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ORIGINAL ARTICLE

Development of the New Zealand White Rabbit Eye: I. Pre- and Postnatal Development of Eye Tunics

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With 3 figures and 5 tables

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Summary

The New Zealand white (NZW) rabbit has been and is right now regularly utilized in ophthalmic surgery evaluation. Inside NZW rabbit eye, the visibility of ocular structures throughout surgical procedure is fantastic. Younger rabbits are used in different ages for the evaluation of ophthalmic surgery. Complete studies of ocular development in the NZW rabbits have not been reported previously. The aim of the present investigation was to describe the major landmarks and the time course of the pre- and post-natal development of the complete eye tunics of the NZW rabbit to give a superb model as well as a fruitful area for further ophthalmological investigations. Serial histological sections of NZW rabbit prenatal (E13–E28) and post-natal (P1–P14) stages were examined, respectively. The eye of the NZW rabbit developed in a similar manner to that of the human and domestic animals eyes; the principal differences were at the time of occurrence of certain developmental events, absence of pigmentation which represent an exploited benefit for ophthalmic surgery, remarkable Bowman's membrane at E25, poor developed ciliary stroma and juvenile retinal layer until P9. In human, the basic morphogenetic processes of the development of eye tunics are completed towards the end of the first half of gestation period. However, the latter represents the beginning stage of the development of eye tunics in the rabbit. Thus, allowing various extensive ophthalmic researches to be performed.

Introduction

The eye of rabbit is the best choice for human ophthalmic research; the animal is docile, easy to deal with, available in numerous sizes. All these reasons offering a peaceful environment to work with York and Steling (1998). The rabbit eye has been proved beneficial for the assessment of each new technologies as well as ophthalmic surgical strategies. (Nishi et al., 2005). The New Zealand white (NZW) rabbit has been and is right now regularly utilized in ophthalmic surgery evaluation. Inside NZW rabbit eye, the visibility of ocular structures throughout surgical procedure is fantastic, and video or photography is without a problem. (Gwon and Gruber, 2004). Rabbits of different age are used in different types of the evaluation of ophthalmic surgery. Specifically, younger rabbits tend to have a greater post-operative inflammatory response and are similar to that of young children (Odrich et al., 1985). In addition to all the above-mentioned, rabbits are kept more and more as pet species, and thus, eye disease may be presented to veterinarians in general practice. The ontogeny of the eye has been formerly described in the human and most domestic animals (Barber, 1955; Mann, 1964; Pei and Rhodin, 1970; Aguirre et al., 1972; Bistner et al., 1973; O'Rahilly, 1975, 1983; Barishak, 1992; McMenamin and Krause, 1993; Tamm, 2011; Tamm and Ohlmann, 2012; Abdo et al., 2014). The real development of the eye includes ectoderm, neural crest cells and mesenchyme. The neural tube ectoderm offers ascend to the retina, the iris and ciliary body epithelia, the optic nerve, the smooth muscles of the iris and a portion of the vitreous body. Surface ectoderm offers ascend to the lens, the

conjunctival and corneal epithelia, the eyelids and the lacrimal device. The staying visual structures begin from mesenchyme (Khurana, 2005). In the rabbit, a complete developmental research on the eyeball is uncommon. In this study, we aimed to describe the major landmarks and the time course of the pre- and post-natal development of the eye tunics of the New Zealand white (NZW) rabbit to give a superb model as well as a fruitful area for further ophthalmological investigations.

Materials and Methods

Experimental animals

The New Zealand white (NZW) rabbits were used in this study (obtained from Public Service centre for Veterinary Consulting, USC, Egypt). All techniques had been performed in consistent with the Association for Research in Vision and Ophthalmology (ARVO) Statement for the use of animals in ophthalmic and vision research. Institutional Ethics Committee was gotten before the start of experiments.

Prenatally

Forty-Six embryos and foetuses were obtained from the mated does. The domestic rabbits are induced ovulators; the ovulation occurred only after copulation by 10–12 h (Sirotkin et al., 2010). Thus, the day after mating has expressed as embryonic day **(E0)**.

Postnatally

Fifty young rabbits were used, taken the day of birth as post-natal day **(P0)**. The prenatal and post-natal stages used in this experiment are listed in Table 1. There was no possible indicated malformation in all specimens.

