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ORIGINAL ARTICLE

Development of the extraocular muscles during the fetal period

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Abstract

Purpose The aim of this study was to investigate the morphometric development of the extraocular muscles in the fetal period and to create a modified Tillaux spiral.

Methods We dissected 157 fetal eyes (82 right eyes, 75 left eyes) obtained from 79 fetuses (46 boys, 33 girls) between 13 and 40 weeks of gestation. The tendon widths of the extraocular muscles and the distances of the tendon attachment sites to the limbus were measured. Tillaux's modified spiral was created.

Results In addition to the rectus muscles, we added tendon widths and tendon–limbus distances of the upper (SO) and lower (IO) obliques to the modified Tillaux spiral. When tendon widths were compared between genders, no statistically significant difference was observed. When tendon widths were compared between the sides, it was determined that SO was more in the left eye, whereas other extraocular muscles were more in the right eye. There was no statistically significant difference between genders when the distances of tendon attachment sites to the limbus were compared. There was no statistically significant difference in SO and IO values between the sides. There was a statistically significant difference in the rectus muscles and this difference was found to be higher in the right eye.

Conclusion We think that the findings obtained will contribute to disciplines such as fetopathology, obstetrics, ophthalmology and plastic surgery and to future studies on this subject.

Keywords Fetus · Evolution · Extraocular muscles · Tillaux

Introduction

There are seven extraocular muscles related to the eyeball. Four rectus muscles (inferior rectus muscle (IR), medial rectus muscle (MR), superior rectus muscle (SR), lateral rectus muscle (LR)) and two oblique muscles (superior oblique muscle (SO), inferior oblique muscle (IO)) make the eyeball move in various directions [17]. The extraocular muscles develop from the prechordal mesenchyme entering the primitive node and transform into a characteristic muscle at week

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14 after the onset of differentiation from early myoblasts at week 5 [14, 17]. The prechordal cells move to the rostral side and transform into a notochord epithelial structure and remain as a mesenchymal structure after the basal lamina is acquired. Sevel [15] described superior and inferior mesenchymal complexes in a histological study conducted on fetuses, and later when the annulus of Zinn and eyeball were divided into two on the transverse axis, the researcher said that the muscles in the upper part developed from the superior mesenchymal complex, while the muscles in the lower part developed from the inferior mesenchymal complex [15].

The common tendinous ring, also called the annulus of Zinn, is a tendinous ring originating from the rectus muscles [17]. The rectus muscles begin from the annulus of Zinn. The course of the rectus muscles suddenly arches towards the bulbus 10 mm behind the equator of the eyeball, and they adhere to the sclera at different distances to the corneal limbus [21].

In the fetal period, many causes such as the tendon attachment sites of the rectus muscles, structural abnormalities, length, size, and elasticity cause congenital exotropia (inward shift) [15]. In the study conducted on 472 exotropic patients, it was shown that deviation occurred at birth in 204 of the patients [2]. Thus, it can be said that most of the abnormalities of the extraocular muscles that may cause exotropia are shaped in the intrauterine period. The variations and abnormalities of the extraocular muscles and/or tendons are associated with certain conditions such as strabismus, optic neuritis, obliquus superior sheath syndrome (Brown's syndrome), thyroid myopathy, and ptosis [10]. In the literature, there are more studies on the abnormalities of the extraocular muscles accompanying craniofacial malformations such as Crouzon, Apert, Pfeifer or Goldenhar–Gorlin syndromes. Strabismus is regarded as a common complication in these diseases [2, 5, 13, 20]. The evaluation of the development of the extraocular muscles and the investigation of the attachment sites to the corneal limbus are important in strabismus surgery [1].

The spiral of Tillaux is the name given to the spiral that connects the insertions of the rectus muscles into the sclera. It was described by Paul Jules Tillaux in 1887 [19]. Figure 1 presents the schematized state of the spiral of Tillaux. The aim of this study was to investigate the morphometric development of the extraocular muscles in the fetal period and to create a modified Tillaux spiral.

