

# The relationship between prenatal testosterone and developmental stuttering in boys

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Stuttering is a multi-factorial speech disorder characterized by various dysfluencies in the beginning and/or smooth flow of speech. Its incidence is about 1% in the general population, with 80% of stuttering cases seen in children aged three to eight years. The etiology of developmental stuttering has not been precisely explained. Several researchers report that neurological factors, especially atypical lateralization of the speech and language processes, play an important role in the etiology of stuttering. Various hypotheses suggest that prenatal testosterone causes atypical hemispheric lateralization. The aim of this study was to investigate the role of prenatal testosterone in the etiology of developmental stuttering by the use of the ratio of second- and fourth-digit lengths (2D:4D).

Totally 133 boys (49 boys who stutter and 84 boys who do not stutter) were included in the study. The age range of children participating in the study was determined as 2–12 years. In the comparative evaluation conducted between the stuttering group and the control group in terms of their right 2D:4D and left 2D:4D ratios, it was found that the left 2D:4D ratio of the patients was significantly higher than that of the control group.

We are of the opinion that prenatal testosterone may play a role in the etiology of developmental stuttering. The present study is the first study in the literature to reveal a relationship between prenatal testosterone and developmental stuttering.

*Key words:* stuttering, testosterone, childhood, boys, callosal hypothesis.

Stuttering is a multi-factorial speech disorder characterized by the repetition of sounds, syllables, and words resulting in the prolongation or blocking of sounds or syllables at the beginning of speech or interrupting its smooth flow.<sup>1</sup> Its incidence is about 1% in the general population with 80% of stuttering occurring in children aged three to eight years. The incidence of stuttering in preschool and school-age children is about 4%.<sup>1,2</sup> Stuttering is more common in males than in females in all age groups.<sup>3</sup> It is not known why stuttering is more common in males; however, it is thought that this may be associated with prenatal testosterone levels.<sup>4,5</sup>

Even though the etiology of developmental

stuttering, the most frequent type, has not yet been elucidated, it has been associated with various factors such as atypical neurophysiology, a motor dysfunction in speech, cognitive processing abilities, genetics and environmental impacts.<sup>6,7</sup> Several researchers state that neurological factors play an important role in the etiology of stuttering.<sup>8</sup> Numerous studies reported in the literature support a relationship between stuttering and atypical cerebral lateralization.<sup>7</sup> Variations in hemispheric lateralization are thought to be associated with varying prenatal testosterone exposure. The Geschwind Behan Galaburda (GBG) hypothesis<sup>9,10</sup> and the callosal hypothesis<sup>11,12</sup> suggest that among

the androgens, prenatal testosterone causes atypical cerebral lateralization and this atypical cerebral lateralization may result in problems related to language development and skills.<sup>13</sup>

The aim of this study was to examine the relationship between prenatal testosterone and developmental stuttering in boys. With stuttering considered to be a speech disorder occurring largely in the three to eight years' age range, the question of how to evaluate prenatal testosterone during the postnatal period in order to examine the relationship between stuttering and prenatal testosterone, presents a challenge.

It has been suggested that from the late first trimester, the ratio of the length of the 2<sup>nd</sup> digit (index finger) to the 4<sup>th</sup> digit (ring finger) (2D:4D) has a negative correlation with prenatal testosterone levels and a positive correlation with prenatal estrogen levels.<sup>14</sup> Studies on rats have revealed that prenatal testosterone elevated by genetic and hormonal manipulation will stimulate the growth of the fourth fetal phalanx.<sup>15,16</sup> Additionally, growth of the adrenal gland has been found to increase prenatal androgen levels and cause a low 2D:4D ratio in children with congenital adrenal hyperplasia.<sup>17</sup> 2D:4D ratio has been used to evaluate the correlation between prenatal exposure to testosterone and some neurodevelopmental conditions such as autism.<sup>18,19</sup> Within the literature covering this topic, it can be suggested that the 2D:4D ratio is a marker for testosterone exposure in the prenatal period. In the present study, the right and left hand 2D:4D ratios were compared between boys who stutter and boys who do not stutter.

