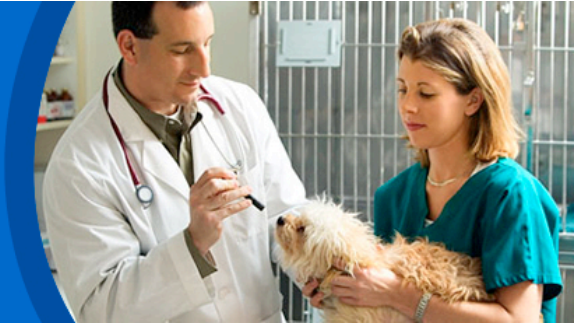




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Placental architecture and the limits of translation: A comparative anatomical perspective on artificial placenta research in the sheep (*Ovis aries*)

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ABSTRACT

Artificial placenta systems now support premature lambs for weeks, and clinical translation is under active discussion. Almost the entire evidence base has been generated in sheep (*Ovis aries*), with contributions from goats (*Capra hircus*) and pigs (*Sus scrofa*). These species differ from humans in placental architecture not in degree but in kind. Ruminants possess a cotyledonary synepitheliochorial placenta in which the uterine epithelium persists and is modified by migrating trophoblast binucleate cells, whereas the human placenta is discoid and haemochorial, with trophoblast bathed directly in maternal blood. The interposed cell layers, the mechanisms of macromolecular transfer and the immunological relationship between dam and fetus therefore differ substantially. This review asks what those differences imply for the interpretation of artificial placenta experiments. Four areas of divergence are examined: the architecture of the interhaemal barrier and its consequences for transfer; the absence of prenatal immunoglobulin transfer in ruminants, which leaves the ovine fetus agammaglobulinaemic when placed on an extracorporeal circuit and makes ovine infection data difficult to extrapolate; umbilical cord and vessel morphology in relation to cannulation; and placental vascular resistance, which determines the afterload imposed on the fetal heart in pumpless circuits. Recent porcine work, in which circulatory collapse was attributed to supraphysiological circuit resistance, illustrates that outcomes are not conserved across models. We argue that comparative morphology is a determinant of which preclinical findings should transfer, and propose that anatomical reasoning be incorporated explicitly into study design and reporting.

Keywords: Extracorporeal membrane oxygenation, Infant (extremely premature), Placenta, Placentation, Sheep, Translational research (biomedical)

1 | Introduction

Extreme prematurity remains a leading cause of neonatal death and long-term morbidity, and a substantial part of the injury sustained is iatrogenic, arising from mechanical ventilation of lungs that are not structurally prepared to serve as organs of gas exchange (De Bie *et al.*, 2021) [1]. The response that has attracted most attention over the past decade is conceptually straightforward. Rather than compelling an immature lung to breathe, the placenta is replaced: gas exchange is handed over to a membrane oxygenator plumbed into the umbilical circulation, while the fetus lies immersed in artificial amniotic fluid so that its lung remains liquid-filled and goes on maturing as it would have done in utero (Partridge *et al.*, 2017) [2]. Two groups have reported the most substantial results. Partridge *et al.* (2017) [2] maintained extremely premature lambs in a pumpless, umbilical-cord-interfaced system within a closed fluid circuit for up to four weeks, with stable haemodynamics, normal blood gas parameters and preserved patency of the fetal circulation. Usuda *et al.* (2019) [3] subsequently supported ovine fetuses at a developmental stage approximating the human border of viability using ex vivo uterine environment therapy. Both achievements are considerable. Both rest on the sheep.

This is where an anatomical difficulty arises. The sheep was adopted for reasons that are largely practical: fetal size is convenient, gestational physiology is well characterised, surgical access is manageable, and decades of ovine fetal research supply comparative data. None of these reasons is anatomical. The ovine placenta was not selected because it resembles the human placenta. It does not resemble it. The two differ in

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gross form, in histological organisation, in the number and identity of the cell layers separating the two circulations, and in the range of substances able to cross between them.