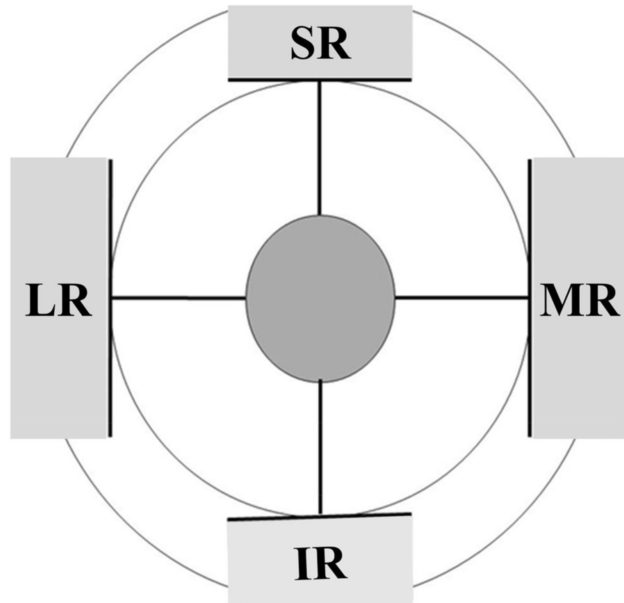

Fig. 1 The spiral of Tillaux. *MR* medial rectus muscle, *LR* lateral rectus muscle, *SR* superior rectus muscle, *IR* inferior rectus muscle

Materials and methods

Our study was carried out on 157 eyes (82 right eyes, 75 left eyes) obtained from 79 fetuses (46 male, 33 female) aged between 13 and 40 gestational weeks and not having external abnormality and pathology, which were provided by Maternity and Children Hospital by receiving permission from the families between 1996 and 2014. Approval was obtained from the Faculty of Medicine Ethics Committee for this study (Date: 11.19.2014, Decision no: 185). The gestational age of the fetuses was determined according to the biparietal diameter, head circumference, femur length, and foot length. The fetuses in the fetal period were evaluated by being divided into the following three groups: the fetuses between 13 and 25 weeks were determined to be in the 2nd trimester, the fetuses between 26 an 37 weeks were determined to be in the 3rd trimester, and the fetuses between 38 and 40 weeks were determined to be full term.

The eyeballs of the fetuses were removed from the orbit. Afterward, the tissues surrounding the eyeball were cleaned in such a way that the extraocular muscles became evident. Intraocular pressure was measured using a Schiotz tonometer and compared to normal values by scale. Physiological saline solution was injected into the eyes with low intraocular pressure and it was provided to reach normal pressure values according to the scale. Tendon lengths, widths of the extraocular muscles and distances of tendon attachment sites to the corneal limbus were measured with digital caliper (Fig. 2).

Statistical analysis was performed using SPSS Inc. SPSS for Windows. 20.0 statistical package program. Since data were normally distributed, the independent samples T-Test and one-way ANOVA test were used to analyze the data, and Pearson's correlation test was used in the correlation

