

Accessory Placental Structures—A Review

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Abstract

Many studies have reported on the different types of placenta in different species, but accessory or paraplacental structures are mentioned only in species that have such a nutrient-exchanging mechanism. Hystricomorph rodents possess a subplacenta, swine and equines have the placental areola, equines have the chorionic girdle, and carnivores have hemophagous organs that are equivalent to the placental hematoma in ruminants. These accessory structures are specialized tissues for specific nutrient exchanges in different species, and they are adaptive modifications exhibited by domestic and wild species to remedy the nutritional deficiencies that are related to permeability of the main placenta to important nutrients for the growth and development of the fetus during the gestation.

Keywords

Placental Areola, Chorionic Girdle, Placental Hematoma, Hemophagous Organs, Subplacenta

1. Introduction

The functions of the extra-embryonic membranes are related to embryo growth and development during gestation [1]. The fetal membranes undergo changes to provide embryonic needs during development. These membranes may provide a favorable environment for embryonic growth, such as the amniotic membrane, or serve as an organ of maternal-fetal physiological exchange, such as the placenta that is formed during gestation.

The placenta promotes nutrient exchange between the mother and the fetus. These embryotrophic nutrients can be divided in two groups, histotrophic and hemotrophic [2]. The histotrophic nutrients are secretions of the uterine glands that result from the decomposition of maternal tissue and leakage of maternal blood. The hemotrophic nutrients arise from the maternal bloodstream through the placenta [1].

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Several accessory structures of the main placenta transfer nutrients and assist the physiological exchange from the mother's blood through the chorioallantoic placenta. Structures such as the vitelline sac function before the emergence of the chorioallantoic placenta, but all of these structures eventually act together. The placental hematoma and hemophagous organ occur in some species, and leakage of maternal blood and adjacent trophoblasts digests maternal erythrocytes. The areola is also an accessory structure of the placenta that is found in many ungulates. The areola has the shape of a dome lined by trophoblastic cells with absorptive function that are located on the opposite side of the openings of the uterine glands [1].

The subplacenta in rodents of the suborder Hystricomorpha has been studied from the moment it appears until its involution during the final stages of gestation [3]. Theoretical evidence of subplacental function suggests that it is a center of gonadotrophic activity or a site where decidual proteins are absorbed [4]. Another accessory structure with a noticeable characteristic occurs during equine embryogenesis, in which the chorionic girdle develops on the outer surface of the chorion 25 to 35 days after ovulation, and its subsequent invasion of the maternal endometrium between days 36 and 38 [5]. This chorionic girdle is originated from a series of shallow undulations on the chorion [6].

Given all of this placental variability, especially regarding accessory placental organs, we performed a literature review for describing the morpho-functional characteristics of said accessory organs, providing detailed data for future research in this field.

2. Review

2.1. Fertilization, Implantation and Placenta Formation

The fusion of the male and female gametes results in the zygote. The zygote becomes the blastocyst and embryo after several repeated cell divisions, and organ differentiation results in the fetus. The embryo in viviparous and oviparous vertebrates develop extra-embryonic membranes that perform important functions during embryonic and fetal life. One of these functions is related to nutrient transport. The physiological exchange processes during this period, such as respiration and nutrition, demand a specific arrangement of maternal and fetal tissues [1]. The intimate connection between the fetal membrane and the endometrium provide these functions, followed by the implantation process. This process forms the placenta, which is comprised of a fetal component and a modified uterine barrier [7]. The fetus and the placenta form the conceptus. The development and attachment of the fetal membrane to the uterine epithelium results in the development of the placenta, *i.e.*, the placentation process [8]. The embryo requires nutrients during its growth and development, and the maternal-fetal exchange may occur in structures other than the chorioallantoic placenta because some species have specialized accessory structures. The subplacenta is an accessory structure in hystricognath rodents [9]. Other accessory structures to the placenta include the placental areola in swine and equines [10], the hemophagous organ in carnivores [11], and placental hematomas in ruminants [12].