Comparative placentation has a long descriptive literature, most of it produced by anatomists and reproductive biologists and much of it predating the artificial placenta field by decades. It is applied routinely in reproductive toxicology, where the dependence of placental permeability on interhaemal architecture is well recognised (Furukawa *et al.*, 2014) [4]. It has been applied relatively little in the artificial placenta literature, which is written mainly by neonatologists, fetal surgeons and bioengineers, and which has tended to treat the ovine placenta as a functional stand-in rather than as a structure with properties of its own.

Our purpose is not to question the value of the ovine work, which is substantial and carefully executed. It is to ask a narrower question falling squarely within the competence of the anatomical community. Given what is known about the structure of the ruminant and human maternal-fetal interfaces, which findings from these experiments should be expected to translate, which should be regarded as properties of the model, and where does the existing evidence simply not address the human case?

1.1 | Approach taken

This is a narrative rather than a systematic review. Literature was identified through PubMed, *Scopus* and Web of Science using combinations of the terms artificial placenta, artificial womb, extracorporeal fetal support, comparative placentation, synepitheliochorial, epitheliochorial and haemochorial, supplemented by hand-searching of reference lists. Preclinical device studies were included where they reported the species used and the circuit configuration. Morphological sources were selected for their descriptive authority rather than recency, since the underlying comparative anatomy is long established. No formal quality appraisal was applied, and the review does not attempt exhaustive coverage of the device literature.

2 | The maternal-fetal interface in ruminants and in humans

2.1 | Classification and its functional basis

The chorioallantoic placentae of eutherian mammals are conventionally classified according to the number and nature of the tissue layers interposed between maternal and fetal blood. Three principal types are recognised on this basis: the epitheliochorial type of horses, pigs and ruminants; the endotheliochorial type of carnivores; and the haemochorial type of primates, rodents and rabbits (Furukawa *et al.*, 2014) [4]. The classification is not merely descriptive. How many layers lie within the interhaemal area governs how readily nutrients pass from the maternal side to the fetal, and is regarded as among the principal determinants of interspecies differences in placental permeability (Furukawa *et al.*, 2014) [4]. Reproductive toxicologists have long treated this as a first-order consideration when extrapolating transfer data between species, and the same logic applies with equal force to any technology that intervenes at the maternal-fetal interface.

Ruminants occupy a position requiring qualification. The trophoblast of sheep and cattle (*Bos taurus*) contains binucleate cells which migrate across the microvillar junction and fuse with the uterine luminal epithelium, generating a fetomaternal hybrid tissue: multinucleate syncytial plaques in the ewe, trinucleate cells in the cow. Because the interface therefore contains hybrid elements and is not strictly epitheliochorial, the term synepitheliochorial is preferred for ruminants, with epitheliochorial reserved for species in which only trophoblast and intact maternal epithelium meet (Wooding, 2022) [5]. Binucleate cells constitute a consistent proportion of the trophoblast across the ruminants examined and deliver placental lactogen, pregnancy-associated glycoproteins and other products into the maternal compartment (Wooding, 2022) [5].

The human placenta is discoid and haemochorial. Maternal blood is delivered into an intervillous space where it contacts syncytiotro-

phoblast directly; no maternal epithelium or endothelium intervenes. The functional consequences are a short and comparatively permissive diffusion pathway and, critically, an interface across which receptor-mediated macromolecular transport operates.

2.2 | Gross organisation and its haemodynamic implications

The gross architectures are equally dissimilar. The ovine placenta is cotyledonary: fetal cotyledons interdigitate with endometrial caruncles to form discrete placentomes, which in sheep may number from a few dozen to well over a hundred, with considerable variation in size and villous architecture between individual placentomes and between animals (Wooding, 2022) [5]. Exchange is thus distributed across many small, semi-independent units, supplemented by interplacentomal regions where attachment remains epitheliochorial and where histotrophic nutrition proceeds through areolae. The human placenta, by contrast, is a single discoid organ with a unitary vascular supply.