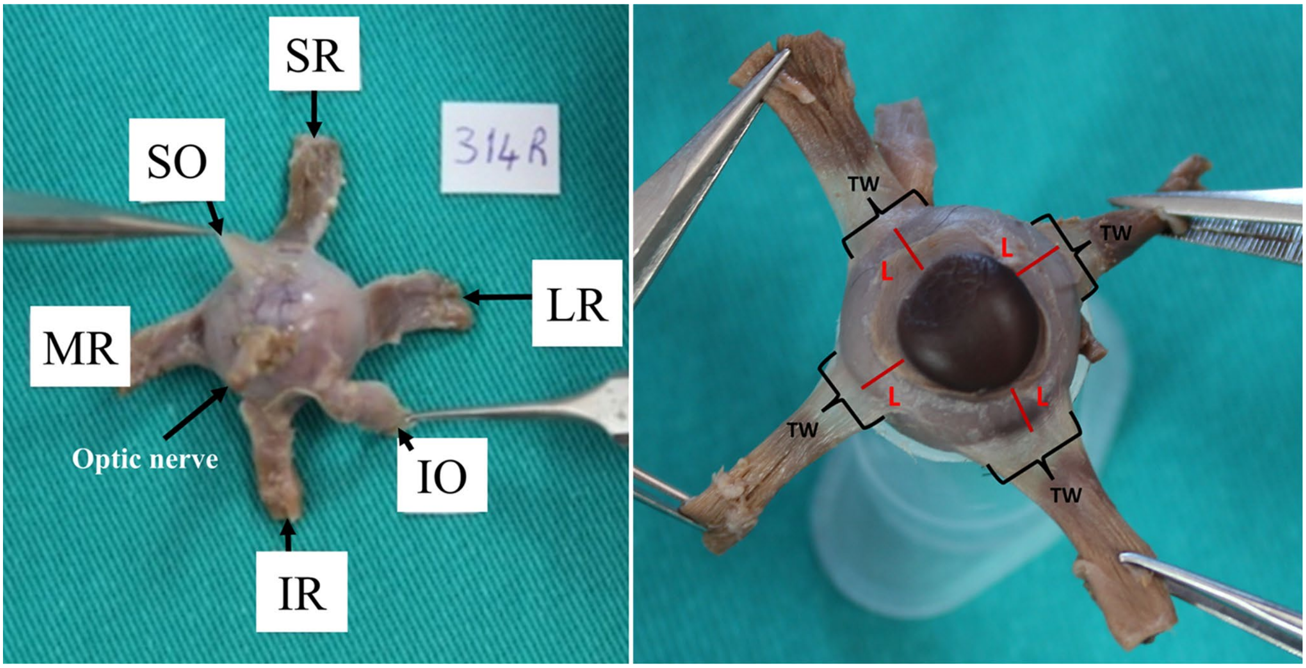

Fig. 2 Extraocular muscles of a fetus at 40 weeks of gestation. *SO* superior oblique muscle, IR: inferior rectus muscle, *IO* inferior oblique muscle, *MR* medial rectus muscle, *SR* superior rectus muscle, *LR* lateral rectus muscle, *TW* tendon width. *L* distance of tendon attachment sites from the corneal limbus

analysis. The significance level was taken as $p < 0.05$ in statistical analyses.

Results

Measurements could not be performed in the eyes that were damaged or perforated during dissection while evaluating some parameters, and these cases were excluded from the study. Therefore, a different number of cases was used for each parameter, and they were evaluated statistically separately. Minimum, maximum and average values, and standard deviations of all parameters evaluated in our study are presented in Table 1.

The widths of the tendons of the extraocular muscles were measured, and the mean and standard deviations of these parameters were found according to the trimesters (Table 2). The widths of the extraocular muscle tendons were compared between the trimesters. It was determined that the tendon widths of the extraocular muscles increased

Table 1 Minimum, maximum, mean values and standard deviations of all parameters

	N	Minimum (mm)	Maximum (mm)	Mean (mm)	Standard deviation
Superior oblique muscle TW	114	1.40	7.72	3.67	1.39
Superior oblique muscle L	111	4.13	12.06	8.08	1.71
Superior rectus muscle TW	139	2.01	9.27	5.42	1.33
Superior rectus muscle L	138	2.25	11.35	6.85	1.77
Lateral rectus muscle TW	140	2.58	8.24	5.60	1.12
Lateral rectus muscle L	139	2.98	12.93	7.43	1.82
Inferior oblique muscle TW	140	2.48	8.93	5.32	1.29
Inferior oblique muscle L	139	2.51	16.00	8.95	2.26
Inferior rectus muscle TW	140	2.73	8.46	4.62	1.15
Inferior rectus muscle L	139	2.84	9.85	6.28	1.34
Medial rectus muscle TW	140	2.51	9.08	5.21	1.25
Medial rectus muscle L	139	3.28	11.13	5.79	1.46