2.2. Subplacenta

The subplacenta as a structure of considerable size, located on the roof of the central excavation of the placental disc. It is composed of giant cells as a result of a peculiar transformation of the peripheral syncytial layer. The term subplacenta was used subsequently to indicate a different structure of the placenta in guinea pigs [2]. The subplacenta is found in rodents of the suborder hystricomorphous, and it has been described in the Brazilian porcupine, *Coendou prehensilis* [13]; the guinea pig, *Caviaporcellus* [4] [14]-[16], the Coypu, *Myocastor coypus* [17]; the Mongolian gerbil, *Meriones unguiculatus* [18]; the capybara, *Hydrochaerus hydrochaeris* [19]-[21]; the rock cavy, *Kerodon rupestris* [22]; Spix's yellow-toothed cavy, *Galea spixii* [3]; the common agouti, *Dasyprocta aguti*; the lowland paca, *Agouti paca* [23]; and the Brazilian punaré, *Thrichomys laurentinus* [24].

The location of the subplacenta differs between species. It is located in the central and mesometrial portions of the placental disc in the Mongolian Gerbil, *M. unguiculatus* [25]. However, it is located on the roof of the central excavation in the guinea pig, *C. porcellus* [4] [15]; the capybara [19] [20] [23]; and the rock cavy [22].

That the subplacenta of the rock cavy corresponds to a large circular lobe encrusted between the main placenta and the decidua basalis, but septa composed of connective tissue separates these structures. The subplacenta is divided internally into small irregular lobes separated by connective tissue containing fetal blood vessels. It is composed of trophoblastic cells of syncytial and cellular natures, which correspond to the syncytiotrophoblast and the cytotrophoblast, respectively [22].

The subplacenta as having a circulation promoted by maternal vessels until approximately the 20th day, but this circulation ceases in all regions of the subplacenta around the 28th day. Few fetal vessels are found in the central excavation at the time of subplacental formation, but these vessels do not contact the trophoblast. The first fetal vessels penetrate deeper between the trophoblast lobes when the maternal circulation recedes between the 23rd and 27th days. Fetal vascularization of the subplacenta is completed on the 32nd day, but these vessels are obliterated after the 55th day during the degenerative processes of the subplacenta. Only a few fetal vessels are observed in this region after the 58th day [14].

Initially that the subplacenta and main placenta were together and touched the maternal blood channels in its outer border prior to becoming a distinctive organ. The subplacenta has two fetal vessels and maternal blood channels in the beginning of the pregnancy and during the middle of the gestation, but debris obstructs some of the spaces with maternal blood. All other studies of the middle stage of the gestation observed that only fetal vessels supply the subplacenta. The subplacenta is reduced near birth, and only vestiges of its tissue can be found. The subplacenta develops as layers of cellular and syncytial proliferative trophoblasts in the fetal mesenchyme, similar to the main placenta [3].

The subplacenta as a specialized zone of the chorion between the placental disc and the decidua basalis [26]. The placental syncytium of the fetal ectoderm and the inversion of the vitelline sac defines the origin of the subplacenta from the chorionic ectoderm [4]. Minot (1889) [27] used the term “subplacenta” for the first time regarding the rabbit placenta, and it was later used in guinea pigs [4].

The subplacenta, or accessory organ to the placenta, in two animals, the *C. porcellus* (guinea pig) and the Brazilian porcupine (*C. prehensilis*), both hystrichomorphous rodents [28]. The chorioallantoic placentation of the *G. spixii* and the subplacenta as a component of the placenta that served as a point of origin of invasive trophoblasts [3]. The placenta of the red-rumped agouti *Dasyprocta leporina* and that the subplacenta is related to the production of hormones secreted in the fetal blood but not on maternal tissues [29]. Evolutionary transformations of the chorioallantoic placenta in hystricognath rodents and found macroscopic changes in these animals, primarily the formation of a ring-shaped arrangement of placental regions with maternal arteries situated centrally with a subplacenta [30].

Characteristics identified the placenta of rodents as experimental models for humans, such as a prominent vitelline placenta and fewer placental hormones. The superficial invasion of trophoblasts in the rat and the transformation of arteries depend on maternal hormones. These characteristics are ideal for pathogenesis research [31] [32].

2.3. Placental Areolas

The placental areolae of swine are dome-shaped structures located at the openings of the uterine glands. Their epithelium forms tall columns with long microvilli, tubular systems and vesicles, which indicate a high absorptive capacity of the epithelium [33].