This difference is not cosmetic. A distributed, multi-unit exchange organ and a single discoid one differ in the topology of their vascular trees, in the distribution of resistance across those trees, and in the manner in which regional perfusion failure manifests. When the native placenta is replaced by an extracorporeal oxygenator, the pertinent question is what precisely the circuit is replacing, and the answer is not the same in the two species. We return to the haemodynamic consequences in Section 3.4, where they turn out to be the point at which the comparative anatomy has already been shown to bite.

3 | Where the ovine model and the human case diverge

3.1 | Barrier architecture and macromolecular transfer

The most immediate consequence of the structural difference concerns what is able to cross. Where several cell layers are interposed, as in the ruminant placentome, transfer of large molecules is restricted; where trophoblast is directly exposed to maternal blood, it is not (Furukawa *et al.*, 2014) [4]. For an artificial placenta this matters in a particular way. The device does not reproduce the native barrier at all. It substitutes a synthetic membrane whose transfer characteristics are set by polymer chemistry and circuit design rather than by biology.

It follows that the change imposed by connecting a fetus to an artificial placenta is not the same change in the two species, because the baseline departed from is not the same. An ovine fetus is moved from a multilayered, transfer-restrictive interface to a synthetic one. A human fetus would be moved from a permissive, receptor-equipped interface to a synthetic one. The direction and the magnitude of the alteration in what reaches the fetus therefore differ. Observations of nutritional adequacy, of drug and metabolite handling, and of the accumulation or depletion of circulating factors in lamb experiments cannot be assumed to describe what would occur in a human infant, and in some instances the expected direction of error can be predicted from the anatomy alone.

3.2 | Immunological transfer: the sharpest divergence

The clearest and most consequential difference is immunological. In synepitheliochorial and epitheliochorial placentae, transfer of immunoglobulin from dam to fetus does not occur, except where the placenta is pathologically altered; passive immunity in these species is acquired after birth, through ingestion and absorption of colostrum (Chucuri *et al.*, 2010) [6]. In haemochorial placentae the mechanism of transfer is by comparison facilitated, and substantial maternal immunoglobulin reaches the fetus before birth (Chucuri *et al.*, 2010) [6].

The implication for artificial placenta research is direct and, in our assessment, underappreciated. A lamb placed on an artificial placenta before term is essentially agammaglobulinaemic, and will remain so for the duration of support, because the route by which it would normally acquire antibody is colostral and is unavailable to a fetus submerged in artificial amniotic fluid. A human infant at 22 to 24 weeks, by contrast, would arrive on such a circuit having already received maternal immunoglobulin transplacentally, although the quantity at

that gestation is modest, since transfer accelerates through the third trimester.

Infection has been among the most persistent obstacles in this field. Circuit-related sepsis and contamination were identified explicitly among the problems that earlier systems had to overcome (Partridge *et al.*, 2017) [2], and infection has repeatedly limited survival in ovine work. The comparative anatomy suggests two things. First, the ovine model may systematically overstate infectious risk relative to the human case, because the experimental subject is immunologically naive in a way the human subject would not be. Second, antimicrobial and asepsis strategies validated in an agammaglobulinaemic lamb are not necessarily the strategies appropriate to a partially protected human infant. Neither inference can be drawn from the ovine data considered alone. Both follow from placental structure, and both are testable.

There is a corollary that deserves emphasis for a veterinary readership. The agammaglobulinaemia of the newborn ruminant is not an incidental feature of the model but the central fact of neonatal ruminant immunology, familiar to every practitioner who has managed failure of passive transfer in calves and lambs. That a field of human neonatal engineering should have adopted, as its principal model, a species whose defining neonatal vulnerability is precisely the one the human neonate does not share, is a point that the veterinary anatomical community is well placed to make and that has not, so far as we can determine, been made forcefully.

3.3 | Umbilical vasculature and the cannulation interface

Every system of this kind depends upon establishing and maintaining vascular access through the umbilical vessels, and the umbilical cord is the one component that cannot be engineered around. Cord length, vessel calibre, wall structure, the extent and distribution of Wharton's jelly, and the propensity to vasospasm together determine whether cannulation can be achieved atraumatically and whether flow can be sustained over weeks. These are anatomical properties, and they are species-specific.