Histological staining

The embryos and foetuses up to E19 were fully fixed in 10% neutral-buffered formalin for light microscopic examination. While the eyeballs of both post-natal stages and foetuses (E21–E28) were enucleated and injected into the vitreous cavity with a fixative [10% formalin and 4% glutaraldehyde in 0.2 M sodium phosphate buffer (pH 7.2)].

All specimens were washed briefly in tap water, dehydrated through a graded series of ethanol, cleared in xylene and embedded in paraffin. Axial serial cross sections (5 μm) of each stage were cut on a microtome (LEICA RM-2155, Nussloch, Germany). The sections were stained with haematoxylin–eosin (HE), Masson's trichrome and Toluidine blue stains (Bancroft and Stevens, 1996). All stained sections were examined on Olympus CHS microscope (Olympus Optical CO., LTD., Tokyo, Japan).

Table 1. Pre- and post-natal stages with GL of collected samples

Age	GL[a] (mm)	Tissue type	Number of specimens
E13	10–12	Whole foetus	9
E16	14–16	Whole foetus	6
E19	18–20	Whole foetus	6
E21	25–30	Eyeball	4
E23	35–40	Eyeball	8
E25	45–50	Eyeball	5
E28	55–68	Eyeball	8
P0	–	Eyeball	15
P1	–	Eyeball	12
P3	–	Eyeball	10
P7	–	Eyeball	5
P14	–	Eyeball	4
P30	–	Eyeball	4

[a]GL, the greatest length, Peces-Peña et al. (2013).

Photomicrography

Digital images were captured with a digital camera (Olympus DP71 camera) attached to a microscope (Olympus IX71). An image analysis program, DP Controller and DP Manager as software were used. There was no adjustment of the captured images except for adjustment of contrast and brightness in Adobe Photoshop Elements (Adobe Systems, Tokyo, Japan).

Results

Prenatal stages

The outer fibrous tunics (cornea and sclera)

The corneal epithelium was the first layer appeared at E16 by separation of surface ectoderm from the lens vesicle. By the end of E16, the stromal mesenchymal cells invaded in between the optic cup margin and surface ectoderm, respectively (Fig. 1a,b). At E23, irregular arranged collagenous stroma containing keratoblast as well as Bowman's membrane could be recognized (Fig. 1c). At E25, the corneal endothelium laid on a fibrous acellular zone, however, an unmistakable Descemet's membrane was not self-evident (Fig. 1d; Table 2). Distinct scleral mesenchymal condensation around the optic cup with extraocular muscle appeared at E16. Slight faint positive Masson's trichrome staining collagen fibrous tissue was visible only at the posterior margin of the optic cup by E16 (Fig. 1f). Extensive collagen fibrous tissue could be distinguished surround the whole scleral layer, substantia propria, as well as

