Placentation in different mammalian species

La placentation dans différentes espèces de mammifères

Pascale Chavatte-Palmer *, Anne Tarrade

UMR BDR, INRA, ENVA, université Paris Saclay, domaine de Vilvert, bâtiment 231, 78350 Jouy-en-Josas, France

Abstract

The placenta is a complex, transient organ associated with viviparity, which is located at the interface of the dam and fetus during pregnancy. It is formed after attachment, or implantation, of the blastocyst on the uterine lining and derives from complex cellular and molecular interactions between uterine and embryonic tissues. In mammals, there are many forms of placentation but this organ has the same function in all species: it is responsible for orchestrating materno-fetal exchanges, together with endocrine and immunological functions.

Keywords: Placenta; Mammals; Comparative anatomy; Pregnancy

1. Introduction

The implantation of the embryo into the uterus is an evolutionary process associated with viviparity and placentation. This reproductive strategy ensures an efficient protection and nutrition of the embryos and thus promotes their survival. In all placental mammals, the establishment of an intimate contact between the embryo and the mother follows a succession of common critical steps whose chronology and timing may considerably vary from species to species. Moreover, these processes present a great diversity based on anamato-histology of the uterus as well as endocrine and molecular interactions between the uterine and the embryonic tissues.

2. Anatomical and physiological considerations

The structure of the placenta is dependent on the anatomical structure of the uterus. The uterine anatomy differs among mammalian species (Fig. 1) and is adapted to certain characteristics of their reproductive biology, such as trans-uterine migration of blastocysts and litter size. There are three main types of uteri:

- double uterus (rodents, lagomorpha) with 2 uterine cervices and two separate uterine horns;
- bicornuate uterus (ruminants, swine, equidae, carnivores, cetaceans) with 1 cervix, 1 uterine body of variable length and 2 communicating uterine horns;
- simplex uterus (primates, bats) with 1 cervix and 1 large uterine body without uterine horns.

The uterine tissue is composed of an external muscular coat (myometrium) surrounding an inner mucosa (endometrium) to
which the embryo attaches, forming the placenta: this is referred to as the implantation. The endometrium, more or less wrinkled depending on species, consists of a single luminal epithelium resting on a connective tissue (stroma) richly vascularised and interspersed with uterine glands that open into the uterine lumen. This basic structure is common to all mammals and generally all of the endometrial surface is responsible for the establishment and formation of the placenta. There are, however, anatomical peculiarities specific to certain species. Thus in ruminants, areas of endometrial thickening appear during organogenesis where uterine glands are not present. These areas, called caruncules, are lead to the development of distinct placental structures named placentomes. They are aligned along the uterine horns and their number varies according to the species from 5 (deer) to 150 (giraffe).

The timing of the implantation, which corresponds to the beginning of placental development and the length of gestation also varies between species and is described in Table 1.

### 3. Extra-embryonic membranes

The placenta per se (sometimes referred to as the fetal placenta) is derived from the fertilized egg and therefore contains the same genetic heritage and is of the same sex as the conceptus [1].

<table>
<thead>
<tr>
<th>Species</th>
<th>Day of implantation (embryonic stage)</th>
<th>Definitive placentation</th>
<th>Gestational length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>4.5 (blastocyst)</td>
<td>14.5</td>
<td>20</td>
</tr>
<tr>
<td>Rat</td>
<td>5.5</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>Hamster</td>
<td>4</td>
<td>–</td>
<td>16–19</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>6</td>
<td>–</td>
<td>68</td>
</tr>
<tr>
<td>Rabbit</td>
<td>6.5 (gastrula)</td>
<td>–</td>
<td>31</td>
</tr>
<tr>
<td>Human</td>
<td>6–7 (blastocyst)</td>
<td>90</td>
<td>280</td>
</tr>
<tr>
<td>Cat</td>
<td>13</td>
<td>–</td>
<td>63</td>
</tr>
<tr>
<td>Swine</td>
<td>13–14 (gastrula)</td>
<td>–</td>
<td>115</td>
</tr>
<tr>
<td>Sheep</td>
<td>15 (neurula)</td>
<td>40</td>
<td>145</td>
</tr>
<tr>
<td>Cattle</td>
<td>19–20 (neurula)</td>
<td>50–60</td>
<td>280</td>
</tr>
<tr>
<td>Horse</td>
<td>30–38 (organogenesis)</td>
<td>60</td>
<td>330</td>
</tr>
</tbody>
</table>

#### 3.1. Trophoblast

The main tissue in direct contact with the uterus is the trophoblast or trophectoderm. This epithelium results from cell segregation at the blastocyst stage into an embryonic lineage and an extra-embryonic lineage. During development, the extra-embryonic mesoderm from the embryo migrates and merges with the trophoblast to form the chorion that surrounds the embryo and fetus and its annexes (Fig. 2).

