

Why Do the Fetal Membranes Rupture Early after Fetoscopy? A Review

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Keywords

Amnion · Chorion · Fetoscopy · Iatrogenic preterm premature rupture of membranes · Matrix metalloprotease · Preclinical model

Abstract

Iatrogenic preterm premature rupture of the fetal membranes (iPPROM) remains the Achilles' heel of keyhole fetal surgery (fetoscopy) despite significant efforts in preclinical models to develop new therapies. This limited success is partially due to incomplete understanding why the fetal membranes rupture early after fetoscopy and notable differences in membrane physiology between humans and domestic species. In this review, we summarize aspects of fetoscopy that may contribute to iPPROM, the previous efforts to develop new therapies, and limitations of preclinical models commonly used in fetal membrane research.

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Introduction

Keyhole fetal surgery (fetoscopy) is used to treat complicated monochorionic twin pregnancies or fetuses with congenital abnormalities [1, 2]. These procedures are generally performed at mid-gestation using a camera and instruments inserted into the amniotic space through ports in the uterus and fetal membranes [3]. The ports can be positioned percutaneously or the uterus can be partially exteriorized and the ports inserted directly [4]. More complex fetoscopic procedures require gaseous distension of the amniotic cavity (amniotic insufflation) to improve visibility within the uterus and allow easier manipulation of surgical instruments [5]. While fetoscopy aims to improve postnatal outcomes, postoperative iatrogenic preterm premature rupture of the fetal membranes (iPPROM) remains its Achilles' heel. iPPROM complicates ≈30% of fetoscopic procedures, but rates can be as high as 85–100% following complex procedures using amniotic insufflation [5–10]. iPPROM increases the risk of lung hypoplasia due to prolonged oligohydramnios, chorioamnionitis, and preterm birth, all of which have significant implications

Table 1. Potential mechanisms of iatrogenic PPRM and novel therapies

Potential mechanisms of iatrogenic PPRM	Novel therapies	Pre-clinical studies	Clinical studies
1. Postoperative chorioamniotic separation	Membrane plugs Membrane patches Membrane sutures Tissue sealants and glues Oblique port entry	[12–19] [17, 23–25] [14] [14, 17, 28, 91–97] [90]	[20–22] – [4, 27] – –
2. Membrane apoptosis or tissue damage at the port site	Seldinger technique Reducing port number/diameter	– –	[3, 21, 26] [3, 11, 26, 27]
3. Membrane overdistension	Reducing insufflation pressures	–	[27]
4. Membrane dehydration and desiccation	Heated humidified amniotic insufflation	[4, 27, 29]	[29–31]
5. Diluting the amniotic fluid	Amniotic fluid substitute	–	–

for the fetus and potentially offset the benefits of surgery [11]. Although perinatal outcomes are generally improving after fetoscopy, the risk of iPPROM means these procedures are only considered for the most severely affected fetuses, where the potential advantages of surgery outweigh the significant risks [1, 4, 10].

Techniques to reduce iPPROM after fetoscopy have been investigated extensively in humans and preclinical models (summarized in Table 1) [6]. Efforts have mainly focused on minimizing membrane damage by reducing the number and diameter of fetoscopic ports and using plugs (gelatin or collagen), glues, patches, or sutures to seal the holes left in membranes after surgery [3, 11–28]. More recently, heated and humidified CO₂ gas has been used for amniotic insufflation to prevent the fetal membranes dehydrating and becoming prone to rupture after surgery [4, 27, 29–31]. Although many of these techniques have been shown to protect the membranes from injury or prevent amniotic fluid leakage (amniorrhaxis) in preclinical models, there is limited evidence to show they reduce iPPROM in humans [3, 11, 26, 32]. This difficulty developing and translating strategies to reduce iPPROM is largely due to the limited understanding why the fetal membranes rupture early after fetoscopy. Herein, we summarize the potential mechanisms and preventions of iPPROM after fetoscopy. In addition, we provide an overview of preclinical models commonly used in fetal membrane research and describe their relevance to human fetal membrane physiology.