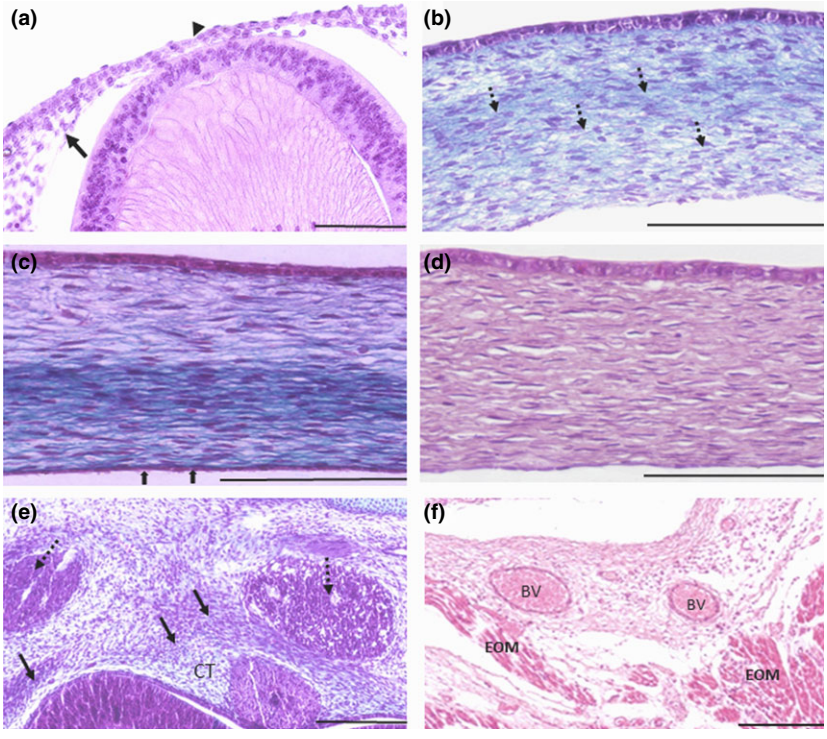

Fig. 1. Development of the cornea and sclera. Masson's trichrome stain (b, c and e); H&E stain (a, d and f). Scale bar: 200 μm. (a) The anterior half of the optic cup of E16 rabbit embryo. Arrow head; anterior corneal epithelium, arrow; invaded corneal stromal mesenchymal cells. (b) Cornea of E23 rabbit foetus. Dotted arrows; irregular arranged collagenous stroma containing keratoblast. (c) Cornea of E25 rabbit foetus showing regular arranged collagenous stroma condensed in the lower half of the cornea. Arrow; corneal endothelium. (d) Cornea of P1 rabbit showing all layers of cornea. (e) E16 rabbit embryo. Arrows; scleral mesenchymal condensation around the optic cup, dotted arrows; mesenchymal condensation to form extraocular muscle, CT; faint collagenous tissue. (f) Sclera of P1 rabbit. BV, blood vessels; EOM, extraocular muscle clearly visible.

extraocular muscular tissue became unmistakable at E25 (Fig. 1g).

The uvea (ciliary body, iris, and choroid)

At E16, the anterior edge of the optic cup tapered, thinned and stuck firmly to the lens capsule representing the common primordium of the ciliary body and iris (Fig 1a). The first indication of ciliary processes appeared as small folds before the end of E19. At E25, ciliary processes touch equator of the lens and become well established. Here, the ciliary ring and iris could be distinguished (Fig. 2d,e). Ora serrate make a wavy circle before the end of E25 (Fig. 2c). Ciliary matrix showed faint positive collagen fibrous connective tissue with small blood capillary swimming within the matrix in addition to a slight condensation in the mesenchymal cells at E23 (Fig. 2b, Table 3). The pigmented epithelium of ciliary processes and iris began a slight pigmentation at E23. The choriocapillary layer of choroid was the first of its layer to appear at E16, as small sinusoids just external to pigmented epithelium of the optic cup. Bruch's membrane appeared at this stage (Fig. 2a). The first indication of outermost large choroid vessels was at E25 (Fig. 1g). Suprachoroid stroma consisted in the posterior pole at E25 while became throughout at E28.

Table 2. Developmental timetable of New Zealand white rabbit eye – fibrous tunics

Part or event	Present by gestational age (E) or post-natal age (P) in days
Cornea	
Separation of lens vesicle from surface ectoderm	E16
Corneal epithelium and stromal mesenchymal invading.	E16
Collagenous stroma containing keratoblast as well as Bowman's membrane	E23
Differentiation of endothelium from stroma mesenchyma	E25
Distinct area with Descemet's membrane	P1
Multilayered corneal epithelium	P9
Sclera	
Scleral mesenchymal condensation with extraocular muscle condensation	E16
Extensive collagen fibrous tissue	E25
Extraocular muscular tissue became unmistakable	E25
Fibrous scleral tunics extending around the whole eye	P3

The retina

By the end of E16, the optic cup was established and consisted of an inner and outer layer. The pigmented epithelium was simple epithelium with no pigmentation. The neural retina (NR) consisted of an external limiting membrane, outer neuroblastic layer, transient fibre layer, inner neuroblastic layer, inner marginal layer and the internal