That the placental areolae is formed from a portion of the fetal tissue and maternal tissue surrounding the areolar cavity. These areolae accumulate histotrophic secretions from one uterine gland (regular areola) or several uterine glands (irregular areola). Regular areolae appear as opaque, circular spots measuring a few millimeters that are variably translucent and form larger structures when observed through the fetal membranes (chorioallantoic/chorioamniotic) [34].

Miglino *et al.* (2001) [35] mention that regular areolae can total 7000 per conceptus, but irregular areolae exhibit a higher or lower frequency of approximately 1500 per placenta. Other structures are present in the fetal placenta, such as the cysts, hippomanes, and petrifications.

The fetal surface of swine placenta displays a capillary network that forms papillae with protrusions and areolar cavities or converge into a circle in the direction of the areola's periphery. Irregular areolae have indistinct boundaries and are characterized by the opening of one or more uterine glands. The arrangement of the blood vessels of irregular and regular areolae results in the inflow of blood to the areola at the level of capillaries and arterioles. The capillary flow of the areolae includes the convergence of venules to one or two areolar veins, which leads the venous blood from that areolar area in a distinctive manner and suggests that this architecture favors the control mechanisms for the uterus, placenta, and fetus [35].

The inter-microvillous attachment in the areolar regions is interrupted in the pig and camel, and the exchange of substances between the mother and the fetus occurs through the areolar cavity. The trophoblast absorbs the

histotrophic secretions of the endometrium in swine areola to develop the embryo during the pregnancy [36].

The calcium and iron pass through the same areolar cell and trophoblast using different paths. Calcium crosses through the cytoplasm, but iron and its carrying protein (uteroferrin) bind to the membrane during absorption through a vesicle or lysosome [37]. Uteroferrin is an important substance in iron transport through the areolar cavity from the mother to the fetus in horses [37] and other species, such as the pig [33] [38]. However, only maternal and fetal microcotyledonary epithelial cells transport glucose [37].

The areolar glands are subunits specialized in the transfer of maternal-fetal substances [33]. Bazer (1975) [39], Chen *et al.* (1975) [40] and Raub *et al.* (1985) [41] reported that the columnar to cuboidal epithelium of the uterine glands is involved in the synthesis of iron-binding proteins, including uteroferrin. Uterine secretions in the areolar cavity contain substances with metabolic enzymatic activity [33].

Abd-Elnaeim *et al.* (2003) [36] demonstrated that regular areolae of dromedaries are similar to regular areolae in swine [35], in which only one uterine gland opens to the inner area of the areolar cavity. However, these areolae differ from mares, which have more than one uterine gland opening at this location.

2.4. Chorionic Girdle

The chorionic girdle is observed in mares between days 15 - 47 and 53 - 57 of pregnancy. This structure disappears as gestation progresses, which suggests that its function of synthesis and proliferation occurs only at the beginning of pregnancy [42].

That many aspects of embryogenesis in the mare are unique to the genus *Equus*, especially the development of the chorionic girdle and its posterior invasion of the endometrium [10].

Trophoblastic cells form an avascular tissue called the chorionic girdle that surrounds the conceptus between days 25 and 35 of gestation in the mare. These cells invade the uterine endometrium on the 35th day of gestation and form 0.5- to 1.0-cm structures called endometrial cups in 48 hours. The equine chorionic gonadotrophin (eCG) hormone stimulates the accessory luteal glands that aid in the maintenance of gestation [43].

The high eCG concentrations appear in the maternal serum at the beginning of gestation. Placental structures, called endometrial cups, secrete the eCG. These structures originate from the trophoblastic cells of the chorionic girdle and are destroyed by the immune system after a certain period of activity [44].

That eCG binds to follicle-stimulating hormone (FSH) and luteinizing hormone (LH) receptors, and it is the only gonadotropin capable of binding both receptors in mammals, except equines. The eCG is secreted between the 33rd and 120th day of gestation, and its concentration remains high until the 90th day [43]. The concentration of eCG declines after this period, and it is absent at the 150th day. The eCG secretion peaks at approximately 55 and 70 days of gestation, which corresponds to the maximum size of the endometrial cups [10]. The eCG also binds to the LH receptors in the corpus luteum [45]. This binding increases progesterone (P4pregn-4-eno-3,20-dione) production, which plays a fundamental role during early gestation and acts on the endometrial epithelium to induce the secretion of factors that are indispensable to embryonic development [46].

eCG has been largely used in superovulation donor programs and in studies with embryo donors due to its action on FSH [47]. Therefore, the use of eCG in protocols of ovulation synchronization for fixed-time artificial insemination (FTAI) and fixed-time embryo transfer (FTET) has been growing to increase the efficacy of these programs [48].

