

Fetal yawning assessed by 3D and 4D sonography

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Abstract

The capacity of four-dimensional sonography to evaluate complex facial expressions allows recognition of a common behavior, yawning. Although there has been remarkably little interest in yawning in research and medical practice, even though it is an everyday phenomenon, we submit an original interpretation on the basis of knowledge derived from phylogeny and ontogeny. As a flip-flop switch, the reciprocal interactions between sleep- and wake-promoting brain regions allow the emergence of distinct states of arousal. By its ontogenical links with REM sleep, yawning appears as a behavior which procures an arousal reinforcement through the powerful stretch and the neuromuscular rewiring induced. Yawning indicates a harmonious progress in the development of both the brainstem and the peripheral neuromuscular function, testifying to the induction of an ultradian rhythm of vigilance. The lack of fetal yawn, frequently associated with lack of swallowing, associated or not with retrognathia, may be a key to predict a brainstem's dysfunction after birth.

Keywords: *Arousal, fetal behavior, four-dimensional ultrasound, sleep, yawning*

Introduction

The use of ultrasound examinations during pregnancy allows a type of fetal behavior, yawning, to be observed on a daily basis. Few data have been published in the last 25 years on yawning, thus prompting researchers to state “yawning is a universally well known, but poorly understood” [1] and “a rudimentary reflex, appears to have at best an obscure purpose, if any” [2]. Although there has been remarkably little interest in yawning in research, even though it is an everyday phenomenon, we will discuss the meaning of this behavior and how its characterization can enhance ultrasound investigation. As a foreword, it should be noted that human research on prenatal programming of behavior is intrinsically correlational, never manipulatively experimental, and frequently based upon homologies with other vertebrates.

A popular saying states that “the organ generates the function”. However, it is known in embryology that body movement in a fetus is required for maturation of the motor function and is involved in the development of other organs such as the lung. On the other hand, body movement indicates a harmonious progress in the development of both the central motor system and the peripheral neuromuscular function [3].

All the movements that a newborn is able to produce originate during the fetal life and are

performed throughout the life of the individual. Behaviour observed in utero, including breathing, yawning, and others, serves as a continuum to the activity shown in a newborn infant and undergoes a neuromuscular rewiring [4]. The onset and developmental course of fetal motility have been studied since the introduction of ultrasound technology. Four-dimensional ultrasonography (4D-US) provides a tool for movement observations not only for their differentiation but also to categorize specific patterns of behavior. The evaluation of facial expressions was previously impossible using real-time two-dimensional ultrasonography. The capacity of 4D-US to evaluate complex facial expressions helps to identify a common behavior, yawning [5,6].

What yawning is not

Provine and Tate [7] found no support for the popular hypothesis that yawning is a response to elevated CO₂ or depressed O₂ levels in the blood. Subjects breathing pure oxygen did not show a decreased amount of yawning. Studies on fetal yawning (like a fish yawn in water) in amniotic fluid do not make any association between oxygenation capacity and yawning. Yawning occurs frequently when a fish is interrupted in feeding, for example by the approach of a female and before courtship is

initiated. This behavior does not need any particular level of oxygenation.

Atelectasis, the collapse of alveoli, results from alveolar hypoventilation of air. The normal respiratory pattern of spontaneously breathing adults includes periodic sighs or deep breaths (also a type of yawning) that prevent atelectasis by producing alveolar surfactants. But yawning confers no protection against atelectasis in a fluid-filled lung of a fetus which produces surfactant at the time of first breath after birth [8].

How to recognize a yawn

A yawn is a paroxysmic cycle characterized by a standard cascade of movements over a 5–10 s period:

- ample, slow, and very deep inspiration, mouth wide open (Figure 1); in human adults, the expansion of the pharynx can quadruple its at-rest diameter, while the larynx opens up with maximal abduction of the vocal cords;
- a brief interruption, the acme state, often with accompanying limb and neck stretching;
- a rapid passive expiration [9].