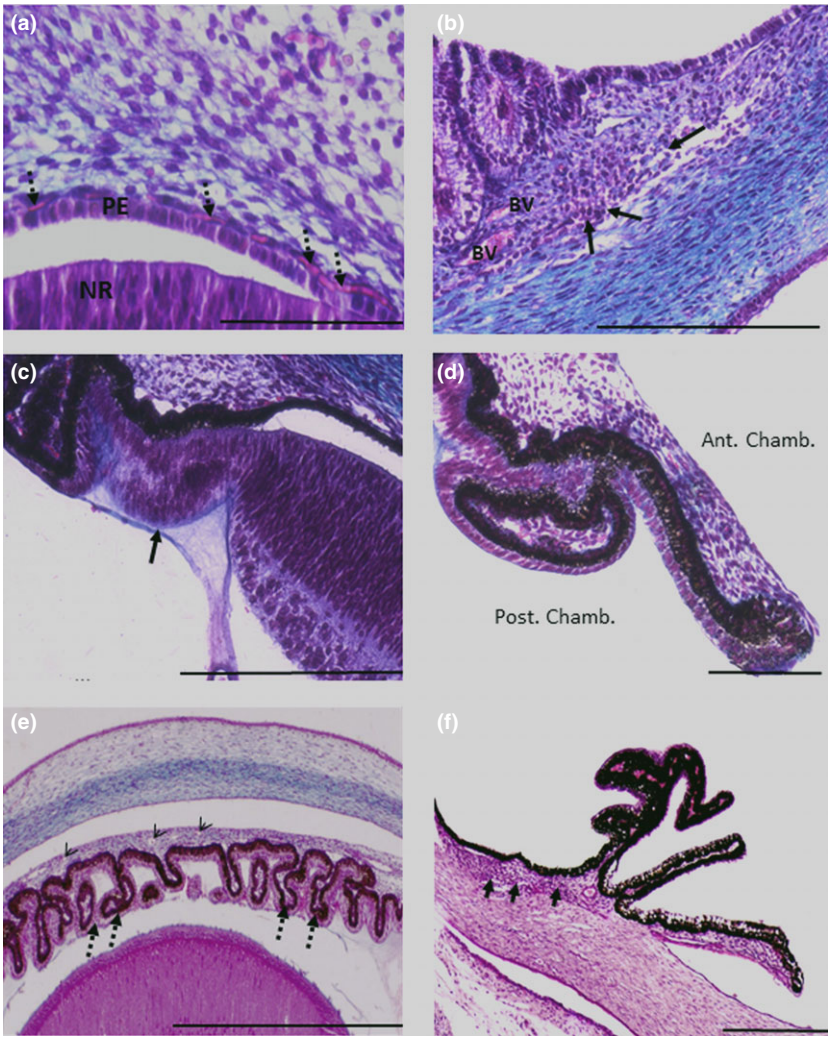

Fig. 2. Development of ciliary body, iris and choroid. Masson's trichrome stain except (e) and (f); H&E stain. Scale bar: 200 μm except (a); 100 μm. (a) E16 rabbit embryo. Showing the choriocapillary layer of choroid surrounding the optic cup (dotted arrows), NR, neural retina; PE, pigmented epithelium. (b) Ciliary body of E23 rabbit foetus showing positive collagen fibrous connective tissue. Arrows; condensation in the mesenchymal cells and BV, blood vessels. (c) E25 rabbit foetus showing ora serrata (arrow). (d) Both of the ciliary ring and iris could be distinguished at E25 rabbit foetus. (e) Ciliary processes become well established at E25 rabbit foetus (dotted arrows), arrows heads: numerous blood vessels. (f) well-confined ciliary muscles at P3 rabbit (arrows).

limiting membrane (Figs 3a,b). The apical processes of a few developing photoreceptors cells were perceived at the outside of the external limiting membrane by the end of E23. Inner neuroblastic layer only showed signs of further differentiation tabulated with Table 4 and Fig. 3c–e. Pigmentation of retinal pigmented epithelium observed at E23. By E25, the optic nerve joining the neural retina with forebrain was apparent (Fig. 3d).

Post-natal stages

The outer fibrous tunics (cornea and sclera)

The corneal epithelium showed a degree of differentiation in its layers achieving full adult morphology by P9. The corneal stroma was characterized by highly organized lamellae separated by attenuated keratocytes from P7. The endothelium consisted of a single layer of flat epithelium-like cells and Descemet's membrane could be identifiable by the end of P1 (Fig. 1e). Fibrous scleral tunics extending around the whole eye with obvious blood vessels, distinct extraocular muscle fibres were seen by P3 (Fig. 1h).

The uvea (ciliary body, iris and choroid)

The stroma of more complex ciliary processes was considerably more vascular at P1. Well-confined ciliary muscle appeared at P3 (Fig. 2f). The iris became more elongated and thickened collagenous stroma contained a considerable amount of blood vessels and no melanocytes by the end of P1. Both of sphincter and dilator muscles became apparent at P2.