TW tendon width. *L* distance of tendon attachment sites from the corneal limbus

Table 2 Mean and standard deviation values of the tendon width of the extraocular muscles and their comparison by trimesters, gender and sides

	SO (mm)	IO (mm)	LR (mm)	MR (mm)	SR (mm)	IR (mm)
2nd trimester	2.60 ± 0.98	4.50 ± 1.34	4.79 ± 1.01	4.43 ± 1.09	4.68 ± 1.30	3.98 ± 0.97
3rd trimester	3.61 ± 1.22	5.35 ± 1.09	5.67 ± 0.93	5.25 ± 1.03	5.65 ± 1.34	4.74 ± 1.13
Full term	4.56 ± 1.42	6.12 ± 1.12	6.31 ± 1.08	5.94 ± 1.37	5.74 ± 1.08	5.06 ± 1.11
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Right	3.20 ± 1.10	5.78 ± 1.29	5.98 ± 1.22	5.73 ± 1.38	5.84 ± 1.29	5.00 ± 1.27
Left	4.46 ± 1.48	4.87 ± 1.15	5.23 ± 0.89	4.70 ± 0.87	5.00 ± 1.26	4.24 ± 0.89
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Male	3.57 ± 1.34	5.32 ± 1.38	5.59 ± 1.14	5.20 ± 1.31	5.53 ± 1.42	4.68 ± 1.15
Female	3.82 ± 1.46	5.34 ± 1.19	5.63 ± 1.12	5.23 ± 1.19	5.26 ± 1.21	4.54 ± 1.16
P	0.346	0.928	0.832	0.889	0.227	0.479

SO superior oblique muscle, *IR* inferior rectus muscle, *IO* inferior oblique muscle, *MR* medial rectus muscle, *SR* superior rectus muscle, *LR* lateral rectus muscle

Table 3 The order of tendon widths of extraocular muscles in fetuses according to trimesters

Group	Order
2nd trimester (13–25 hf)	SO < IR < MR < IO < SR < LR
3rd trimester (26–37 hf)	SO < IR < MR < IO < SR < LR
Full Term (38–40 hf)	SO < IR < SR < MR < IO < LR

SO superior oblique muscle, *IR* inferior rectus muscle, *IO* inferior oblique muscle, *MR* medial rectus muscle, *SR* superior rectus muscle, *LR* lateral rectus muscle

during the trimesters and there was a statistically significant difference between the trimesters ($p < 0.001$) (Table 2). The tendon widths of the extraocular muscles were determined from small to large in each trimester group and presented in Table 3.

When the tendon widths of the extraocular muscles were compared between the genders, no statistically significant difference was observed (Table 2). When the tendon widths were compared between the right and left sides, it was determined that the tendon width of the OS was greater in the left side ($p < 0.001$), and the tendon widths of other extraocular muscles were greater in the right eye ($p < 0.001$) (Table 2).

The distances of the attachment sites of the tendons of the extraocular muscles to the eyebaall from the midpoint to the corneal limbus (tendon–corneal limbus distance) were measured, and the mean and standard deviations of these parameters were determined according to the trimester groups (Table 4). It was determined that the distances of the tendon attachment sites of the extraocular muscles to the corneal limbus increased during the trimesters and there was a statistically significant difference between the trimesters (Table 4). In the trimester groups, the order of the distances of the extraocular muscles to the corneal limbus from small to large was in the form of MR < IR < SR < LR < SO < IO in the three trimester groups.