Structure of the Human Fetal Membranes

The fetal membranes surround the fetus during pregnancy and play a critical role in maintaining the pregnancy to term (shown in Fig. 1) [33]. The innermost membrane, the amnion, provides the majority of structural integrity [33]. The amnion is formed 10–14 days postfertilization when mesoderm cells migrate from between the layers of the bilaminar embryo to fuse with the ectoderm lining of the amniotic cavity [34]. The ectoderm gives rise to the cuboidal amniotic epithelium which lines the surface of the amnion facing the fetus and is held in place by a basement membrane composed of collagens (type I and III) and glycoproteins (laminin, nidogen, and fibronectin) [34–36]. The amniotic mesoderm forms a layer of compact type I and III collagen beneath the basement membrane that provides the amnion with its tensile strength [33, 35, 36]. This compact layer is produced and maintained by fibroblasts in an adjacent layer of loose collagen also derived from the mesoderm, known as the fibroblast layer [35, 37]. The human amnion is almost completely avascular, sourcing nutrients, and exchanging wastes with the amniotic fluid [34, 38].

The amnion is separated from the outer chorionic membrane by a space known as the intermediate or spongy layer (shown in Fig. 1) [34, 37]. This space is liquid filled until 12–15 weeks' gestation when the expanding amnion adheres to the chorion. The loose collagen adhesions and hydrated proteoglycans within the intermediate layer allow the amnion to slide independently over the chorion which increases the membrane's tensile strength [33, 35, 36].