The field has encountered this directly. Spasm of the umbilical arteries, and the wider problem of securing durable access to those vessels, were among the recognised failures of earlier circuits; a redesigned method of achieving that access was one of the three elements to which the success of the EXTEND system was attributed (Partridge *et al.*, 2017) [2]. The clinical significance of the interface is likewise recognised in work on the transfer of a fetus from the uterus to a liquid-based support system, which has been examined through simulation in the context of perinatal life support development (van Haren *et al.*, 2024) [7].

What has been less thoroughly addressed is the comparative morphology underlying all of this. It is notable that when investigators sought an alternative species, umbilical cord anatomy was among the stated reasons for the choice: preterm Yucatan miniature piglets were selected in part because they resemble extremely preterm human infants in size and share comparable umbilical cord anatomy (Charest-Pekeski *et al.*, 2021) [8]. That the choice of model was justified anatomically, rather than on grounds of convenience, is precisely the reasoning we are advocating. A detailed quantitative comparison of ovine, porcine and human umbilical cord architecture at equivalent developmental stages, expressed in terms relevant to cannula selection and to the mechanics of a cord-mounted interface, remains a contribution that anatomists are equipped to make and that the engineering literature currently lacks.

3.4 | Placental vascular resistance and pumpless circuit design

A design feature distinguishing the more successful recent systems is the absence of a mechanical pump. In the pumpless arteriovenous configuration, flow through the oxygenator is generated by the fetal heart alone, so that the circuit constitutes an afterload imposed upon a fetal myocardium of limited reserve. Among the principal obstacles that defeated earlier systems was circulatory deterioration traceable to a mismatch between what the oxygenator demanded of the fetal heart

and what that heart could deliver, on both the filling and the ejection side (Partridge *et al.*, 2017) [2]. Whether such a design is viable therefore depends on how the resistance of the artificial circuit compares with the resistance of the placenta it replaces.

This is not a speculative concern, and the evidence that it is decisive comes from precisely the kind of cross-species comparison we are advocating. Charest-Pekeski *et al.* (2021) [8] supported preterm miniature pigs on an artificial placenta and observed umbilical venous flow below physiological values, tachycardia, and a right ventricle that enlarged progressively while contracting less effectively, the sequence ending in hydrops and collapse of the circulation. They attributed this outcome to excessive afterload imposed by supraphysiological circuit resistance together with augmented sympathetic activity. A configuration that sustained lambs for weeks did not sustain pigs, and the failure was haemodynamic.

Complementary evidence comes from controlled manipulation within the ovine model. Cao *et al.* (2025) [9] clamped the oxygenator circuit incrementally in lambs supported by the EXTEND system and demonstrated that as circuit resistance rises, combined cardiac output falls significantly, with the reduction most pronounced in the right ventricle; umbilical arterial, umbilical venous and inferior caval velocities decline while middle cerebral arterial velocity increases. The authors state explicitly that their findings provide a basis for the manipulations of circuit resistance that may be required to create optimal haemodynamic conditions when the technology is applied to humans, and that the approach establishes experimental models for studying abnormal placental vascular resistance.

Taken together these two studies establish the point this review is concerned with. Circuit resistance is a critical determinant of survival; the tolerable range is not identical across species; and the native placental vascular architecture against which the circuit is matched differs between a cotyledonary ruminant placenta of many placentomes and a single discoid human organ. The corollary is that resistance parameters optimised in the lamb should not be carried across to human application without anatomically informed adjustment, and that morphometric characterisation of the human placental vascular tree is a prerequisite rather than a refinement.