Table 4 Mean and standard deviation values of distance of tendon attachment sites of the extraocular muscles from the corneal limbus and their comparison by trimester, gender and sides

	SO (mm)	IO (mm)	LR (mm)	MR (mm)	SR (mm)	IR (mm)
2nd trimester	6.53 ± 1.53	7.21 ± 2.09	6.23 ± 1.80	4.85 ± 0.96	6.08 ± 1.76	5.41 ± 1.17
3rd trimester	8.07 ± 1.50	9.24 ± 1.67	7.74 ± 1.76	6.24 ± 1.52	7.04 ± 1.72	6.46 ± 1.11
Full term	9.12 ± 1.46	10.16 ± 2.42	8.06 ± 1.42	5.92 ± 1.37	7.31 ± 1.68	6.85 ± 1.51
P	< 0.001	< 0.001	< 0.001	< 0.001	0.006	< 0.001
Right	8.15 ± 1.60	9.37 ± 2.20	7.84 ± 2.02	6.19 ± 1.29	7.50 ± 187	6.65 ± 1.45
Left	7.97 ± 1.90	8.53 ± 2.27	7.01 ± 1.51	5.40 ± 1.53	6.20 ± 1.41	5.92 ± 1.13
P	0.602	0.029	0.007	0.001	< 0.001	0.001
Male	8.15 ± 1.90	8.99 ± 2.16	7.30 ± 1.89	5.99 ± 1.57	6.80 ± 1.87	6.28 ± 1.37
Female	8.00 ± 1.45	8.90 ± 2.42	7.61 ± 1.74	5.52 ± 1.26	6.941.63	6.30 ± 1.33
P	0.646	0.838	0.322	0.056	0.654	0.925

SO superior oblique muscle, *IR* inferior rectus muscle, *IO* inferior oblique muscle, *MR* medial rectus muscle, *SR* superior rectus muscle, *LR* lateral rectus muscle

In the comparison of the distances of the tendon attachment sites of the extraocular muscles to the corneal limbus between the genders, no statistically significant difference was observed (Table 4). In the comparison between the right and left sides, there was no statistically significant difference in the distance of tendon attachment sites of the SO from the corneal limbus (Table 4). A statistically significant difference was found in the distances of the tendon attachment sites of the rectus muscles and inferior oblique muscle to the corneal limbus and this distance was determined to be greater in the right side (Table 4).

In the study conducted by Tillaux, the tendon widths of the rectus muscles and the distances of the tendon attachment sites to the corneal limbus were measured in adults, and the spiral of Tillaux was formed. We also formed the modified spirals of Tillaux specific to the 2nd trimester, 3rd trimester, and full term of the fetal period. Furthermore, in our study, we added the tendon width and the tendon–corneal limbus distances of the superior and inferior oblique muscles to the modified spirals of Tillaux, in addition to the rectus muscles (Fig. 3).

Discussion

The investigation of the development of the extraocular muscles in the fetal period and the introduction of standard parameters will guide studies to be conducted on this region and the diagnosis and treatment of diseases. Many authors have emphasized the importance of knowing the primary structural changes of the extraocular muscles in the etiology of strabismus. The detailed knowledge of the anatomy and variations of the extraocular muscles in strabismus surgery enables successful and safe strabismus surgery [1, 8, 14, 18].

Harayama et al. [8] measured the widths of the rectus muscle tendons and the distances of the tendon attachment sites to the corneal limbus in 220 fetuses aged between 12 and 28 weeks and determined that the distances of the attachment sites of the rectus muscle tendons to the corneal limbus increase rapidly with age and reach the first peak value at weeks 16–19. Furthermore, it was reported that the distance between the tendon attachment sites of the rectus muscles and the corneal limbus exhibits a linear increase with the eyeball and corneal size along with gestational age. In the studies conducted on the extraocular muscles of adult cadavers, the distances between the insertion of the rectus muscles and the corneal limbus, and the tendon widths were measured (Table 5) [1, 4, 12]. Upon evaluating the tendon widths in adult cadavers, it is observed that the smallest tendon width belongs to the LR, while the largest tendon width belongs to the SR. In our study, it was observed that the smallest tendon width in the fetal period belonged to the SO, and the largest tendon width belonged to the LR. Accordingly, it was determined that the tendon width of the LR in the fetal period develops proportionally slower compared to other muscles with age after birth and the shortest tendon width in adulthood belongs to the LR. Moreover, it was observed that the tendon width of the IO in the fetal period increases from the 3rd trimester to full term (Table 5).

