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Original Article

Malocclusion and perinatal factors: a retrospective study

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Abstract: Aim: To evaluate the relationship between perinatal risk factors, including use of pro- and antilabordrugs, and development of dental malocclusion. Methods: Forthis retrospective cohort study, 31 patients with malocclusion (test group) and 31 control subjects were recruited.All study participants were children (aged 6-8 years) with deciduous or mixed dentition. The children's mothers responded to a questionnaire regarding their perinatal experiences, which was administered byan interviewer who was blinded to the study aim. Following identification of significantly associated variables by univariate analysis, potentially confounding variables were included in the multivariate analysis of significant variables to account for possible bias. Results: No association between breastfeeding and childhood malocclusion risk was found. Pregnancy less than 9 months appeared to enhance malocclusion risk(odds ratio [OR]: 3.48) despite lack of statistical significance. Use of tocolytic drugs was strongly associated with malocclusion risk (OR: 135, 95% CI: 21.0-872), whereas firstborn delivery exhibited a much weaker association (OR: 3.71, 95% CI: 1.03-13.4). Birth by cesarean delivery (OR: 0.446) and same position of fetus during last two months of pregnancy (OR: 0.225) seemed to be slightly protective against malocclusion risk, although the lack of association was not significant. Conclusion: Risk of childhood malocclusion is very strongly associated withprolonged use of beta tocolyticsduring pregnancy. Our study sheds light on the impact of various perinatal risk factors on occurrence of the fetal stomatognathic alterations that ultimately result in malocclusion during childhood.

Keywords: Malocclusion, drugs, betatocolytics, oxytocin, teeth

Introduction

Malocclusion can be caused by several genetic and environmental factors, but we know relatively little about the role of perinatal factors in the development of malocclusion [1, 2]. Many newborns exhibit an asymmetric shape of the skull defined as plagiocephaly. This anomaly results from pressure that develops *in utero* when the malleable skull is pressed against a tough surface for a prolonged period of time [3-6]. Similarmuscular and positional push and pull forces applied to the craniofacial massifduring the perinatal period may induce the onset of malocclusions. It has been previously shown that compression and strain forces applied to the occipital condyles of the skull during labor and eutocic delivery can lead to the development of several respiratory, neurologic,and behavioralabnormalities in newborns [6]. Some investigators have suggested anassociation between labor and delivery stress and malocclusion [7, 8]. They hypothesize that stress directed to the occipital condyles may induce bilateral dysfunction of the 12th cranial (hypoglossal) nerve, which exits the skull via the hypoglossal canal located in theoccipital condyle. The 12th cranial nerve is the motor nerve for intrinsic and extrinsic tongue muscles [9]. Tongue function disorders, such as atypical swallowing, may be one of the mechanical or functional mechanisms by which labor and delivery stress induces the development of malocclusion [10]. Moreover, asymmetric mechanical forces could induce deviations in malleable craniofacial bones, likely resulting in altered occlusal relationships [1].

Some drugs are administered during the pre- and perinatal period to reduce the odds of spontaneous miscarriage [11] or to reduceor stimulate uterine muscle contractions [12, 13],

Table 1. Perinatal factors included in the univariate analysis

Variable	OR	95% CI
Duration of labor	1.43	0.305-6.70
Delivery complications	0.587	0.180-1.91
Head presentation at birth	1.00	0.227-4.42
Breastfeeding	1.00	0.284-3.53
Weight at birth	0.999	0.998-1.00
Orthopedic disease	1.30	0.477-3.51
Kristeller maneuver	1.63	0.528-5.05
Cesarean delivery	0.446	0.159–1.25
Duration of pregnancy less than 9 months	3.48	0.644-18.8
Adenoid or tonsillar disease	1.54	0.535-4.46
Otitis	1.58	0.532-4.70
Trauma during delivery	1.79	0.390-8.27
Same position of fetus during last 2 months	0.225	0.0237-2.14
Tocolytics	135	21.0-872
Firstborn delivery	3.71	1.03-13.4
Oxytocin	1.54	0.535-4.46
Bad oral habits	1.92	0.699-5.29

depending on the time of labor onset and pathophysiological condition of mother and child.Betatocolyticsare drugs commonly used to avoid preterm delivery by reducinguterine muscle contractions [14]. These drugs act as nonselective beta adrenergic agonists that independently interact with beta receptors 1 and 2. In preterm delivery,beta tocolytics stimulatethe beta 2 receptors in uterine smooth muscles and inhibit their ability to contract. Consequently, these drugscould alterthe biomechanical environment in which the skeletal structures of the child's head and face are sustained. The aim of our work was to characterize the relationship between various perinatal factors, including administration of drugs used to delay (betatocolytics) or induce (oxytocin) labor and delivery, and risk of subsequentmalocclusion in the child.