The retina

Both of Ganglionic cell and inner plexiform layers were well established in newborn rabbits (P0). By the end of P9, full lamination of the retina was completed in the

Table 3. Developmental timetable of New Zealand white rabbit eye – uvea

Part or event	Present by gestational age (E) or post-natal age (P) in days
Iris and Ciliary body	
Tapering of optic cup margin and common primordium of the ciliary body and iris	E16
1st indication of ciliary processes	E19
Ciliary matrix showed positive collagen fibrous connective tissue	E23
Condensation of ciliary Stroma	E23
Ora serrata	E25
Sphincter and dilator muscle of iris	P2
Well-confined ciliary muscle	P3
Choroid	
Choriocapillary layer	E16
Bruch's membrane	E16
Suprachoroid stroma at posterior pole	E25
Suprachoroid stroma throughout	E28
Large choroidal vessels	E25

both posterior pole and peripheral retina. Details on the development of the retina post-natal are tabulated with Table 4 and Fig. 3f–h.

Discussion

Throughout the discussion of these results, it should be kept in mind that the normal structures of the developing eye in New Zealand white (NZW) rabbits are described to define and document the timing of major milestones in the differentiation of various ocular tissues. Awareness of these developmental events will be considered to be a prerequisite for more detailed studies of particular tissues. The conception of rabbits was rigidly controlled, and the precise ages of foetuses and post-natal animals were accurately determined (Sirotkin et al., 2010). The shared developmental timetable of the mentioned events between New Zealand white rabbits and the human eye is sorted out with Table 5. In human, the basic morphogenetic processes of the development of eye tunics are completed towards the end of the first half of gestation period.

