 33.13            | 9.72                 |          |
| Sex                                   |                  |                      |          |
| Male                                  | 24 (44 %)        | 7 (58 %)             | 0.36     |
| Female                                | 31 (56 %)        | 5 (42 %)             |          |
| Gestational age                       |                  |                      |          |
| <37 weeks                              | 7 (13 %)         | 4 (33 %)             | 0.08     |
| ≥37 weeks                             | 48 (87 %)        | 8 (67 %)             |          |
| Birth weight (g)                      |                  |                      |          |
| Mean                                  | 3217             | 3039                 | 0.41     |
| SD                                    | 661              | 733                  |          |
| Grade of CP                           |                  |                      |          |
| 1. Submucous cleft or bifid uvula    | 1 (2 %)          | 0 (0 %)              | 0.23     |
| 2. Soft palate only                   | 9 (17 %)         | 5 (42 %)             |          |
| 3. Soft palate and segment of hard palate | 32 (59 %)    | 4 (33 %)             |          |
| 4. Total palate up to incisive foramen | 12 (22 %)    | 3 (25 %)             |          |
| Associated disorders                  |                  |                      |          |
| Non-isolated RS                       | 32 (58 %)        | NA                   | NA       |
| Isolated RS                           | 16 (42 %)        |                      |          |

* Due to missing values, the results for certain variables presented in this table do not correspond with the total participants per investigated variable

Robin sequence, iCPO isolated cleft palate only, SD standard deviation, NG-tube nasogastric tube, NA not applicable

*p value < 0.05 was considered statistically significant

| Variable                              | Study group (RS) | Control group (iCPO) | p value* |
|---------------------------------------|------------------|----------------------|----------|
| Total number of patients              | 69               | 64                   |          |
| With feeding difficulties             |                  |                      |          |
| Sex                                   |                  |                      |          |
| Male                                  | 27 (43 %)        | 15 (40 %)            | 0.74     |
| Female                                | 36 (57 %)        | 23 (61 %)            |          |
| Gestational age                       |                  |                      |          |
| <37 weeks                              | 7 (11 %)         | 5 (13 %)             | 0.76     |
| ≥37 weeks                             | 56 (89 %)        | 33 (87 %)            |          |
| Birth weight (g)                      |                  |                      |          |
| Mean                                  | 3237             | 3289                 | 0.68     |
| SD                                    | 644              | 586                  |          |
| Grade of CP                           |                  |                      |          |
| 1. Submucous cleft or bifid uvula    | 2 (3 %)          | 3 (8 %)              | <0.001   |
| 2. Soft palate only                   | 9 (15 %)         | 19 (50 %)            |          |
| 3. Soft palate and segment of hard palate | 37 (60 %)    | 10 (26 %)            |          |
| 4. Total palate up to incisive foramen | 14 (23 %)    | 6 (16 %)             |          |
| Associated disorders                  |                  |                      |          |
| Non-isolated RS                       | 36 (57 %)        | NA                   | NA       |
| Isolated RS                           | 27 (43 %)        |                      |          |
| With NG-tube feeding                  |                  |                      |          |
| NG-tube feeding duration (days)        |                  |                      |          |
| Mean                                  | 59.00            | 9.56                 | <0.001   |
| SD                                    | 33.13            | 9.72                 |          |
| Sex                                   |                  |                      |          |
| Male                                  | 24 (44 %)        | 7 (58 %)             | 0.36     |
| Female                                | 31 (56 %)        | 5 (42 %)             |          |
| Gestational age                       |                  |                      |          |
| <37 weeks                              | 7 (13 %)         | 4 (33 %)             | 0.08     |
| ≥37 weeks                             | 48 (87 %)        | 8 (67 %)             |          |
| Birth weight (g)                      |                  |                      |          |
| Mean                                  | 3217             | 3039                 | 0.41     |
| SD                                    | 661              | 733                  |          |
| Grade of CP                           |                  |                      |          |
| 1. Submucous cleft or bifid uvula    | 1 (2 %)          | 0 (0 %)              | 0.23     |
| 2. Soft palate only                   | 9 (17 %)         | 5 (42 %)             |          |
| 3. Soft palate and segment of hard palate | 32 (59 %)    | 4 (33 %)             |          |
| 4. Total palate up to incisive foramen | 12 (22 %)    | 3 (25 %)             |          |
| Associated disorders                  |                  |                      |          |
| Non-isolated RS                       | 32 (58 %)        | NA                   | NA       |
| Isolated RS                           | 16 (42 %)        |                      |          |