4D-US helps to identify this typical development: the fetal mouth, previously closed, opens widely for 4–6 s with simultaneous retraction of the tongue, followed by rapid closure, and mostly combined with retroflexion of the head and sometimes elevation of the arms (pandiculation) (Figure 2). This harmonious sequence is markedly different to a brief

swallowing episode [10]. Using a color Doppler technique, it is possible to observe the flow of amniotic fluid through the fetal mouth, oropharynx, pharynx, and trachea to the lungs. This movement pattern is non-repetitive in the fetus, in contrast with that in adults [11].

Yawning is not just a matter of opening one's mouth, but a generalized stretching of muscles, those of the respiratory tract (diaphragm, intercostal), face, and neck (Figure 3). This association of complex and synergic movements is a very stereotypical behavior that can be classified as a reflex due to its involuntary occurrence. The reflex arc is thought to be in the hypothalamus, the reticular system in the brainstem, and it involves the respiratory neurons in the medulla, the motor nuclei of the 5th, 7th, 9th, 10th, and 12th cranial nerves, the phrenic nerves (C1–C4), and the motor supply to the intercostal muscles. Also, it can be inferred that yawning is a part of the generalized stretch that generally accompanies the yawn [9].

Embryology and mechanisms

In 1973, T. Dobzhansky remarked: “nothing in biology makes sense except in the light of evolution” [12], and Ernst Haeckel (1834–1919) stated “ontogenesis is a brief and rapid recapitulation of phylogenesis, determined by the physiological functions of heredity (generation) and adaptation (maintenance)” [13]. The exactitude of these quotations is illustrated by yawning. Indeed, the ultrasound investigation specifies is ontogenesis precociousness between 12 and 15 weeks of gestation (Figure 4) [4]. Indeed,

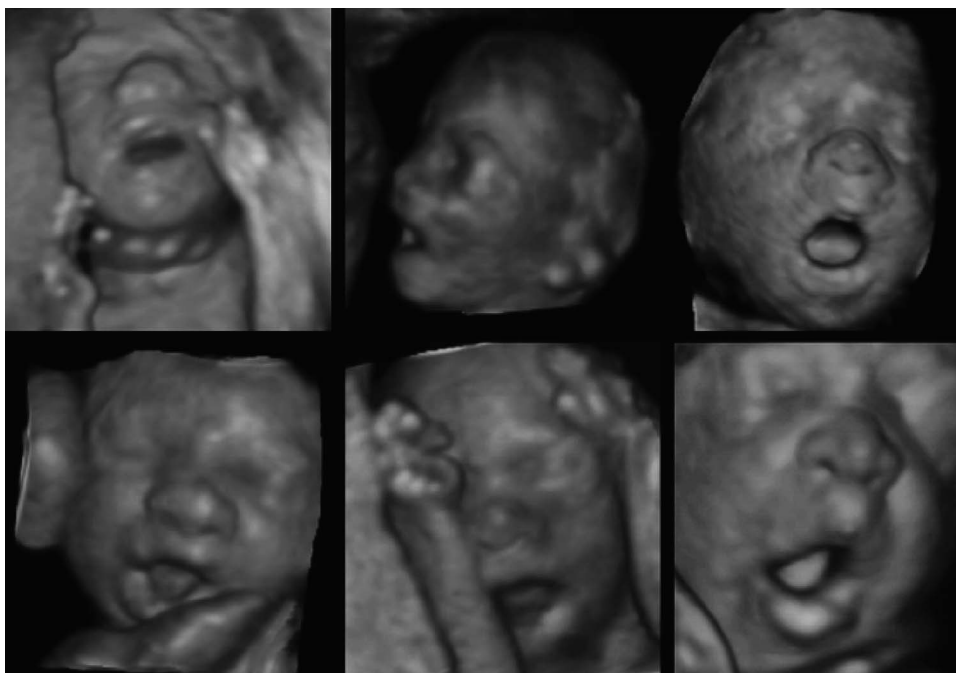


Figure 1. 3D US serial imaging demonstrating fetal yawning during the second to third trimester. Note the generalized stretching of muscles in the face and neck.