The placental trophoblast structure varies according to species and during pregnancy. Only pigs and cetaceans possess a cytotrophoblast, i.e., a mononuclear trophoblast throughout gestation. There are no invasive process in these species. In ruminants and equines, a fraction of the mononuclear trophoblast cells differentiates into binucleated cells with distinct properties in both orders, in connection with an invasive process. In the vast majority of other orders of mammals, the original cytotrophoblastic layer splits into a layer of cytotrophoblast which is retained and another that forms a syncytiotrophoblast by cell fusion and which provides most of placental functions.

#### 3.2. Amnion

The amnion is the membrane delimiting the fluid-filled cavity containing the fetus. Although the amnion partially merges with the chorion, it is not directly involved in the structure of the placenta in most mammals. It nevertheless represents a significant placental annex to fetal development. The amniotic cavity provides mechanical protection of the fetus and its development in liquid medium, freeing external pressures.

#### 3.3. Yolk sack

The yolk sack is a vestige of vertebrate evolution. In many mammals, it is the first vascularised extra-embryonic structure. The yolk sac is formed during the migration of the extra-embryonic mesoderm. Sandwiched between the trophoblast itself and the parietal endoderm, it merges with the latter to define a cavity inside the blastocoele (or exocoelome). A primitive vascular network then differentiates within the yolk sack mesoderm.

The fate of the yolk sack during pregnancy is variable depending on the species. In most rodents, the yolk sack undergoes a
reversal of its membranes and persists until the end in the form of a choriovitellin placenta. In other orders of mammals, the yolk sack is either highly developed and functional transiently in early gestation (carnivores, ungulates) ensuring primitive vascularization of the placenta, or possesses no particular role and quickly regresses (Primates).

3.4. Allantois

The allantois is formed from an endodermic budding of the primitive gut, at the urogenital sinus of the embryo. The allantoic diverticulum is then covered by the extra-embryonic mesoderm, which will develop the allantoic vessels which form the umbilical vessels.

The development of the allantois during gestation seems to be linked to the mode of implantation of the blastocyst. In ungulates and carnivores (superficial implantation, as explained below), the allantoic sack grows dramatically to line the chorionic sack almost entirely and persist until parturition. Its fusion with the chorion results in a true chorioallantoic placenta. It communicates with the urinary apparatus of the fetus and acts as waste reservoir of fetal metabolism. In rodents and primates (deep interstitial implantation), the allantois regresses very early in development to remain at term as a diverticulum enclosed into the wall of the umbilical cord.

4. Classification of placentas

Various criteria are used to classify the placentas, i.e., morphology, organization of the cell layers and histological structures between the maternal and fetal blood [2]. Placental structures develop gradually during pregnancy and only the final forms are described here (Table 2).

4.1. Morphological classification

This classification is based on the distribution of placental villi on the chorionic sack enclosing the fetus (Fig. 3).

4.1.1. Diffuse placenta (Swine, Cetaceans, Equidae)
The villi or folds of the chorion in contact with the uterine endometrium are distributed over the entire surface of the chorionic bag forming either folds (like in pigs) or affixed over the entire surface of the endometrium and collected into microcotyledons distributed over its entire surface (equidae).

4.1.2. Cotyledonary placenta (ruminants)
Chorionic villi are grouped in bunches or cotyledons along an elongated chorionic bag occupying the entire volume of the uterine horns. The number of cotyledons varies among species

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal characteristics of mammalian placentas.</td>
</tr>
<tr>
<td>Order</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Cetaceans</td>
</tr>
<tr>
<td>Suids</td>
</tr>
<tr>
<td>Equids</td>
</tr>
<tr>
<td>Ruminants</td>
</tr>
<tr>
<td>Carnivores</td>
</tr>
<tr>
<td>Lagomorphs</td>
</tr>
<tr>
<td>Rodents</td>
</tr>
<tr>
<td>Primates (Human)</td>
</tr>
</tbody>
</table>
Fig. 3. Morphological classification of placentas.

and depends on the number of uterine caruncles to which they attach to form placentomes.