In considering the possible effects of prenatal testosterone on hemispheric lateralization and the possibility that atypical hemispheric lateralization plays an important role in the etiology of developmental stuttering, the hypothesis of this study was that prenatal testosterone plays a role in the etiology of developmental stuttering. In the literature, we found only two studies that investigated the relationship between prenatal testosterone and stuttering. The first study, by Montag et al.<sup>20</sup>, was conducted with adults and there was no significant relationship between prenatal testosterone (2D:4D) and stuttering. The second study, by Mohammadi et al.<sup>21</sup>, was

conducted with children. Also there was no significant relationship between prenatal testosterone (2D:4D) and stuttering. The current study was conducted with child patients as childhood is the period when stuttering most frequently occurs, therefore this study is considered to be the second in the literature.

## Material and Methods

### Population

This cross-sectional study was conducted in the child psychiatry clinics of Inonu University and Necmettin Erbakan University Medical Faculty Hospital. Approval for the study was obtained from the Malatya Clinical Trials Ethics Committee (Ethics Committee decision number: 2015/93, date Jun 17, 2015). The aim and methods of the research were explained in detail to the boys and their families, and after signing consent forms they were included in the study. In total, 133 boys (49 boys who stutter and 84 boys who do not stutter) were included. The age range of children participating in the study was determined as 2–12 years. The stuttering group consisted of boys who had applied to the child psychiatry clinics due to problems with stuttering and who were subsequently diagnosed with developmental stuttering. The control group consisted of completely healthy boys. Stuttering is more common in males than in females and gender was thought to be a confounding factor, so only boys were included in the study. In both groups, individuals with a family history of stuttering were not included in the study in order to prevent genetic factors from affecting the outcome of the study. Additionally, individuals with mental retardation, neurological disease or comorbid chronic disease, a history of head or hand trauma were not included.

### Evaluation and measurements

Diagnosis of developmental stuttering was established by child psychiatrists based on diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IVTR).<sup>22</sup> Duration and severity of stuttering of individuals with stuttering were evaluated. Clinical Global Impression-Severity Scale (CGI-S) was used in the evaluation of severity of stuttering. CGI-S is a 7-point single-item scale (0=no evaluation; 1=normal, no illnesses; 2=borderline; 3=mild;

**Table I.** The Duration of Stuttering and the Severity of Stuttering of Individuals with Stuttering (N=49).

Duration of stuttering	N (%)
0-6 months	7 (14.3)
7-12 months	7 (14.3)
13-24 months	6 (12.2)
25-36 months	6 (12.2)
>36 months	23 (46.9)
Severity of stuttering	3.511.44± (range: 1-7)

Clinical Global Impression-Severity Scale (CGI-S) was used to evaluate the severity of stuttering.

4=moderate; 5=prominent; 6=severe; 7=most severe), used by investigators in order to record either illness severity.<sup>23</sup>

The lengths of the 2<sup>nd</sup> and 4<sup>th</sup> digits of both hands were measured from the ventral proximal line. Measurements were performed by the authors (Dönmez YE and Bilgiç A) using a digital vernier caliper with 0.01 mm precision. The ratio of the 2<sup>nd</sup> digit to the 4<sup>th</sup> digit in both hands was calculated as right 2D:4D and left 2D:4D. The stuttering group and the control group were compared in terms of right and left 2D:4D.

**Statistical analysis**

The Statistical Package for the Social Sciences (SPSS) 22.0 program was used in the study. The results of Shapiro-Wilk normality analysis showed that the data of age showed a normal distribution and an independent sample t-test was used. But the data of right and left 2D:4D ratios was not normally distributed therefore a Mann-Whitney U test was used in the comparison of the groups. P values less than 0.05 were considered statistically significant.

**Results**

The mean age of the stuttering group was 7.062.33± years (range: 2-12 years) and control group was 6.792.36± years (range: 2-12 years).

There was no statistically significant difference between the groups in terms of age (p=0.487). The descriptive data of duration and severity of stuttering of individuals with stuttering are shown in Table I.

In the comparative evaluation conducted between the stuttering group and the control group in terms of their right 2D:4D and left 2D:4D ratios, it was found that the left 2D:4D ratio of the patients was significantly higher than that of the control group (p=0.017). However, there was no significant statistical difference between the groups in terms of right 2D:4D ratios (p=0.595; Table II).