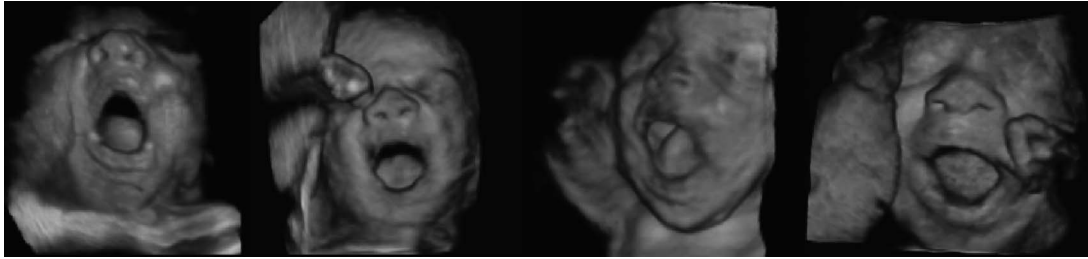


Figure 2. 3D US serial imaging showing an ample, slow, and very deep inspiration, with the mouth wide open in fetal yawning.

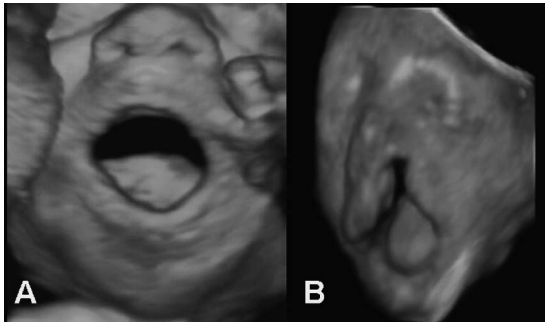


Figure 3. Visualization of all facial muscles in yawning expression, leading to multiple expressions in no particular order. The expansion of the pharynx can quadruple its at-rest diameter, while the larynx opens up with maximal abduction of the vocal cords. Note the differences between fetal yawning in (A) a normal fetus and (B) a fetus with a cleft-lip anomaly.

yawning is also a phylogenetically old, stereotypical event that occurs in reptiles, fish, birds, and mammals. Its survival without evolutionary variations postulates a particular importance in terms of developmental needs [9]. The strong muscular contraction that signifies a yawn is metabolically expensive. If we accord with the terms of Darwin's evolutionary propositions, the costs of brain activity must be outweighed by the advantages gained in terms of developmental fitness. Thus, a structural hypothesis suggests activation in the synthesis of neurotrophins, which lead to a cascade of both new synapse formation or recruitment, and activation through the diencephalon, brainstem, and spinal cord. The phenomenon of activity-dependent development has been clearly shown to be one mechanism by which early sensory or motor experience can affect the course of neural development.

Activity-dependent development may be a ubiquitous process in brain maturation in which activity in one brain region can influence the developmental course of other regions [14]. The ability to initiate motor behavior generated centrally and linked to arousal and respiratory function is a property of the brainstem reticular formation, which has been remarkably conserved during the phylogeny of vertebrates including agnathans, fishes, amphibians, reptiles, and birds. Therefore, conservative developmental mechanisms orchestrating the organogenesis of the brainstem in all vertebrates are probably crucial for arousal and breathing [15].

A wealth of data have accumulated on genes that are expressed in the embryo and govern the hindbrain segmentation. Hox homeobox genes form four conserved clusters encoding transcription factors that orchestrate ontogenesis along the rostro-caudal axis of the body, including hindbrain segmentation and limb formation [16]. This might explain craniofacial congenital developmental abnormalities that ultrasound investigation helps to reveal; hence, "the face predicts the brain".