* Modified from Jensen et al. cleft palate classification (1988) [34], according to the division made in the Dutch Cleft Registry database

b Presence of a syndrome or other associated anomalies or chromosomal defects
other studies [24, 42, 52, 67, 68]. In addition, the duration of NG-tube feeding in isolated vs. syndromic RS patients was not different. However, other underlying problems (e.g., neuromotor dysfunction) might persist longer, having a negative effect on feeding capacity despite adequate relief of airway problems [17, 47, 52]. In some studies, a higher rate of gastrostomy placement has been found in syndromic than isolated RS patients [41, 69]. In conclusion, we suggest that infants with a syndromic diagnosis need closer follow-up to monitor growth and feeding capacity [70].

### Analysis and treatment of FD

It is important to distinguish between respiratory-related FD and neuromotor disabilities that affect sucking and swallowing coordination [42, 71, 72]. Although numerous papers mention FD, there is still no scientific agreement about what they exactly encompass [36]. Consequently, these difficulties are regularly manifested in objectified measures, such as weight or the incidence of NG-tube feeding [36]. Also, several symptoms are proposed to confirm the presence of FD, such as dysphagia or gastroesophageal reflux (GER).

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**Table 5** Variable effects on growth measured by weight (in grams) over the nine measured time points

| Variable effects on growth | EMM (g) | SE | 95 % CI (upper bound–lower bound) | p value* |
|---------------------------|--------|----|----------------------------------|---------|
| Time points 1–9 (birth to 24 months of age) | iCPO | 5620 | 96 | 5263–5678 | 0.008 |
| | RS | 5261 | 95 | 5240–5581 | |
| Time points 1–4 (birth to 6 months of age) | iCPO | 3805 | 65 | 3676–3934 | 0.044 |
| | RS | 3619 | 65 | 3471–3746 | |
| Time points 5–9 (9 to 24 months of age) | iCPO | 9833 | 143 | 9551–10,114 | 0.026 |
| | RS | 9390 | 138 | 9119–9661 | |
| Time points 1–9b (birth to 24 months of age) | iCPO | 5588 | 106 | 5380–5796 | 0.030 |
| | RS | 5268 | 112 | 5047–5490 | 5268 |
| Feeding difficultiesc, f | Yes | 6902 | 87 | 6147–6488 | 0.467 |
| | No | 6767 | 192 | 6094–6849 | |
| NG-tube feedingc, f | Yes | 6584 | 189 | –396–346 | 0.893 |
| | No | 6559 | 189 | –346–396 | |
| Grade of CPc, f | 1. Submucous cleft or bifid uvula | 5468 | 237 | 5019–5953 | 0.308 |
| | 2. Soft palate only | 5540 | 130 | 5283–5797 | |
| | 3. Soft palate and segment of hard palate | 5489 | 107 | 5278–5699 | |
| | 4. Total palate up to incisive foramen | 5198 | 146 | 4911–5486 | |
| Associated disordersd, f | Isolated RS | 6479 | 151 | 6181–6777 | 0.517 |
| | Non-isolated RS | 6621 | 154 | 6317–6825 | |
| Intervention typed, f | Surgical | 6902 | 203 | 6504–7301 | 0.052 |
| | Conservative | 6484 | 179 | 6132–6836 | |
| Surgical intervention subtypec, f | MDO | 7965 | 188 | 7587–8344 | 0.007 |
| | TLA | 7720 | 336 | 7049–8391 | |
| | Tr | 8765 | 223 | 8317–9213 | |
| | TLA + Tr | 6423 | 752 | 4920–7927 | |
| | MDO + Tr | 8383 | 412 | 7555–9210 | |