Upon examining the previous studies, it was observed that they were performed without paying regard to the difference in the development of the extraocular muscles in the fetal period between the right and left sides and without differences in gender. In our study, while examining the development of the extraocular muscles, comparisons were also performed between the genders and the right and left sides. While parameters related only to the rectus muscles were given in previous studies, in our study, oblique muscles were also examined in addition to the rectus muscles. In our study, it was determined that the distances of the tendon attachment sites of the extraocular muscles to the corneal limbus increased during the trimesters and there was a statistically significant difference between the trimesters. It was observed that there was no statistically significant difference between the genders. No statistically significant difference

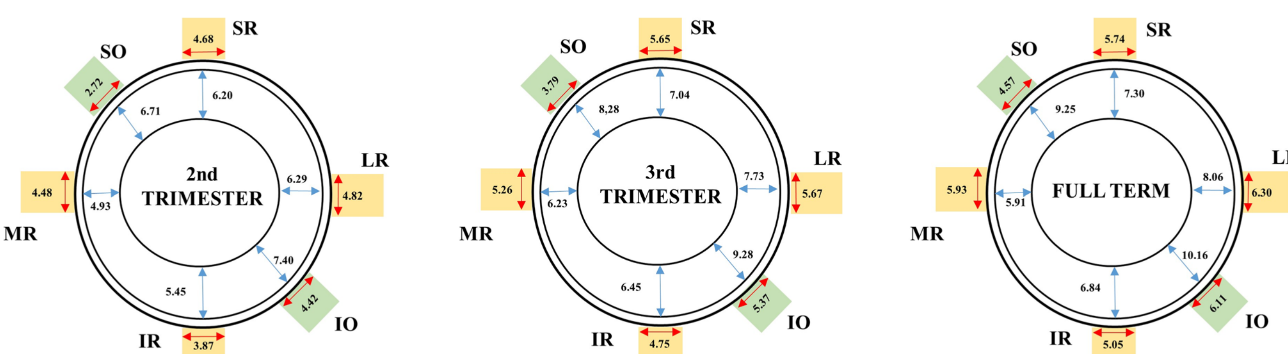

Fig. 3 Modified spirals of Tillaux according to trimester groups (the units of numerical values are mm). *SO* superior oblique muscle, *IR* inferior rectus muscle, *IO* inferior oblique muscle, *MR* medial rectus muscle, *SR* superior rectus muscle, *LR* lateral rectus muscle

Table 5 The order of tendon widths and the tendon attachment sites to the corneal limbus of extraocular muscles in adult cadavers and in present study

Previous studies	Study group	Tendon width order	Tendon–limbus order
Apt (1980)	Adult	LR < IR < MR < SR	MR < IR < LR < SR
De Gottrau et al. (1994)	Adult		MR < IR < LR < SR
Mukhopadhyay et al. (2014)	Adult	LR < IR < MR < SR	MR < IR < LR < SR
Present study	2nd trimester (13–25 weeks)	SO < IR < MR < IO < SR < LR	MR < IR < SR < LR < SO < IO
	3rd trimester (26–37 weeks)	SO < IR < MR < IO < SR < LR	MR < IR < SR < LR < SO < IO
	Full term (38–40 weeks)	SO < IR < SR < MR < IO < LR	MR < IR < SR < LR < SO < IO

SO superior oblique muscle, *IR* inferior rectus muscle, *IO* inferior oblique muscle, *MR* medial rectus muscle, *SR* superior rectus muscle, *LR* lateral rectus muscle

was determined in the comparison of the tendon–limbus distances of the SO between the right and left sides. However, it was found out that the distances of the tendon attachment sites of the IO and rectus muscles to the corneal limbus were greater on the right side and this difference was statistically significant.