The facial bone structure and the brain differentiate from a common embryonic structure, the ectoblast. The cephalic pole comprises an original embryological encephalo-facial and encephalo-cervical segmentation with a strict topographical correspondence: the naso-frontal and premaxillary structures are joined to the forebrain; and the maxillo-mandibular and anterior cervical structures are joined to the brainstem and its nerves. At the beginning of the third month, the embryo becomes a fetus with the occurrence of the first oral and pharyngeal motor sequences under the control of the neurological development of the brainstem, development of the suction-deglutition, and yawning activity (Figure 4). Therefore, suction and yawning have the same embryological origin, thus demonstrating the importance of the brainstem in the neurophysiological development of the oropharyngeal activity coordinated with the respiratory, cardiac, and digestive regulations which have the same neuroanatomical localization. Its occurrence marks the developmental stage when the brainstem is already individualized and the pituitary gland has become functional, whereas the extension of the temporal and frontal neocortex takes up to 22–24 weeks to reach completion [17,18].

Movements of the tongue or jaws assist the development of the palate by promoting the horizontal elevation of vertically orientated palatal shelves (Figure 3). Activity of the neck and tongue muscles is always accompanied by mouth-tongue movement [19]. The relationship between the neural network of mouth-tongue movement and respiratory activities is not perfectly understood. It seems that information about central respiratory and locomotor rhythms that is necessary for cerebellar control of the coordination between respiration and locomotion converges at the level of the lateral reticular nucleus [20].

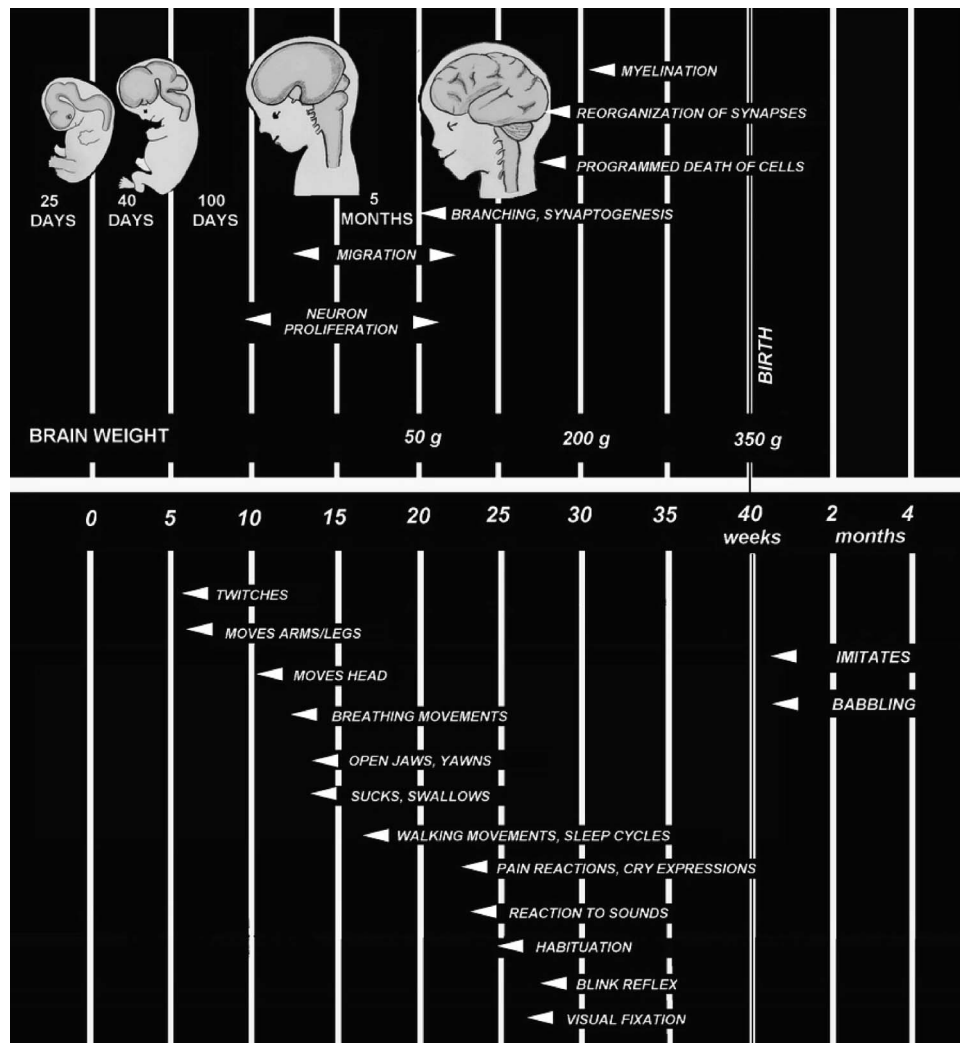


Figure 4. Development of brain and fetal CNS: Change in size and appearance from an early premature structure into a late mature structure. Note also the chronology of the functional development of the fetal movement.