4.1.3. Zonal placenta (carnivora)
The villi are concentrated in an equatorial band surrounding the chorionic sack.

4.1.4. Discoid placenta (rodents, lagomorphs, primates, insectivores)
The villi are collected on a single (mice, man) or double disc (macaque monkeys, rabbits). In humans, the villi are grouped in clusters separated by uterine septa, forming twenty nickname visible cotyledons on the maternal side of placental disc.

4.2. Structural classification

Placentas can be classified according to the architecture of the chorionic membranes in contact with the maternal tissues.

4.2.1. Folded placenta (swine)
The chorionic folds line the wrinkled surface of the uterine epithelium.

4.2.2. Villous placenta (ruminants, primates, equidae)
The chorion develops into villi consisting of trophoblastic columns (primary villi) that branch and within which the extra-embryonic mesoderm infiltrates (secondary villi). Tertiary villi, where more exchanges take place, include the blood vessels of fetal origin.

4.2.3. Labyrinthine placenta (Rodents, lagomorphs, carnivores, insectivores, bats)
The feto-maternal space (or labyrinth) form a network formed from the merging of chorionic villi surrounding maternal blood lacunae. In rodents and lagomorphs, junctional or spongiotrophoblast areas anchor the placenta into the uterine lining.

4.3. Histological structure

This classification is based on histological observation of the different cell layers separating the fetal circulation from the maternal circulation and the degree of invasion of the endometrium by the lamina propria (Fig. 4). In this terminology, the first part of the qualifier refers to the maternal tissue in contact with the chorion.

4.3.1. Epitheliochorial placenta (swine, Equidae, Cetaceans, lemurs)
The trophoblast is apposed on the intact uterine epithelium and interdigitation with apical microvilli of cell membranes ensures cohesion. Six layers of tissue separate the maternal from the fetal blood throughout gestation. In addition, para-placental related structures, called areolas, develop in contact with
4.3.2. Synepitheliochorial placenta (ruminants)

The contact between maternal and chorionic tissues is the same type as in the epitheliochorial placenta. In ruminants, however, syncytia (multinucleated cell masses) develop among the uterine epithelial cells. The presence of this syncytium at the maternal-fetal interface gives its name to this type of placenta. The syncytium is formed from the merging of uterine epithelial cells with trophoblastic binucleated cells (CBN) resulting in a hybrid cell mass which is a unique structure among mammals, containing a maternal nucleus and nuclei of embryonic origin. From a functional standpoint, the syncytium enable the transfer of hormones and trophoblastic proteins to the maternal circulation, of which the Pregnancy-Associated Glycoproteins that can be detected in maternal serum and are used as markers in the diagnosis of pregnancy in cattle [3].

4.3.3. Endotheliochorial placenta (carnivores, elephants)

In this type of placenta, the uterine epithelium and endometrial connective tissue are being eroded by the syncytiotrophoblast that comes into direct contact with the basement membrane of the endothelium of the uterine blood capillaries without invading. Four tissue layers thus separate the maternal and fetal blood.

4.3.4. Hemochorial placenta (rodents, lagomorphs, primates)

This is the form in which placental trophoblast is most invasive. All the endometrial tissue is eroded during the migration of trophoblast cells into the uterine lining. In the final form of the placenta, the chorion is immersed directly in maternal blood. The composition of the trophoblastic layer that is in contact with the maternal circulation varies from one species to another and defines two subtypes of hemochorial placentas:

- hemodichorial placenta (primates, lagomorphs, insectivores): 1 layer of syncytiotrophoblast upon one layer of cytotrophoblast based on a basal layer;
- hemotrichorial placenta (rodents): 1 layer of cytotrophoblast based on 2 layers of basal syncytiotrophoblast.

5. Placental exchanges

The placenta is responsible for the vast majority of exchanges between mother and fetus, including that of water, oxygen and carbon dioxide, as well as nutrients to the fetus. It is also a selective filter, blocking or allowing the transfer of certain molecules. The exchange function is intimately linked to fetal growth, with a positive correlation between fetal weight and placental weight in physiological conditions [4], the ratio of fetal weight on placental weight reflecting the overall effectiveness of the placenta. This efficiency must adapt to the needs of the fetus, which
increase in late pregnancy in all mammals. It is not correlated to the number of cell layers present between maternal and fetal circulation.

Exchange mechanisms have been fully described elsewhere [5]. They have been well studied in humans, mice and sheep, but much is less known in other species.

Blood gases (such as oxygen, carbon dioxide, nitrogen), urea and ethanol passively diffuse through the membranes. Gas exchange between the fetus and mother are facilitated in many mammals, including humans, by the presence of fetal hemoglobin that has a higher affinity for oxygen. Fetal hemoglobin is, however, not present in horses, dogs, rabbits and mice.