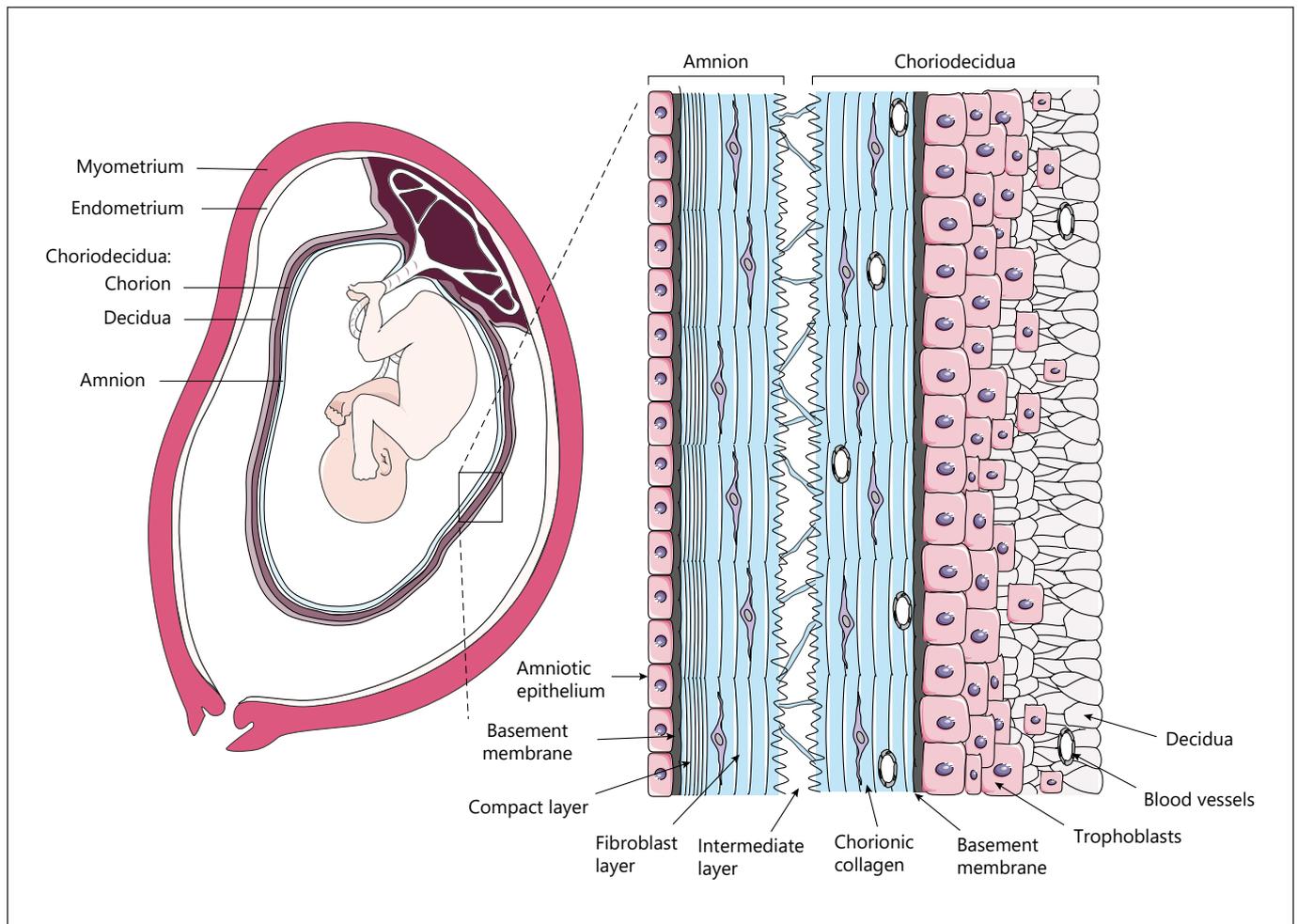


Fig. 1. The arrangement and structure of the human fetal membranes. The human fetal membranes comprise the amnion and choriodecidua. The amnion is composed of a single layer of amniotic epithelium, basement membrane, and underlying collagen. The chorionic collagen faces the amnion and sits on a layer of trophoblasts derived from the placenta. The decidua fuses with the outer surface of the chorion to form the choriodecidua.

The chorion surrounds the amnion and is formed by fusion of the mesoderm with the outer cells of the embryo known as the trophoblasts [34]. The chorionic mesoderm differentiates to become a layer of loose reticular collagen and fibroblasts that face the amnion (shown in Fig. 1) [34]. This collagen is supplied by a network of fetal blood vessels arising from the allantois and its outer surface is lined by the trophoblasts. The outer surface of the chorion is covered by a layer of maternal cells known as the decidua that were once the endometrium overlying the implanted embryo. The decidua is rich with maternal blood vessels and immune cells and fuses with the chorion during early gestation forming the choriodecidua [34].

Rupture of the Fetal Membranes at Term

During pregnancy, there is little change in the composition of the fetal membranes; however, from 37 to 38 weeks gestation, the membranes overlying the cervix become thin and weaken [39–42]. This localized weakening makes the amnion and chorion more susceptible to rupture as the descending fetus and contracting uterus progressively stretch the membranes [37]. The final failing of the membranes plays an important role in promoting the onset of labor and is characterized by membrane separation (chorioamniotic separation) which then promotes rupture of the choriodecidua and amnion in turn (shown in Fig. 2) [33].