Yawning is under the control of several neurotransmitters and neuropeptides at the central level. The paraventricular nucleus of the hypothalamus is the hypothalamic center, which adapts and coordinates hormonal and autonomic responses for the appropriate behavior, and controls yawning. Oxytocinergic neurons are stimulated by dopamine, excitatory amino acids, acetylcholine, serotonin, nitric oxide, and adrenocorticotrophic hormone-related peptides (all implicated in arousal), while opioid peptides inhibit this behavior. They project to the hippocampus, and the reticular formation of the brainstem, which play a key role in the expression of this behavioral event. Other neurotransmitters, i.e., noradrenaline and neuropeptides, hypocretin and sexual hormones, influence this behavioral response [21].

Why yawning shares a link with arousal

The phylogenetic appearance of sleep proposes that the nocturnal resting in poikilotherms most probably manifests in mammals as a form of rapid eye movement (REM) sleep or paradoxical sleep, which

is characterized by peripheral muscular atonia originating in the dorsal part of the brainstem, rostral to the pons [22].

Based on numerous studies of fetuses and infants in a variety of mammalian species, it is widely believed that the earliest form of sleep is properly characterized as active sleep, that is an immature form of REM sleep and preponderant at birth. Accordingly, it is thought that quiet sleep, an immature form of slow-wave sleep (SWS), emerges as REM sleep's predominance diminishes during ontogeny [23].

In the early intra-uterine life, a diffuse collection of phasic and cyclic motor events occur that gradually coalesce. For the fetus, sleep and wakefulness are reliably characterized, respectively, by periods of myoclonic twitching expressed against a background of muscle atonia and high-amplitude behaviors (e.g., locomotion or stretching–yawning) expressed against a background of high muscle tone. Movements of the limbs, such as stretching, yawning, and kicking, are typically considered to indicate periods of wakefulness. Periods of twitching are almost always followed

by the abrupt onset of high-amplitude awake behaviors, thus completing the cycle. Although myoclonic twitching during active sleep in infants is more prevalent and more intense than that seen during REM sleep in adults, its similarities to the adult behavior and its linkage to periods of atonia suggest developmental continuity between the infant and adult sleep states. The maturation of the central nervous system, based on myelination, starts in the spinal cord and then proceeds to the brainstem and forebrain. Thus, paradoxical sleep mechanisms located in the brainstem are the first to mature and the only ones to function. Then, the slow-wave sleep and waking structures become mature. Namely, the widespread control of neuronal activity exerted by specific REM sleep processes help to direct brain maturation through activity-dependent developmental mechanisms. It may be inferred that REM sleep (and possibly yawning) directs the course of brain maturation in early life through the control of neural activity [24].

Behavioral pattern continuity from prenatal to post-natal life shows a strict parallelism between the ontogeny of REM sleep and yawning (Figures 5 and 6) [6]. Basically, REM sleep in the human declines from 50% of total sleep time (8 h) and a frequency of 30–50 yawns per day, in the newborn, to 15% of total sleep time (1 h) and less than 20 yawns per day, in the adult. This decrease takes place mainly between birth and the end of puberty [25].

The emergence of distinct states is followed by dramatic changes in the amounts, duration, and cyclicity. An ultradian rhythm may be graded; in a period from 50 to 60 minutes appears an alternation of moment characterized by motor activity and by rest, as in newborns. Each period of rest switches over a period of activity by a yawn. Thus a periodicity of one or two yawns per hour can be noticed [4]. Yawning appears 2 weeks before any discernible sleep–wake states, and its expression gradually becomes linked. No changes in the incidence of yawns between 20 and 36 weeks of gestational age

have been observed by Roodenburg and colleagues [26] in the fetus. In full-term infants, yawns are frequently observed on the first day of life. The embryo and fetus are exposed to 24 h periodicity with the mother's parameters of the circadian cycle, which may play a role in the normal development of the fetal pacemaker. There are no data available for how a fetal's yawn links up fetal rhythm with maternal rhythm.