Glucose, the main energy source of the fetus, is transported through the placenta by facilitated diffusion and fetal glycemia is directly correlated to maternal glycemia. Glucose transporters belong to the SLC proteins (Solute Carrier Family, formerly known as GLUT) family. The placental location and nature of the transporters differ between species [6] and the rate of transfer also differs between species, with highest transfers found in hemochorial placentas [4].

Maternal proteins do not pass the placental barrier. Amino acids are transported by active transfer, as they are transferred in the opposite direction of the maternal-fetal gradient for most amino acids. There are many specific transporters classified according to their dependence on sodium and the type of amino acids (neutral, acidic or basic) they carry [7,8]. Their location varies, but they are mostly located on the plasma membrane of the syncytiotrophoblast. Amino acids are also metabolized in the placenta by specific metabolic pathways in each, which can lead to net transfers that may appear reversed (from the fetus to the mother).

The transport of fatty acids has been reviewed by Duttaroy [9]. Triglycerides are hydrolyzed to the apical membrane of the syncytiotrophoblast and transferred in the form of free fatty acids through specific membrane transporters. In the trophoblast, they can be stored as triglycerides, used for energy through β-oxidation, or converted to active derivatives such as eicosanoids. The fatty acids are transferred to the foetus through transporters present on the basal membrane and the trophoblast fetal vessels. Cholesterol is transported to the placenta via lipoproteins. These lipoproteins interact with receptors (LDL-R, VLDL-R, SR-BI...) located on the apical trophoblastic membrane and the complex is then internalized into the cytoplasmic compartment. Cholesterol is transported to the fetal compartment through ABC transporters.

Immunoglobulins are transferred by transcytosis from mother to fetus in the case of hemochorial and endochorial placentas. In other animals (epitheliochorial and syncytiotrophoblastic placentas), immunoglobulins do not cross the placenta and the offspring is dependent on colostrum intake at birth for passive transfer of the immunity.

6. Hormonal function of the placenta

The placenta is characterized by the intensity and specificity of its hormonal functions. Placental hormones play a vital role in the establishment and maintenance of pregnancy, the adaptation of the maternal organism to pregnancy, growth and development of the fetus and in the parturition mechanism. These hormones are synthesized and secreted by the trophoblast and particularly by the syncytiotrophoblast covering the placental villi. Secretion profiles and serum concentrations vary widely from one species to another. The hormonal secretion of placentas in various species has been reviewed elsewhere [6,10].

6.1. Steroids

The most important placental steroids are progesterone and estrogen. Progesterone is a muscle relaxant hormone essential to the success of pregnancy. Estrogens stimulate the growth of the endometrium and myometrium.

In humans, for the first six weeks of pregnancy, the production of progesterone is mainly provided by the corpus luteum during pregnancy. Placental Production then takes over with the gradual implementation in the syncytiotrophoblast of different enzymes of steroidogenesis. In other mammals, in early gestation, progesterone is also secreted by the corpus luteum, which in some species such as the pig, goat and rabbit, remains indispensable for the duration of gestation [11]. Luteal production of progesterone or progesterone metabolites is relayed by the placenta in sheep, cattle, horses and guinea pigs. For these species but for the horse, the corpus luteum nevertheless continues to produce progesterone throughout gestation. In other species, the production of progesterone relies on the presence of the corpus luteum.

The placenta of mammals also produces estrogens, at generally lower levels than those of progesterone. Their blood levels increased steadily during gestation in most species (except in horses), with a maximum reached just before parturition. In women, placental biosynthesis of estrogen greatly increases after the 9th week of pregnancy, simultaneously with the trophoblastic invasion and expansion of uteroplacental arteries [12]. Estrone sulfate (E1S) is the major form of circulating estrogen in cows and sheep, whose concentrations exceed those of ovarian origin estrogen during the last two thirds of pregnancy. Therefore, the E1S rates are a good indicator of placental function and fetal viability [13]. In the mare, maternal estrogens are principally estrone and estradiol as in other mammals, but other estrogens, equilin and equilinin, are specific to the equine gestation, but their role remains unknown [14].

7. Polypeptidic placental hormones

The human syncytiotrophoblast secretes many polypeptide hormones. These are essentially hCG (human chorionic gonadotropin), hPL (placental lactogen) and in lesser amount, placental growth hormone (placental GH). The placenta of other mammals, particularly trophoblast, also secretes many polypeptide hormones [10].