**Discussion**

When the results of the present study were examined, a significant difference was found between the stuttering group and control group in terms of left 2D:4D ratios. The left 2D:4D ratio of the stuttering group was significantly higher than that of the control group. This result indicates that patients had experienced low prenatal testosterone exposure, and this suggests that prenatal testosterone may play a role in the etiology of developmental stuttering.

Only two studies have been found in the literature that examined the relationship between prenatal testosterone and stuttering. In the first study by Montag et al.<sup>20</sup>, the sample

**Table II.** Comparison of Digit Ratio Measurements.

	Percentiles			p value
	25th	50th (median)	75th	
Right 2D:4D	1.0069	1.0331	1.0545	0.595
Left 2D:4D	1.0049	1.0253	1.0487	0.017*

2D:4D: the ratio of the length of the 2<sup>nd</sup> digit (index finger) to the 4<sup>th</sup> digit (ring finger)

consisted of adult patients and no significant correlation between stuttering and prenatal testosterone (2D:4D) was identified. However, they reported a negative correlation between the left digit ratio and negative experiences of people who stuttered, using the Overall Assessment of the Speaker's Experience of Stuttering (OASES), suggesting that higher prenatal testosterone is linked to more negative experiences due to stuttering. The second study, by Mohammadi et al.<sup>21</sup>, was conducted with children. Once again, there was no significant relationship between prenatal testosterone (2D:4D) and stuttering. But they showed that postnatal serum levels of testosterone and its metabolites, dihydrotestosterone and oestradiol, were significantly higher in child who stuttered compared to child who did not stutter. They also found a significant positive correlation between postnatal testosterone, dehydroepiandrosterone and cortisol levels and stuttering severity. In the present study, there were no evaluations and comparisons in terms of severity of stuttering. Severity and duration of stuttering were given to know patients' stuttering characteristics. The results of our study are different from these two studies, which were done using similar methods (by the use of 2D:4D ratio). For this reason, our study is the first study in the literature to reveal the relationship between prenatal testosterone (2D:4D) and developmental stuttering.

In the literature review carried out to clarify the role of prenatal testosterone in the etiology of developmental stuttering, various pathophysiological mechanisms were identified that could explain this relationship. Although these mechanisms do not directly explain the relationship between prenatal testosterone and developmental stuttering, it can be possible to explain this pathophysiology in two steps by establishing a cause-effect relationship. While the first step explains the relationship between prenatal testosterone exposure and atypical hemispheric lateralization, the second step explains the relationship between atypical hemispheric lateralization and developmental stuttering.

The GBG hypothesis and the callosal hypothesis, both of which are important theories, endeavor to explain the relationship between prenatal testosterone exposure and

hemispheric lateralization.<sup>13</sup> The hypotheses differ in terms of the biological mechanism used to describe the relationship. The GBG hypothesis suggests that prenatal testosterone slows down the growth of some cortical areas in the left hemisphere during the prenatal period, which is a critical time in terms of neurodevelopment.<sup>9</sup> High levels of testosterone lead to the right hemisphere being dominant in relation to functions such as language skills through a disruption of the development of the left hemisphere.

On the other hand, the callosal hypothesis suggests that low prenatal testosterone decreases axonal pruning in the corpus callosum and this leads to atypical lateralization by affecting the flow of information between the hemispheres.<sup>11,12</sup> The corpus callosum is the main pathway between the two hemispheres and axonal pruning in this area increases hemispheric specialization related to various functions.<sup>24</sup> Axonal pruning is thought to improve functional circuits by selectively eliminating connections between neurons and synapses and thus causing more efficient brain functions.<sup>25</sup> However, in the case of low prenatal testosterone exposure, it is suggested that sufficient axonal pruning does not occur in the corpus callosum, resulting in problems in hemispheric specialization.

When comparing these two hypotheses, it can be concluded that the results of the present study support the callosal hypothesis. The left 2D:4D ratio of the stuttering group was significantly higher than the control group and this indicated that the stutterers were exposed to less prenatal testosterone.