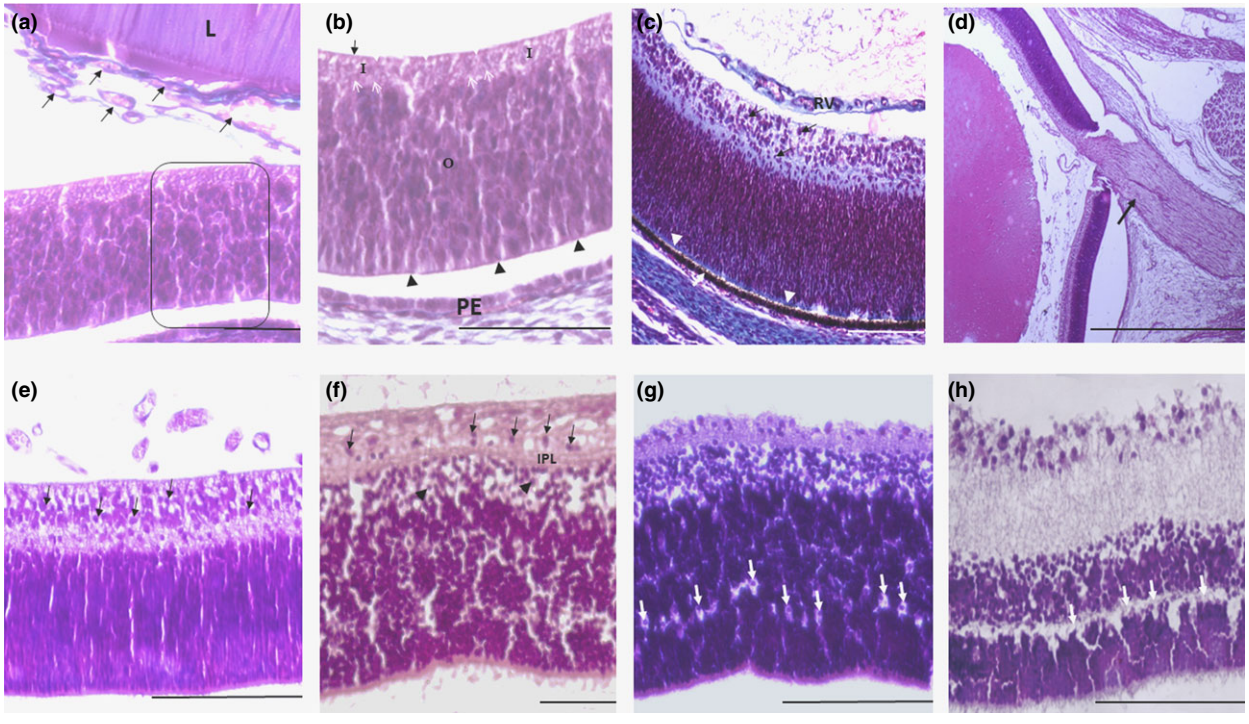

Fig. 3. Development of retina. H&E stain except (a), (b) and (c); Masson's trichrome stain. Scale bar: 200 μm except (b); 100 μm. (a) the retina of E16 rabbit embryo. Arrows; tunica vasculosa lentis; L, lens. (b) Enlargement of black-boxed region in (a). PE, pigmented epithelium; O, outer neuroblastic layer; I, inner neuroblastic layer; black arrow heads, external limiting membrane; black arrow, internal limiting membrane; white arrows, transient fibre layer; white arrow heads, nerve fibre layer. (c) The retina of E25 rabbit foetus showing cell proliferation within inner neuroblastic layer as well as ganglion cells with round nuclei (black arrows). RV, retinal vessels; white arrow, pigment granules in the PE, white arrows heads; pre-cursors of the outer segments of developing photoreceptors. (d) The optic cup at E25 rabbit foetus showing a distinct optic nerve (arrow). (e) The retina of E28 rabbit foetus showing stratified ganglionic cell layer (arrows). (f) The retina of P1 rabbit showing establishment of ganglion cell layer and inner plexiform layer (IPL). Arrows heads, rapid proliferation of inner nuclear layer. (g) The retina of P3 rabbit showing horizontal cells (arrows) among the outer neuroblastic cells. (h) The retina of P7 rabbit showing the earliest indication of a nascent outer plexiform layer (arrows).

Table 4. Developmental timetable of New Zealand white rabbit eye – retina

Part or event	Present by gestational age (E) or post-natal age (P) in days		
	Posterior	Middle	Peripheral
Outer neuroblastic layer, transient fibre layer, inner neuroblastic layer and a non-nucleated inner marginal fibre layer	E16	E16	E16
Inner and outer limiting membrane	E16	E16	E16
Proliferation of ganglionic cells	E25	E25	E26
Appearance of a distinct GCL	E28	E28	E28
Establishment of IPL and GCL	P0	P0	P0
Proliferation of INL	P1	P1	P1
HC appearance	P3	P3	P3
Faint line of OPL	P7	P7	P7
Establishment of OPL and ONL	P9	P9	P10
Well-formed optic nerve	E25	–	–
Retinal vessels	E25		

GCL, ganglionic cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer; OPL, outer plexiform layer.

Table 5. The shared developmental timetable between human and New Zealand white rabbit eye

Age (relative number[a])	CVRL (mm)	Equivalent age in human[b] (relative number[a])	Morphological status (shared by rabbit/human)
E13 43.3%[a]	10–12	5th week 12.5%[a]	Optic cup and stalk, lens vesicle and cavity
E16 53.3%[a]	14–16	6th–7th week 17.5%[a]	Corneal epithelium formed, choriocapillary layer in choroid, scleral condensation, RPE and inner/outer neuroblastic layer
E20–E28 66.6[a]–93.3%[a]	30–68	10th–14th week 25[a]–35%[a]	Ciliary folds and primitive iris, optic nerve formed and Ganglion cell layer
P1–P9	–	16th–20th week 40[a]–50%[a]	All layers of cornea formed, retinal lamination completed
P10	–	20th–25th week 50[a]–62.5%[a]	Lid opening

RPE, retinal pigmented epithelium.
[a]Relative number (percentage to the total gestation period).
[b]Based on O'Rahilly (1975).

However, the latter represents the beginning stage of the development of eye tunics in the rabbit, thus allowing extensive and various ophthalmic research to be performed. Different stages of morphogenesis of certain ocular tissues have been investigated in various species of animals. In mouse, the development of the eye in the prenatal period was described as having seven stages (Pei and Rhodin, 1970); In rat, development of the iris was studied electron microscopically (Imaizumi and Kuwabara, 1971); In monkey, the development of anterior chamber has been studied (Smelser and Ozanics, 1971); In canine, the development of eyeball was described (Aguirre et al., 1972); in bovine, the whole eyeball development has been studied (Bistner et al., 1973); in rabbit, the development of retinal area and shape were evaluated using retinal whole mount (Reichenbach et al., 1991); in dromedary camel, the prenatal development of the eye tunics has been documented (Abdo et al., 2014). Our finding confirmed that the New Zealand white rabbit eye develops in a comparable way to the human and domestic animals. However, because of distinction in the gestational period among different animals and human being, the timetable of mentioned events is entirely different. The present result revealed that the prenatal development of rabbit eye shows active growth in between E20 and E28, that is 66–93% of the gestational period. However, in the post-natal stages, P1–P9 is the most active and final developmental period. The eye tunics after these stages of the post-natal development continued to differentiate with the greatest change occurring only in the thickness of the different layers of the eyeball, and there are no significant changes in the structures.

