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IFPA Senior Award Lecture: Mammalian fetal membranes

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ABSTRACT

Background: Fetal membrane development varies greatly across mammals with significant implications for models of human placentation.
Method: Therefore the major patterns of fetal membrane development are reviewed with special focus on functions of the inverted yolk sac in murine rodents.
Findings: In most mammals, yolk sac and chorion form a choriovitelline placenta to support the early embryo, although this soon is supplanted by a chorioallantoic placenta. Human and haplorrhine primates follow a second pattern where precocious development of the extraembryonic mesoderm leads to formation of a secondary yolk sac within the exocoelom. In rodents there is an inverted visceral yolk sac that encloses the embryo and amnion and functions as an accessory to the chorioallantoic placenta through term. Where present, the inverted yolk sac performs a number of functions that in human are assumed by the syncytiotrophoblast of the chorioallantoic placenta. These include transfer of passive immunity, iron, cobalamin and lipoprotein; protein and lipid synthesis; haematopoiesis; and germ cell storage. Most mammals have a large, fluid-filled allantoic cavity. This is not the case in human and haplorrhine primates where there is an allantoic stalk but no allantoic cavity. Some rodents have a small allantoic cavity, but the mouse and other murine rodents do not. The evolution of amnion, yolk sac and allantois is explored.
Conclusions: Fetal membranes deserve close attention. In particular, the mouse model is incomplete unless the yolk sac is studied along with the chorioallantoic placenta.

1. Introduction

The fetal membranes of amniotes are the allantois, amnion, chorion and yolk sac. Both their development and their contribution to placentation vary greatly across mammals. This also is true of the cavities they enclose; in addition to those of the allantois, amnion and yolk sac, these include the exocoelom. In human development, there is an allantoic stalk, but no allantoic cavity; the yolk sac is a short-lived structure; and the exocoelom is obliterated by the end of the second trimester. The mouse commonly is used as a model of human placentation. Here, too, there is no allantoic cavity. In contrast, the inverted visceral yolk sac supports the embryo until the chorioallantoic placenta is formed (around E10) and acts as an accessory placenta through term. It has a wealth of functions [1,2] yet frequently the yolk sac is discarded or ignored in the laboratory either through ignorance or because it has no obvious equivalent in human pregnancy. In ruminants, which are important to veterinary research and as models in fetal physiology, there is yet another pattern. The first object of this review is to explain these differences and examine why they may be important.

The advent of molecular phylogenetics has put classification of mammals on a surer footing and enabled predictions to be made about placental evolution. Most authors have focused on the definitive chorioallantoic placenta. Three features in particular have attracted attention: placental shape, interdigitation between maternal and fetal components and the placental barrier [3–6]. There has been less focus on evolution of the fetal membranes and the second aim of this review is to redress the balance.

A third aim is to highlight the research opportunities offered by the fetal membranes. The yolk sac in particular is important during early embryonic development in a range of species including our own. In the mouse and other rodents, the inverted yolk sac performs several of the functions that are assigned to the syncytiotrophoblast of human placenta. Therefore the mouse model is incomplete unless the membranes are studied together with the placenta.

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2. Amniote fetal membranes

The yolk sac is the oldest of the fetal membranes. It is found in all vertebrates and is the basis of placentation in viviparous fish [7]. Amniotes have much more than a yolk sac (Fig. 1A). Indeed, the cleidoic egg was a major step in evolution, not least because the fluid-filled amnion offered a safe environment for embryonic development. In addition the allantois acted as a respiratory organ [8]. The whole was packaged in a leathery shell beneath which was found the chorion. There was still the risk of desiccation and a calcified shell was evolved in turtles, crocodiles and dinosaurs (including birds) [9]. An alternative solution, chosen by many reptiles, is viviparity, which often is supported by a choriovitelline and/or chorioallantoic placenta (Fig. 1B).

A placenta is an organ for maternal–fetal exchange between maternal and fetal vessels (haemotrophic nutrition) or by pinocytosis and phagocytosis of uterine secretions, cell debris and maternal red cells (histiotrophic nutrition). As the name suggests, a chorioallantoic placenta is derived from the chorion, which supplies the trophoblast, and the allantois, which supplies fetal blood vessels and associated connective tissue. A choriovitelline placenta, on the other hand, derives its vasculature from the yolk sac. It is the principal form of placentation in marsupials, but in the so-called placental mammals may be either completely absent, form a temporary structure or continue as an inverted yolk sac until term. In common parlance "placenta" often refers to compact structures such as the placental disk of rodents or the placentomes of ruminants, but the fetal membranes can form additional or paraplacental structures such as the inverted yolk sac of rodents or the interplacentomal chorioallantois of ruminants.