Saper and coworkers [27] propose a model for reciprocal interactions between sleep- and wake-promoting brain regions, which produces a flip-flop switch. This model could explain the rapid transitions from awaking in sleep and from REM sleep to waking. From a survival point of view, it is necessary to ensure that there is a period of sleep for body repair to take place but also for the individual to have the capacity to flee a predator (arousal). The transition is controlled by integrative autonomic structures that encompass regulated changes occurring in anticipation of the event. Yawning (a stretch syndrome) can be seen as a behavior, a testifier of this switch/transition, like a reinforcement of muscle tone. Waking is controlled by some four different and redundant circuits mainly located in the reticular formation of the pons (adrenergic), the peduncle (dopaminergic), the hypothalamus (histaminergic), and the Meynert basifrontal region (cholinergic). The permissive networks controlling waking must be tonically reinforced by the hypocretin's system originating from the lateral hypothalamus. Next, neuronal activation of the ventrolateral preoptic nucleus (VLPO) is correlated with the amount of sleep. The powerful muscular contraction caused by yawning releases arousal by activation of the reticular-formation (locus coeruleus) to which the cranial nerves send retro-projections. At awakening, the yawning and stretching reverse the muscular atonia which characterize REM sleep. On the other hand, when the pressure to sleep increases, it is thought that the firing of the GABA and galanin VLPO's neurons reduce the muscular tone of antigravitational muscles, notably those of the neck and masseters. Thus, yawning seems to be averse to this pressure. F. Giganti and coworkers observed yawning in premature infants in all behavioral states, except during quiet sleep, and viewed it as a transitional state, suggesting a spreading activation of facial motor patterning. Thus, yawning may be seen as a nervous reflex loop which occurs as arousal reinforcement [28–30].

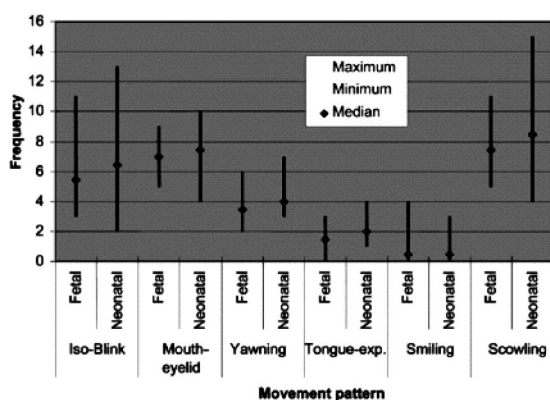


Figure 5. Comparison between the frequency of facial expression of fetuses in the third trimester and neonates. Note the frequency of fetal yawning measured in 30 min. Thick line: median; boxes: 25–75% quartiles; bars: minimum–maximum. Adapted from [6].

Yawning or not: A pathology?

Yawning occurs with a regular recurrence, about once or twice per hour. When a yawn is observed during a 4D-US examination, it is obviously by chance or after a very long investigation (Figure 6). Yawning appears preferentially after a period of rest and indicates awakening. If normal swallowing is seen (much more frequent), the search for yawning



Figure 6. (A) Fetal yawning demonstrated in utero using 4D ultrasound similar to the neonatal period (B). Yawning is a stereotypical behavior characterized by a standard cascade of movements over a 5–10 s period. Yawning is parallel to a reflex accompanied by the relaxation of all participating muscles. The mouth closes shut, and the larynx returns to its normal position.

seems to be of no additional interest for the indication of harmonious brainstem maturation. Conversely, the lack of, or dysfunction in, swallowing requires time to appreciate the collection of phasic and cyclic motor events that characterizes the ultradian fetal rhythm and thus increase the opportunity to notice a yawn. If the ultrasound examination suggests the absence of yawn and deglutition, it is imperative to search for mandibular hypoplasia and glossoptosis often associated with cleft palate.