In our results, both of corneal anterior epithelium and invading stromal mesenchyme appear at E16, 53% of the gestational period, the anterior corneal epithelium in adult rabbit consists of three thick layers (Kaye and Pappas, 1962). At P9, multilayered corneal epithelium appeared. The collagenous fibrous connective tissue surrounds the whole scleral tissue invading the corneal stroma through corneoscleral junction by E23 to reach the maximum positive Masson's trichrome staining by E25. The existence of a distinct Bowman's membrane in the adult rabbit cornea is dubious (Jakus, 1954, 1961; Kaye and Pappas, 1962). However, the results from present study confirm the appearance of Bowman's membrane prenatally by E23 and become unmistakable and measured 1.5 μm by E25 with positive Masson's trichrome stained cornea, and this finding is strongly supported by (Hayashi et al., 2002).

The morphogenesis of ciliary body and iris is described through little attempts (Weingeist, 1970; Lucchi et al., 1974; Johnston et al., 1979; Peces-Peña et al., 2013). The morphological uniqueness between the iris and the ciliary body was appeared by the end of the E25 stage as well as ora serrata appears at the same stage as an abrupt separation between the anlage of the ciliary body and the retina. The structure of ciliary body and iris is completed during the late prenatal stages (E23–E25) and early post-natal

stages (P1–P3). This finding agrees with the previous finding by (Weingeist, 1970). In stark contrast to mouse (Pei and Rhodin, 1970), rat (Imaizumi and Kuwabara, 1971), monkey (Smelser and Ozanics, 1971), canine (Aguirre et al., 1972), bovine (Bistner et al., 1973) and dromedary camel (Abdo et al., 2014) which showed a significant pigmentation in iris, ciliary and choroid stroma with different stages of development, the results obtained from the present study showed that there is no significant pigmentation in iris, ciliary and choroid stroma. Thus, the visibility of ocular structures throughout the ophthalmic surgical procedure is fantastic in NZW rabbit (Gwon and Gruber, 2004). The ciliary stroma is very poorly developed and comparatively flat, while the ciliary muscle anlage in the rabbit is shown up from the vascular condensed mesenchyme towards the end of P3. These findings agree with the ciliary muscle in human embryos which develops as a condensation in the mesenchyme between the optic cup and the sclera (O'Rahilly, 1975; Peces-Peña et al., 2013).

The development of choroid begins at E16 where the choriocapillary layer starts to differentiate simultaneously with the development of the retinal pigmented epithelium. From then on, a continuous differentiation and maturation process can be observed in the choroid up to the end of E25. Here, a clear distinction between choroid and sclera appears because of numerous blood vessels in the choroid.

Few attempts have been made to study the development of the rabbit retina (McArdle et al., 1977; Reichenbach et al., 1991; Germer et al., 1997). However, only the postnatal development of the retina has been described, and this has not been related to the development. The retinal morphogenetic events have been described in Table 4. The major prenatal developmental events in the rabbit retina occurred in between E23 and E28, while the major postnatal developmental events are in between P1 and P9). At birth, the rabbit retina is undifferentiated when compared with human (O'Rahilly, 1975) and cat (Greiner and Weidman, 1980). However, it is similar to the retina of rat (Weidman and Kuwabara, 1968; Kuwabara and Weidman, 1974) and ferrets (Greiner, 1981). The rabbit eye does not open until the 10th–12th day after birth (Bembridge and Pirie, 1951; Weingeist, 1970), and this is might be credited to juvenile retinal layer until P9. The rabbit retina gives a superb model as well as a fruitful area for further investigation because it grows gradually over long time course both pre- and post-natally.

In conclusion, this is the first study to describe the major landmarks and the time course of the pre- and post-natal development of complete eye tunics of the New Zealand white (NZW) rabbit. The eye of the NZW rabbit developed in a similar manner to that of the human eyes. In human, the basic morphogenetic processes of the development of eye tunics were completed towards the end of the first half of gestation period. However, the latter represented the beginning stage of the development of eye tunics in the rabbit. Thus, allowing an extensive and various ophthalmic research to be performed, the absence of pigmentation which represent an exploited benefit for ophthalmic surgery, remarkable Bowman's membrane at E25, poor developed ciliary stroma and juvenile retinal layer until P9. All considered the principal differences between NZW rabbit and the human eye.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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