About 20% of reptiles are viviparous although not all of those have a placenta [7]. Among mammals, monotremes are a special case. Although they are egg-laying mammals, the first phase of embryonic development occurs in the uterus and is supported by maternal secretions absorbed through the yolk sac [10]. All marsupials have a choriovitelline placenta. The koala, wombats and bandicoots have an additional chorioallantoic placenta [11]. A detailed account of monotremes and marsupials is beyond the scope of this review.

3. Fetal membranes of the pig, cow, horse and tenrec

Relations between the fetal membranes and their role in placentation are best appreciated for a species like the pig (*Sus scrofa*) which undergoes a simple sequence of developmental stages. Fig. 2A shows a stage at which amnion formation is almost complete and the exocoelom is present as a cavity within the extraembryonic mesoderm. Where trophoblast is lined with extraembryonic mesoderm, it constitutes the chorion. Fig. 2B shows an elongated blastocyst in which the allantois has not yet made contact with the chorion. The yolk sac, on the other hand, has attached to the chorion, mainly as a two-layered structure (called the bilaminar omphalopleure), but there is also a small area with vascular mesoderm. This is the choriovitelline placenta (trilaminar omphalopleure). Slightly later (Fig. 2C), the yolk sac has been displaced by expansion of the allantois and formation of a chorioallantoic placenta.

The cow (*Bos taurus*) goes through a comparable sequence, but forms a placenta of the cotyledonary type (Fig. 3A). Note that later in bovine gestation there are two large fluid-filled sacs. The allantoic cavity is defined by the chorioallantois. The amnion fuses in places with the chorion so there is also an amniochorion. Cotyledons form where the chorioallantois comes in contact with the endometrial caruncles. Together cotyledons (fetal) and caruncles (maternal) form placentomes, which are the principal exchange areas. The interplacentomal regions are less complex in structure, but nonetheless play a part in maternal–fetal interactions. The exocoelom is largely obliterated during expansion of the amniotic and allantoic cavities.

Enlargement of the allantoic cavity at the expense of the yolk sac is seen in many other mammals, including the shrew tenrec (*Microgale brevicaudata*) (Fig. 3B) [12].

In the horse (*Equus caballus*), the yolk sac plays an essential role by absorbing the secretions of the uterine glands (histiotrophe). This process begins shortly after dissolution of the blastocyst capsule, around day 20 of gestation, when the yolk sac is exposed to the uterine lumen. In twin pregnancies, survival depends on both yolk sacs having unhindered access to the uterine secretions [13,14]. Subsequently, the yolk sac is reduced in size as the allantois expands (Fig. 3C) [15]. The chorionic girdle between the developing allantois and regressing yolk sac is the source of invasive trophoblast cells that migrate deep into the uterine wall to form the endometrial cups.

4. Fetal membranes of the mouse and other rodents

Despite a long tradition stretching back to Selenka [16] and

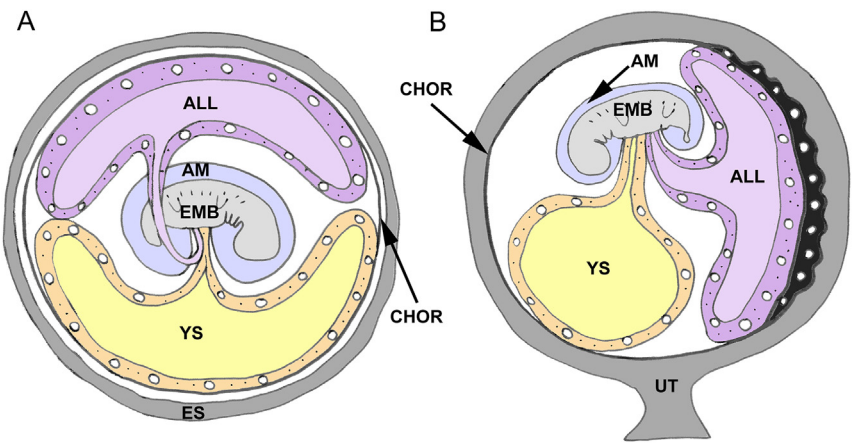

Fig. 1. Origins of the fetal membranes. (A) The amniote egg as found in birds, reptiles, and monotremes. (B) Embryo (EMB) and fetal membranes within the uterus of a generic mammal. The chorion (CHOR) is found beneath the eggshell (ES) in the former and facing the uterine wall (UT) in the latter. In birds and reptiles, the other membranes enclose the amniotic cavity (AM), allantoic vesicle (ALL), and yolk sac (YS). In some marsupials and all placental mammals, the allantois and chorion form a chorioallantoic placenta. Yolk sac and chorion can form a choriovitelline placenta, which may be a temporary or permanent structure or (as in the human) altogether absent. Reprinted from Carter and Mess [68] © 2014 with permission from Elsevier.

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