* p value < 0.05 was considered statistically significant

* All measurements were controlled for gender

* Also controlled for grade of CP

* Also controlled for group

* Only analyzed within the RS group

* Presence of a syndrome or other associated anomalies or chromosomal defects

* For time points 1–9 (birth to 24 months of age)
There is no consensus about which investigations should be performed, and their validity is sometimes questionable [75]. We strongly believe it is important to define feeding issues together with parents, feeding therapists, and pediatricians as early as possible. NG-tube feeding should be started when there is insufficient weight gain [14]. In our institution, infants with FD were more likely to receive NG-tube feeding. When NG-tube feeding was adequately started, no differences in growth were seen between infants with reported FD and those without FD. The high frequency of FD in the iCPO group (72 %) contrasting with the low frequency of tube feeding in this group (12 %) is surprising. An explanation might be the parents’ interpretation of the presence of FD, which does not correspond to the criteria of pediatricians to start with NG-tube feeding. This finding might emphasize that the parental concerns need to be addressed and discussed by the medical team during the treatment of an infant with an iCPO. If GER is clinically suspected, a trial of reflux therapy is started, as the incidence of GER is known to be higher in RS [30]. Marquis et al. [76] stress the importance of hypercaloric feeding and demonstrate a quicker improvement in weight gain and relief of respiratory problems, compared with controls. In addition, many authors advise feeding-facilitating techniques, by stimulating the orofacial and tongue musculature and encouraging sucking to improve neuromuscular coordination by introducing small amounts of bottle feeding [5, 30, 54, 77]. Monitoring of urinary sodium has been suggested, as oral sodium supplementation in cases with a low urine sodium significantly improved weight gain in infants with RS [78]. Besides growth, maternal bonding [79], psychological well-being [80], and social and cognitive development [18, 19, 81] can be negatively influenced by FD and need to be monitored during follow-up.

**Strengths and limitations**

The first limitation is the study’s retrospective nature. We did not examine nutritional status by using other anthropometric measurements, such as mid upper arm circumference and skin fold thickness [82, 83]. FD remains difficult to define and in addition to objective information retrieved from medical charts and growth charts we also included subjective information from parents. Consequently, differences in presence and severity of FD amongst the included infants existed and might also have been influenced by recall-bias. Other forms of promising therapy not used in our institution, such as Castillo Morales [5] or palatal plate therapy [45, 65, 84–87], have been described. Moreover, in our clinic, it is uncommon to perform a gastrostomy in children under 1 year of age; hence, we only provide data on usage of NG-tube. Finally, RS is a heterogenic disorder; thus, the distribution of syndromes or associated anomalies might influence the results. Strengths include that this is the first comparative study to report in detail on feeding issues and growth in two large cohorts over a 2-year study period, using weight at nine measuring moments as objective parameters and analyzing the influence of various parameters.
### Table 6  Significant differences between all group interactions