Petrikovsky and coworkers reported that clusters of yawning activity were observed in a series of anemic fetuses and proposed that yawning repetitiveness helps to track fetal anemia [31].

Diseases for which there are no data

Infants must develop safe and effective respiration and oral feeding skills soon after birth if they are to survive. For this to occur, infants must have the necessary anatomic structures and adequate central control to coordinate swallowing, ventilation, sleep, and arousal. Yawning is associated with all of these behaviors [9]. Although no data is actually collected,

we have built a non-exhaustive inventory of congenital pathologies in which the research of yawning has an interest.

Congenital central hypoventilation syndrome (CCHS), also known as Ondine's curse, after a character from Germanic mythology, results in hypoventilation, most pronounced during sleep, with relative insensitivity to hypercarbia and even less insensitivity to hypoxia, in the absence of other abnormalities of the cardiorespiratory system. CCHS can be associated with Hirschsprung's disease. Abnormality of swallowing or esophageal motility has been identified in a newborn with facial dysmorphism and hypotonia. This suggests a generalized abnormality of gastrointestinal motility and brainstem function [32].

Mandibular hypoplasia is a frequently encountered craniofacial difference and can be classified into congenital and developmental:

- Mandibulofacial dysostosis with a variety of limb abnormalities.
- The Pierre Robin sequence characterized by a posterior U-shaped cleft palate, retrognathia and

glossoptosis. Several arguments favor an embryonic origin consisting of an anomaly in the caudal hind-brain development. Feeding disorders are the most important functional symptom. Testimonies from mothers seem to agree with the lack of yawning at birth and a parallel progress during the first year of life in swallowing and yawning. Also, Pierre Robin syndrome can be seen as prenatal brainstem dysfunction responsible for the oro-facial maldevelopment which can be diagnosed at 23 weeks' gestation during a 4D-US examination [33,34].

- Any syndrome (primary bilateral or unilateral growth anomalies) associated or not with temporo/mandibular joint ankylosis, aglossia/microglossia: Francheschetti syndrome, Goldenhar syndrome, and Richner-Hanhart syndrome.

The Moebius syndrome is characterized by congenital facial diplegia and bilateral abducens nerve palsies by degenerative and involved nuclei of the VI, VII, and XII nerves. Simultaneous occurrence of limb malformations with cranial nerve dysfunction suggests a disruption of normal morphogenesis during a critical period in the development of the embryonic brainstem, most likely from 4 to 7 weeks of gestation. Instances of bilateral paresis of the soft palate and scattered instances of dysphagia (some of which resolve in infancy) have been reported. An inability to close the mouth is the norm [35].

Watershed infarcts in the fetal and neonatal brainstem are clinically expressed as multiple cranial neuropathies, failure of central respiratory drive, dysphagia [36].

Goldenhar Syndrome includes malformations primarily involving the jaw, mouth, and ears, and, in most cases, affect one side of the body. This represents defects in the embryonic first and second brachial arches, the first pharyngeal pouch and brachial cleft, and the primordia of the temporal bone [37].

Joubert syndrome is a rare, genetic disorder characterized by an absence or underdevelopment of the cerebellar vermis and a malformed brainstem. The most common features include ataxia, an abnormal breathing pattern, sleep apnea, abnormal eye and tongue movements, and hypotonia.

It is possible to complete this catalog by referring congenital trismus, Crisponi syndrome, Stüve-Wiedemann syndrome.

Conclusion

With significant advances in image quality, resolution of ultrasound, and now 3D and 4D technology, the use of ultrasound examination during pregnancy is a step forward from anatomical examination to functional evaluation. Recognition of fetal yawning aids to testify of the harmonious progress of brainstem maturation and to understand the neural underpinnings of sleep and arousal systems. An abnormality

yawn's occurrence fosters an intensive research of anemic fetuses (frequency amplified) or brainstem dysfunction with or without mandibular hypoplasia (frequency sparse or null). We hope and expect that upcoming researches will complete the data currently available.

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