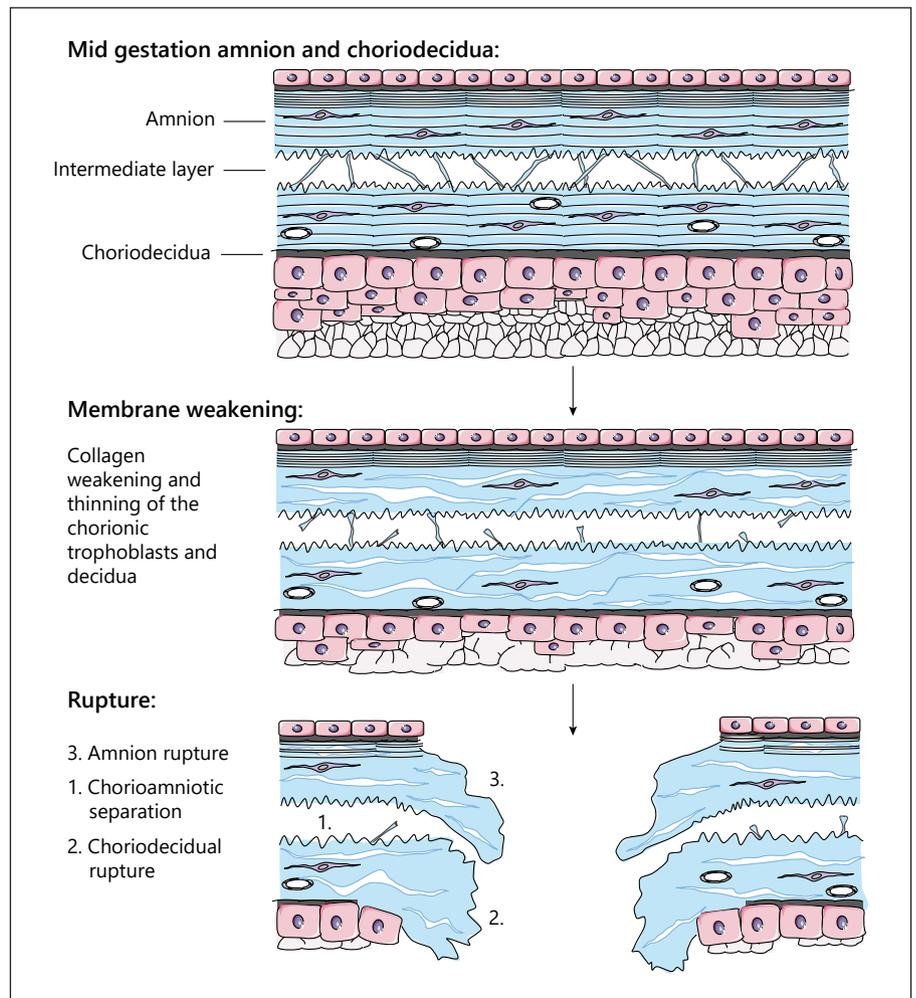


Fig. 2. Fetal membrane weakening and rupture. The amnion and choriodecidua progressively weaken before they rupture both at term and preterm. The final failing of the membranes occurs in 3 phases: (1). the amnion and chorion separate which decreases the tensile strength of the membrane, (2) the decidua and chorion rupture causing the amnion to stretch, and (3) the amnion ruptures [33].

The progressive membrane weakening that precedes term rupture is thought to be mediated by a family of collagen degrading enzymes known as matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs) [43–45]. During late gestation, amniotic epithelial cells and chorionic trophoblasts increase the proportion of activated MMPs, particularly MMP-9, within the membrane while reducing TIMPs [45]. Increased MMP activity causes disruption and degradation of structural membrane collagens which reduces the membrane’s tensile strength [39, 42, 46–54]. These changes overlying the cervix have been described as the “zone of altered morphology” and can be distinguished histologically in human explants as the swelling of membrane collagen and thinning of the chorionic trophoblasts and decidua [36, 47]. Similar changes in fetal membrane collagen have been documented in animal models preceding labor [36, 39, 55–57].

There have been significant efforts to understand the factors that normally induce MMP-associated weakening of the late gestation fetal membranes. Although a common pathway is yet to be identified, various genetic (apoptosis of the amniotic epithelium and chorionic trophoblasts [49, 55, 58–65]), epigenetic (changes in MMP and TIMP promotor genes [66, 67]), physical (increasing membrane stretch [39, 68–70]), inflammatory (cytokines release by local immune cells and accumulating oxidative stress [39, 71, 72]), and hormonal (increased relaxin levels [6, 73]) factors have been suggested.