|                          | Conservative | Surgical | p value* | Surgical intervention subtype | MDO | TLA | Tr | TLA + Tr | MDO + Tr | p value* |
|--------------------------|--------------|----------|----------|------------------------------|-----|-----|----|---------|---------|----------|
| **Total number of patients** | 40 (60 %)    | 27 (40 %) |          |                              |     |     |    |         |         |          |
| **Feeding difficulties, yes** | 34 (85 %)    | 27 (100 %) | 0.04     |                              | 14 (100 %) | 3 (100 %) | 7 (100 %) | 1 (100 %) | 2 (100 %) | n.a. |
| **NG-tube feeding, yes** | 28 (63 %)    | 25 (93 %) | 0.03     |                              | 14 (100 %) | 3 (100 %) | 6 (86 %) | 0 (0 %) | 2 (100 %) | 0.006 |
| **NG-tube duration (days)** | Median = 21.0 | Mean = 72.0 | 0.11    |                              | Median = 36.5 | Median = 183.0 | Median = 461.5 | NC | Median = 38.0 | 0.003 |
| **Sex** | Male 18 (45 %) | 12 (44 %) | 0.96     |                              | 6 (43 %) | 1 (33 %) | 3 (43 %) | 0 (0 %) | 2 (100 %) | 0.48 |
|  | Female 22 (55 %) | 15 (56 %) |          |                              | 8 (59 %) | 2 (67 %) | 4 (57 %) | 1 (100 %) | 0 (0 %) | 0.006 |
| **Gestational age** | <37 weeks 5 (13 %) | 2 (7 %) | 0.50     |                              | 0 (0 %) | 0 (0 %) | 1 (14 %) | 1 (100 %) | 0 (0 %) | 0.006 |
|  | ≥37 weeks 35 (88 %) | 25 (93 %) |          |                              | 14 (100 %) | 3 (100 %) | 6 (86 %) | 0 (0 %) | 2 (100 %) | 0.19 |
| **Birth weight (g)** | Mean = 3139 | Mean = 3409 | 0.10    |                              | Median = 3205 | Median = 3785 | Median = 3920 | Median = 2680 | Median = 3287 | 0.19 |
|  | SD = 713 | SD = 521 |          |                              | Mean rank = 12.11 | Mean rank = 16.33 | Mean rank = 19.07 | Mean rank = 2.5 | Mean rank = 11.75 | 0.13 |
| **Grade of CP** | 1. Submucous cleft or bifid uvula 3 (8 %) | 0 (0 %) | 0.45     |                              | 0 (0 %) | 0 (0 %) | 0 (0 %) | 0 (0 %) | 0 (0 %) | 0.089 |
|  | 2. Soft palate only 5 (13 %) | 5 (19 %) | 0.35     |                              | 4 (31 %) | 1 (33 %) | 0 (0 %) | 0 (0 %) | 0 (0 %) | 0 (0 %) |
|  | 3. Soft palate and segment of hard palate 21 (53 %) | 15 (58 %) |          |                              | 5 (39 %) | 2 (67 %) | 7 (100 %) | 0 (0 %) | 1 (50 %) | 0 (0 %) |
|  | 4. Total palate up to incisive foramen 11 (28 %) | 6 (23 %) |          |                              | 4 (31 %) | 0 (0 %) | 0 (0 %) | 1 (100 %) | 1 (50 %) | 0 (0 %) |
| **Associated disorders** | Isolated 21 (53 %) | 11 (41 %) | 0.35     |                              | 4 (29 %) | 0 (0 %) | 4 (57 %) | 1 (100 %) | 2 (100 %) | 0 (0 %) |
|  | Non-isolated 19 (48 %) | 16 (59 %) |          |                              | 10 (71 %) | 3 (100 %) | 3 (43 %) | 0 (0 %) | 0 (0 %) | 0 (0 %) |

*MDO mandibular distraction osteogenesis, TLA tongue lip adhesion, Tr tracheotomy, NG-tube nasogastric tube, SD standard deviation, n.a. not applicable, NC no calculation possible because of too few cases

*p value < 0.05 was considered statistically significant

*a In the surgical intervention subtypes only the postoperative NG-tube duration was included

*b Modified from Jensen et al. cleft palate classification (1988) [34], according to the division made in the Dutch Cleft Registry database

*c Presence of a syndrome or other associated anomalies or chromosomal defects
Conclusion

In this retrospective study, the prevalence of FD was signifi-
cantly higher and NG-tube feeding was more frequent and for
a longer period in infants with RS than iCPO. Growth in the
first 2 years of life was significantly lower in RS than iCPO
infants, although following a steady curve between the 0 and
−1 SD line compared with healthy counterparts. Neither pres-
ence of associated syndromes nor the type of intervention
negatively affected growth, which might be explained by early
recognition and treatment of FD in our cohort. The subtypes
of surgical intervention did reveal a significant effect on
growth, which might be caused by the heterogeneity of the
treated infants. The cause of the lower growth in RS infants
and the long-term effects, despite an apparent good treatment
regime in terms of airway relief and monitoring of the intake,
mandates further investigation. By gaining insight about this
challenging patient group, treatment strategies can be opti-
mized and expectations of caretakers and parents better
managed.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of
interest.

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