Materials and methods

Study participants and data collection

This retrospective cohort study was approved by the scientific ethics committee of the Uniersity of L'Aquilain Italy (no. 0018365/12). For our study, we recruited 31 patients with malocclusion (test group) and 31 individuals with normal occlusion (control group). These study participants, all of whom were children aged 6-8 years with deciduous or early mixed dentition, were evaluated in the Department of Periodontics, Dental Clinic of University of L'Aquila, between January and April 2013. Participationin this study was voluntary, and written consent was obtained from the study participants' mothers or their lawyers. Those children who experienced tooth decay, loss of anterior teeth because of trauma, and tooth extractions were excluded from the study. The mothers of the study participants responded to a questionnaire regarding their perinatal experiences, which was administered by an interviewer who was blinded to the aim of the study. Multipleperinatal risk factors, including potentially confounding factors that could influence the development of malocclusions, were addressed in the questionnaire. These variables included application of the Kristeller maneuver during birth [15], duration of labor, characteristics of delivery dynamics such as position of fetusduring last two months of pregnancy, administration of tocolytics during pregnancy, natural or cesarean delivery [16], head-down or feet-down position at birth [17, 18], duration of labor [6, 7], duration of pregnancy less than 9 months [19, 20], delivery complications [21, 22], trauma during delivery [6, 7], weight at birth [23, 24], firstborn delivery, administration of oxytocin during delivery [25], performance and duration of breastfeeding [26-31], onset of otitis [32], orthopedic disease [33-35], bad oral habits [36-39], and adenoid or tonsillar disease [40, 41].

Sample analysis

Evaluation of sample size showed that 31 subjects for each group are required to achieve 90% power, with a two-tailed significance level (α=0.05), in detecting a difference in association with malocclusion risk between 50% and 10% of children in the test and control groups, respectively, who were exposed to beta tocolytics or oxytocin.

Statistical analysis

Univariate analysisof variance was performed to determine which variables wereassociated with malocclusion risk. Variables which did not

Table 2. Results of the multivariate analysis

Variable	OR	95% CI
Firstborn delivery	4.14	0.429-39.9
Tocolytics	145	19.9-1059
Bad oral habits	1.66	0.245-11.2

show any statistically significant association were not further analyzed, while those that showed such an association were subjected to subsequent multivariate analysis. Potential confounding variables that showed an elevatedassociation regardless of the significance level were also included in the multivariate analysis to account for possible bias. Data are presented as odds ratios (ORs), with 95% confidence intervals (CIs).

Results

Results of the univariate analysis are reported in **Table 1**. Noassociation with malocclusion risk was found forduration of labor, delivery complications, head presentation at birth, breastfeeding, weight at birth, ororthopedic disease during intrauterine growth. Other variables, including application of Kristeller maneuver at birth, adenoid or tonsillar disease, onset of otitis, and physical trauma during deliveryshowed minimal association butdid not significantly enhance the odds of developing malocclusion. Although pregnancy duration less than 9 monthsseemed to be associated with malocclusion risk (OR: 3.48), the association was not significant. However, only a few of the 62 children in our cohort were born prematurely.

Oxytocin use during pregnancy also appeared to enhance the riskof developing malocclusion, although the association was not statistically significant. Tocolytic drug use during pregnancy exhibited a very strong association with malocclusion risk (OR: 135, 95% CI: 21.0-872), whilefirstborn delivery showed a much weaker association (OR: 3.71, 95% CI: 1.03-13.4). In contrast, birth by cesarean delivery (OR: 0.446) and same position of fetus during last two months of pregnancy (OR: 0.225) seemed to be slightly protective against malocclusion risk, although the lack of association was not significant for either variable. Among the potentially confounding variables, bad oral habits in the first years of life appeared to enhance the risk of developing malocclusion (OR: 1.92); however, the association was not significant. Inclusion of this variable along with the two aforementioned significantly associated variables in the multivariate analysis (**Table 2**) revealed a very strong association with malocclusion riskfor only tocolyticdrugs (OR: 145, 95% CI: 19.9-10-59).