The distances of the tendon attachment sites of the extraocular muscles to the corneal limbus have been determined to be MR < IR < LR < SR in previous studies in adults (Table 5) [1, 4, 12]. According to Table 5, it is observed that the order of the attachment sites of the muscles in the fetal period changes in the adult period. Accordingly, it can be said that the development of the extraocular muscles is completed in adulthood. Moreover, this difference in the tendon attachment sites of the rectus muscles demonstrates that the formation of strabismus may be related to intrauterine development.

Souza-Dias et al. [16] stated that the distance between the corneal limbus and the insertions of the muscles is completed within six months after birth and strabismus surgery can be performed in children six months after birth. However, Sevel [14] stated that the rectus muscle tendons take a normal position between 18 and 24 months and strabismus surgeries can be performed after the 24th month.

Clinical and morphological findings, as well as advanced radiological and surgical approaches, guide the diagnosis and treatment of strabismus. In the prenatal period, ultrasonography (USG) and craniofacial malformation scans, [11] in the postnatal period, computed tomography (CT) and magnetic resonance imaging (MRI) are important in the early diagnosis of the extraocular muscles' state and the functional evaluation of the muscles [3, 7, 9]. In our study, it was thought that fetal morphometric data could be a guide for prenatal and postnatal imaging.

Tillaux established a standard scale by determining the distances of the tendon attachment sites of the rectus muscles to the corneal limbus in adults [19]. This is called the spiral of Tillaux, and it is important in strabismus surgery [5]. In our study, the distances of the tendon attachment sites of the extraocular muscles to the limbus were determined in the fetal period and the modified spiral of Tillaux of the fetal period was formed. While forming the spiral of Tillaux, only the parameters of the rectus muscles were used. In our study, in the modified spiral of Tillaux formed, the parameters of the oblique muscles were used in addition to the rectus muscles. We think that the modified spiral of Tillaux of the trimester groups formed in the fetal period will contribute to the strabismus classification and strabismus surgery.

In the study conducted on adult autopsies, Goldstein [6] indicated that the close location of the insertion of the medial rectus muscle to the corneal limbus might cause exotropia. The present study, it was also observed that the closest distance in the fetal period belonged to the medial rectus muscle. Considering the values in the modified spiral of Tillaux, we think that suspicious conditions for exotropia can be detected during intrauterine examinations.

Conclusions

Knowing the pathology and variations of the extraocular muscles in the fetal period is important in the diagnosis and treatment of eye-related diseases and maxillofacial trauma. Our study is a basic study conducted on a large series related to the extraocular muscles during the fetal period, and the obtained data will shed light on clinical studies and future studies. In addition, we also presented an expanded and modified version of the spiral of Tillaux, which has an important place in the classification and treatment of strabismus. In conclusion, we believe that our study will contribute to the studies, diagnosis, and treatment in disciplines, such as obstetrics, ophthalmology, plastic surgery, and fetopathology, in the determination of abnormalities, pathologies and variations related to the development of the extraocular muscles in the fetal period.

Author contributions BC: protocol/project development, data collection or management, data analysis and manuscript writing/editing. KE: protocol/project development, data collection or management, data analysis and manuscript writing/editing. DA: data collection or management. ÖK: data collection or management. ÖG: data analysis and manuscript writing/editing. TL: protocol/ project development, manuscript writing/editing. TÖ: protocol/ project development, manuscript writing/editing. SO: protocol/ project development, data collection or management, manuscript writing/editing.

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Data availability Datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval Approval was obtained from the Faculty of Medicine Ethics Committee for this study (Date: 11.19.2014, Decision no: 185).

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