3.5 | Endocrine function

The placenta is also an endocrine organ, and here too the species differ in ways traceable to structure. In ruminants the binucleate cell population is the source of placental lactogen and of pregnancy-associated glycoproteins, delivered to the maternal compartment by the very fusion events that define synepitheliochorial placentation (Wooding, 2022) [5]. The human placenta produces an overlapping but not identical repertoire by different cellular means. An artificial placenta replaces gas exchange; it does not replace endocrine function in either species. The endocrine deficit imposed is therefore species-specific in composition, and inferences about growth, maturation and metabolic adaptation drawn from lamb studies carry that qualification. This is not a trivial caveat: reduced somatic and organ growth has been reported in ovine fetuses maintained on artificial placenta support for extended periods, and the contribution of endocrine deprivation to such findings cannot be assumed to be conserved across species.

4 | Implications for interpretation and study design

The argument advanced here is not that ovine work is invalid. It is that the sheep is a model of convenience rather than a model of homology, and that the distinction should be made explicit rather than left implicit. Several practical consequences follow.

4.1 | Reporting

Preclinical artificial placenta studies would be considerably more useful to those attempting translation if they stated plainly which observed outcomes are plausibly independent of placental type and which are not. Circuit patency, thrombosis, cannula performance and mechanical durability fall largely into the first category.

Immunological outcomes, macromolecular transfer, nutritional adequacy, endocrine adaptation and the haemodynamic tolerance of circuit resistance fall substantially into the second. A short statement to this effect in the discussion of preclinical papers would cost little and would materially assist the reader.

4.2 | Model selection

No available species combines haemochorial placentation with a fetus of workable size, and this is a genuine constraint rather than an oversight. Non-human primates are haemochorial but present obvious practical, financial and ethical obstacles. Rabbits and rodents are haemochorial but far too small. The field has chosen size and surgical tractability over placental homology, which is defensible, but the cost of that choice should be stated in the papers that depend upon it. Where a porcine model has been adopted, the anatomical justification offered has centred on fetal size and umbilical cord architecture (Charest-Pekeski *et al.*, 2021) [8], and it is worth noting that the pig remains epitheliochorial: the substitution addresses cord anatomy and body size, not barrier type.

4.3 | Complementary approaches

Where a question is dominated by placental type, ovine experiments will not resolve it and other approaches are required. Ex vivo perfusion of the human placenta, comparative morphometry of the umbilical cord and of the placental vascular tree, and computational haemodynamic modelling parameterised on human rather than ovine anatomy are all within the reach of morphological laboratories. None of these requires the resources of a large fetal surgical programme, and each addresses a question the animal models cannot.

4.4 | Bearing on the ethics of translation

Debate about first-in-human trials of these technologies has been extensive, and has recognised that different technical approaches raise materially different ethical problems (Flake *et al.*, 2023) [10]. That debate necessarily rests on an assessment of how well the preclinical evidence predicts human outcomes. If a portion of that evidence is structurally non-transferable, the assessment of residual uncertainty changes, and so does the justification offered to prospective participants. Comparative anatomy is thus not only a technical input to device design but a relevant input to the ethics of translation, and it should be represented in the bodies that deliberate on it.

5 | Conclusions

Artificial placenta technology has advanced from a sequence of short-lived attempts spanning several decades to systems capable of maintaining premature lambs for weeks, and serious consideration of human application now follows (De Bie *et al.*, 2021; Partridge *et al.*, 2017; Usuda *et al.*, 2019) [1, 2, 3]. The evidence underlying that progress was generated almost entirely in a species whose placenta is synepitheliochorial, cotyledonary and impermeable to immunoglobulin, and it is being used to reason about a species whose placenta is haemochorial, discoid and permissive.

That mismatch does not invalidate the work. It does mean that the preclinical record should be read selectively, with explicit attention to which findings depend on placental type and which do not. The porcine experience, in which a circuit configuration successful in the lamb produced progressive right ventricular failure and circulatory collapse (Charest-Pekeski *et al.*, 2021) [8], demonstrates that this is not a theoretical concern. Making the separation between transferable and non-transferable findings is an anatomical task, and one the comparative morphological community is better placed to perform than the clinical and engineering groups currently carrying the field. We suggest it be performed explicitly, and before rather than after human application begins.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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