Discussion

In the present study, we analyzed the odds of developing malocclusion given a wide variety of perinatal risk factors. Based on the univariate analysis, we focused our attention on betatocolyticuse during pregnancyto determine whether an association exists between this variable and increased odds of malocclusionin the presence of other risk or potentially confounding factors. The results from the multivariate analysis showed ahighly significant association between beta tocolytic drug use and malocclusion risk in our cohort that was independent from other causes. This is a novel risk factor for malocclusion that, to our knowledge, has not been previously reported.

The most commontocolytic agent that was used to treat preterm labor during the pregnancies of children evaluated in our study was Vasosuprina, the active ingredient of which is isoxsuprine hydrochloride [12]. To successfully delay delivery, Vasosuprinaand other tocolytic agents need to be administered only a few times and for a duration of no more than 48 hours [42]. This time delay allows the patient to reach a hospital with a suitable neonatal intensivecare unit [43, 44] and allows the obstetrician to improve the perinatal situation by enhancing fetal lung maturation with corticosteroids before birth [45, 46]. Among our entire cohort, Vasosuprinawas sometimes administered for inappropriately long periods, and most of the malocclusions in the test group were associated with prolonged administration of Vasosuprina during pregnancy. The current guidelinesof The National Institute of Clinical Excellence (NICE) advise against tocolytic therapy for more than 48 hours, because therapy extended beyond this period does not further improve perinatal outcomes [12, 47]. Moreover, the efficacy of oral tocolytic agents as a maintenance therapy after an acute event has not been demonstrated [48], while evidence shows that almost 30% of preterm delivery threats spontaneously resolve [49] and 50% of hospitalized women with such threats ultimately give birth at term [50].

Prolonged use of tocolytic drugs will result in continuous stimulation of beta 2 receptors in uterine smooth muscle. Such persistent stimulation of these receptors may directly alter the muscle tone. This change in muscle tone may, in turn, inhibit the uterus from protecting the head of the fetus. Without this cushioning effect, the head may become be pressed against the mother'spelvic or lower back bones, resulting in disordered skull growth. This alteration in biomechanical dynamics may induce aberrant neuromuscular patterns, which may lead to functional impairment of the stomatognathic-systemand ultimate development of malocclusion [2, 51, 52]. Because beta tocolyticsnon selectively stimulate beta adrenergic receptors located in many other tissues and organ systems [44], prolonged use of these drugs may promote the development of malocclusion by indirect mechanisms of action, such as altering maternal-fetal metabolism or disrupting normal development of other functionally related structures [53-55]. Studies have shown that Vasosuprinacan cause a wide variety of side effects, such as impaired glucose tolerance, pulmonary edema, palpitations, tremor, hemicraniacontinua, rash, nausea, high transaminase levels, paralytic ileus, hypocalcemia, fetal tachycardia, and, in prenatally exposed children, learning difficulties at school [56, 57].

The results of our study must be interpreted in light of some limitations. The data used in our analyses were obtained from retrospective questionnaires administered to the children's mothers, who might not have correctly remembered all the details relating to their pregnancy and delivery (recall bias). Analysis of some variables, such as duration of pregnancy less than 9 months, revealed moderately increased ORs but no significant association. It is possible that the number of premature births in our cohort was too low to detect a true association. Hence, analysis of a larger sample size is warranted to determine whether premature delivery and other perinatal variables can truly increase the odds of developing malocclusion in our population.

Conclusion

Our results showfor the first time that the use of beta tocolytic drugs such as Vasosuprinafor more than 48 hours during pregnancy is strongly associated with increased risk of malocclusion in childhood. In contrast, labor inducing drugs such as oxytocin do not significantly affect malocclusion risk. Our study supports the NICE guidelinesof limiting the duration of tocolytic therapy. Further studies with larger sample sizes are needed to establish the impact of apparently associated perinatal factors on childhood malocclusion risk.

Disclosure of conflict of interest

None.

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