Chorionic gonadotropin hormones (CG) are present in a dozen of primate species (including humans) and in equines. Gene expression has been demonstrated in rabbits, guinea pigs
and mice [15], but the presence of the protein has not been demonstrated.

8. Placental lactogen hormones

The human placenta also secretes very high amounts of hCS (Chorionic Somatomammotropin) in the maternal compartment. This hormone is also found in fetal blood but in much smaller quantities than in maternal blood. The increased secretion of hPL during pregnancy follows the evolution of placental mass and especially the syncytiotrophoblast where it is synthesised. Its physiological role remains unclear but it could prepare lactation by inducing the proliferation and differentiation of cells of the mammary gland, but also play a role in the fetus as suggested by the presence of its receptors in the fetal liver. It is not essential for pregnancy, as evidenced by the normal evolution of pregnancy in case of gene deletion [16].

In other mammals, also the placenta secretes hPL having structural homology and function with prolactin and Growth hormone. Besides a trophic action on the mammary gland, placental lactogen plays a role in fetal growth in ruminants by stimulating the absorption of maternal nutrients and their use by the fetus. Maternal blood levels are generally higher than those of the fetal circulation, except in the cow where the ratio is reversed [17]. In mice and rats, two hPRL, produced by giant cells of the placenta, are secreted, one during the first half of pregnancy, the other in late pregnancy.

9. Placental proteins related to prolactin

Other hormones related to prolactin have been characterized in placenta in ruminants and rodents. The expression of prolactin-related protein (PRP) genes by the binucleated cells of the placenta has been described in cows and sheep [18] and more recently in goats [19]. At least six PRP were identified in bovine placenta and two PRP in sheep or goat placentas. In rats and mice, at least 22 different genes with similarities PRL were identified in the placenta [20]. The activity of the PRP is linked to the establishment and maintenance of pregnancy. They promote maternal-fetal interaction during the period implantation in humans and in rodents. In ruminants, they operate in particular in the remodelling of the extracellular matrix during placentation.

10. Placental growth hormone

The human placental growth hormone, encoded by the GH-V gene, is specifically expressed in the trophoblast and differs from the pituitary growth hormone by 13 amino acids. It gradually replaces the native pituitary growth hormone in the maternal circulation during the second trimester of pregnancy. In sheep, the expression of an ovine placental growth hormone was demonstrated in trophoblastic cells and syncytium between 27 and 75 days of gestation with a peak expression at 40–45 days, during which time placental growth is very important. Placental growth hormone has been detected in goats, but not in cattle.

11. Other polypeptidic hormones

The placenta also secretes many other peptide hormones such as the members of the TGF-β superfamily, inhibin A and activin A, adipokines, resistin, etc. and many neuropeptides similar to those found in the hypothalamus and pituitary or digestive tract (TRH, GnRH, corticotropin releasing hormone or CRH, somatostatin, ghrelin...).

During pregnancy, the placenta and fetal membranes secrete a large amount of CRH. Placental CRH increases gradually during pregnancy related to an increase in gene expression. It has been proposed that the CRH interacts with estrogens, adrenal steroids and prostaglandins, establish an autocrine loop involved in the induction of labor.

Finally, the placenta is the site of expression of many growth factors such as IGFs and cytokines, which are involved in its development and that of placental transfers [21,22].

12. Pregnancy-associated glycoproteins (PAG)

PAG were first identified in the bovine placenta (PAG1 also called BPSP specific protein of gestation B and PSP60, serum protein of 60 kDa of gestation), and subsequently, in all studied ruminants, wild and domestic, as well as that sows, mare and mouse [23]. These proteins belong to the family of aspartic proteases such as pepsin (typical lobed structure), but most are without enzymatic activity [24]. In ruminants, the PAG is a multigene family with about 100 genes for bovine PAG. Over 20 distinct cDNAs were identified in cattle and more than a dozen in sheep, goats and sows while a single cDNA was identified in the mare. The dosage of PAG, unlike that of the P4, allows specific pregnancy diagnosis of the viability of the conceptus and monitoring of placental development in ruminants [15]. The function of PAG is not clear yet but they could intervene in immunoregulation at the maternal-fetal interface.

13. Conclusion

In conclusion, the placenta is a complex organ, still relatively unknown, which plays a fundamental role in reproduction because it allows its exchange functions the development of the embryo and fetus. It is important to understand the differences between species in terms of anatomical and physiological characteristics in order to properly use animal models to properly infer data related to human physiology and human health during pregnancy.

Disclosure of interest

The authors declare that they have no competing interest.

References