2.5. Hemophagous Organ

In the first half the hemophagous organ is a tubular structure, followed by an expanded and bulbous characteristic in the distal half. This accessory organ to the placenta grows, regresses and almost disappears as gestation approaches [49]. The hemophagous organ as a multi-lobular structure is consisting of two relatively large lobes and several smaller lobes. All of the lobes are round, and the larger lobes bind and extend from the allantoic cavity to the back of the embryo at the end of gestation. The proximal extremities of the lobes gather to form a region attached to the maternal surface of the placenta [11].

The term hemophagous organ was proposed for a particular structure found on the placenta of the raccoons (*Procyon lotor*) [49]. This sac-shaped, highly vascularized, macroscopic structure hangs in the interior of the allantoic cavity and emerges from an anti-mesometrial central area of the placental ring in procyonid carnivores. This structure increases in size and complexity until approximately two-thirds to three-fourths of the gestational period, and then it regresses [49]-[51].

Different placental types in different species address 3 types of iron transfer [8] [52]:

- 1) Absorption of iron bound to transferrin through the outer surface of the trophoblast in direct contact with the maternal bloodstream (*i.e.*, hemochorial placenta);
- 2) Absorption of erythrocytes by the chorionic epithelium in direct contact with the accumulation of blood leaked from hemophagous areas (*i.e.*, endotheliochorial and synepitheliochorial placenta); and
- 3) Absorption of iron by the chorionic epithelium in direct contact with the enriched iron originating from endometrial gland secretions (*i.e.*, diffuse placenta).

Another iron absorption mechanism was described as the leakage of blood in the maternal-fetal relationship followed by the phagocytosis of erythrocytes by trophoblastic cells in ovines, bovines, caprines, carnivores, and chiroptera. This absorption occurs in different areas of the placenta, known as placental hematoma or hemophagous areas [53] [54].

That studies were performed as to elucidate iron transfer to the fetus, and iron deficiency leads to some diseases in the newborn, such as high blood pressure, anomalies in the immune system, and compromises in brain function [55] [56].

2.6. Placental Hematoma

One of the main characteristics of carnivore placentas is the presence of placental hematomas. A placental hematoma is a large, compact mass of red blood cells that is well-adhered to the chorioallantoic membrane, and it is found in the medial surface of the placental girdle. Cuboidal epithelium surrounds placental hematomas on the majority of its margin. The largest area is found between the layer adhered to the junctional zone between the maternal and fetal surfaces and the labyrinth zone. The hematoma invades the space previously occupied by the uterine epithelium and its stroma in some areas of the epithelium [2].

The hemophagous organ is equivalent to the placental hematoma of certain carnivores and indicates that the term “hematoma”, which has pathological implications, can be replaced with the functional and descriptive term “hemophagous” in hemophagocytic areas of the placenta [50].

The hematomas are an iron source for embryonic development because trophoblasts phagocytose and digest the maternal red blood cells. Observations in buffalos suggest that these areas also correspond to the iron transfer for the fetus during the final stages of pregnancy [57].

The placental hematomas in buffalos (7 to 10 months of pregnancy) are located exclusively in the base of the chorionic villi. The placental hematomas in these animals are numerous and irregularly distributed along the maternal-fetal interface and contain a variable amount of leaked maternal blood. The authors suggest that an erythrophagocytosis occurs due to the trophoblastic cells from areas adjacent to the hematomas presenting erythrophagosomes [12].

3. Conclusion

The literature suggests that the placenta is vitally important for the exchange of nutrients, but this exchange does not occur solely in the chorioallantoic placenta. Nutrient exchange may also occur in accessory structures that exchange specific nutrients. Therefore, accessory structures are of vital, specialized and specific importance for the transfer of macro- and micro-molecules to the developing embryo/fetus. These modifications of the placenta may have appeared as adaptations in domestic and wild species to satisfy the nutrient requirements during conceptus development.

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