There are various studies in the literature that support the relationship between prenatal testosterone and atypical hemispheric lateralization that fall within the ambit of the callosal hypothesis. Hollier et al.<sup>26</sup> report that a low umbilical testosterone level is associated with atypical hemispheric lateralization related to language. Studies by Lust et al.<sup>27</sup> and Grimshaw et al.<sup>28</sup> examining language based functions both reveal that a high amniotic testosterone level is associated with left hemisphere dominance in terms of language, in other words, high prenatal testosterone accompanies typical hemispheric lateralization.

Several researchers reported in the literature

support a relationship between atypical cerebral lateralization and stuttering. Neuroimaging studies conducted with adults reveal that individuals who stutter have a variety of structural and functional abnormalities relative to healthy individuals.<sup>29-33</sup> In studies on speech production, when individuals with stuttering are compared with individuals speaking fluently, excess activation is observed in the right hemisphere of the stuttering individuals but decreased activation is observed in their left superior temporal, fronto-temporal and temporo-parietal areas. The studies on the relationship between atypical hemispheric lateralization and stuttering have mainly been conducted on adult patients. In a limited number of studies conducted with children, the relationship between atypical hemispheric lateralization and developmental stuttering was reported.<sup>31,34-37</sup> In the study by Sato et al.<sup>7</sup> with three to five year-old children, abnormal hemispheric lateralization related to receptive speech processing in the posterior language area was present in those children with stuttering.

The primary aim of the present study was to determine the relationship between prenatal testosterone and developmental stuttering. Hemispheric lateralization was not evaluated. We have mentioned information in the literature linking prenatal testosterone with atypical hemispheric lateralization and atypical hemispheric lateralization with stuttering for the purpose of bringing a pathophysiological explanation to the relationship we identified between prenatal testosterone and stuttering. The fact that hemispheric lateralization was not evaluated in the present study could be considered a limitation. The hand dominance of the children participating in the study could have been included in the evaluation in order to provide an indication of cerebral lateralization. However, studies have shown that 97% of individuals with right hand dominance have left hemisphere lateralization in terms of language, and 3% have bilateral or right hemisphere lateralization; while 60% of individuals with left hand dominance have left hemisphere lateralization, 30% have bilateral lateralization, and 10% have right hemisphere lateralization.<sup>38</sup> When this information was considered, it was decided that hand dominance would not yield correct or significant results in evaluating

cerebral lateralization. In addition, neuroimaging methods for direct measurement of cerebral lateralization were not used in the present study due to the researchers' concerns about security and adaptation problems (such as waiting inactively for a long time) since the study was to be conducted with children.

When considering the method to be used in the present study for a determination of prenatal testosterone exposure, it was decided to measure the 2D:4D ratio directly by using a digital vernier caliper with 0.01 mm precision. Although more difficult to obtain, direct digit measurements are accepted as being more reliable than indirect methods (scanning, photocopying).<sup>39</sup>

It was observed that different methods were used in the studies assessing prenatal testosterone but not related to stuttering. These methods included measurement of amniotic testosterone concentration<sup>40</sup> and umbilical cord testosterone concentration.<sup>41</sup> Amniotic testosterone concentration and umbilical cord testosterone concentration can both give clearer and more accurate results than the 2D:4D ratio. However, because developmental stuttering develops mainly in the age range of three to eight years, and developmental stuttering was the topic under investigation in the present study, it seemed that the 2D:4D ratio, which is an accepted marker for the evaluation of prenatal testosterone in the postnatal period, was the most logical method to use. But, some researchers have suggested that 2D:4D ratio is not a reliable indicator of prenatal testosterone in the postnatal period.<sup>42</sup>

Another limitation of the present study is that it was a cross-sectional study and the number of the sample was limited. Only boys were included in the study to prevent gender from becoming a confounding factor. Nevertheless, this may be a limitation of the study.

Consequently, as the authors, we are of the opinion that prenatal testosterone may play a role in the etiology of developmental stuttering in boys. However, it will be necessary to conduct further studies evaluating both prenatal testosterone and hemispheric lateralization in order to clarify the pathophysiological mechanisms more explicitly.

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