Possible Mechanisms of Iatrogenic PPROM

While spontaneous PPROM is a complex and multifactorial pathology, many known risk factors damage the fetal membranes and prematurely upregulate membrane

weakening and rupture [37, 74]. Puncturing the membranes with the fetoscopic port, distending the uterus with unconditioned CO₂, and diluting the residual amniotic fluid during fetoscopy may all damage the fetal membranes intraoperatively and increase the risk of iPPROM.

Postoperative Chorioamniotic Separation

Chorioamniotic separation is identified on ultrasound after 20–40% of fetoscopic procedures and significantly increases the risk iPPROM [4, 9, 27, 75–77]. This separation is thought to result from friction between the fetoscopic port and fetal membranes which damages the loose collagen adhesions holding the membranes together [76, 78]. As described above, chorioamniotic separation plays an important biomechanical role in promoting term fetal membrane rupture and similar membrane weakening after fetoscopy may predispose iPPROM [33].

Membrane Apoptosis or Damage at the Port Site

In addition to causing chorioamniotic separation, the fetoscopic ports may damage the cells surrounding the insertion point. Histological studies have identified apoptosis in the amniotic epithelium and chorionic trophoblasts surrounding the port sites as well as disorganization of the membrane collagen [78]. This injury is thought to be due to shearing forces between the fetoscopic port and fetal membranes as the port is inserted or the instruments are manipulated during surgery [3]. Although apoptosis is an important trigger of MMPs, the effect of this injury on the risk of iPPROM after fetoscopy remains unclear [29, 49, 55, 58–65].

Membrane Overdistension

While the fetal membranes tolerate the progressive stretch caused by the growing fetus and excessive stretch, such as in multi-gestation pregnancies or polyhydramnios, trigger membrane weakening increases the risk of spontaneous PPROM [37]. Liquid or gaseous distension of the fetal membranes during fetoscopy may trigger similar weakening mechanisms after surgery and increase the risk of iPPROM. Human case series reporting mean amniotic insufflation pressures of ≈ 15 mm Hg report higher iPPROM rates than centers using ≈ 12 mm Hg [5, 8, 9, 27]. While this difference may represent increased membrane injury and weaken with increased distension during fetoscopy, differences in surgical protocol between these cohorts, such as the use of fetal membrane sutures and heated, humidified CO₂ for insufflation could also explain the differences in iPPROM rates [27].

Membrane Dehydration and Desiccation

The amniotic fluid plays an important role in hydrating amniotic collagen and maintains the membrane's tensile strength [79]. Prolonged amnion exposure to gas in vitro dehydrates amniotic collagen making it brittle and more likely to rupture [79, 80]. While this weakening is reversible in vitro when the amnion is reexposed to liquid, similar dehydration and weakening may occur during amniotic insufflation, increasing the likelihood of iPPROM after fetoscopy [79].

In addition to dehydrating amniotic collagen, the low temperature ($\approx 22^\circ\text{C}$) and humidity (0–5%) of insufflated CO₂ may damage the amniotic epithelium, upregulate MMPs, and increase the risk of iPPROM [81]. Preliminary sheep studies have shown that amniotic insufflation with unmodified (cold and dry) CO₂ increases membrane inflammatory cell counts which may represent a response to amnion damage [30, 31]. Other fields of endoscopy have demonstrated peritoneal and pleural desiccation following exposure to cold, dry CO₂ insufflation [80, 82–85]. While the peritoneum, pleura, and amniotic epithelium are anatomically different, they are all liquid-lined epithelium and appear to be susceptible to injury when exposed to CO₂ for prolonged periods.

Diluting the Amniotic Fluid

The amniotic fluid is often replaced with warmed Ringer's lactate either during fetoscopy or following amniotic insufflation [27, 78]. As Ringer's lactate has lower osmolarity than normal amniotic fluid, surgeons rely on fetal secretions (urine, lung, nasal, and salivary) and intramembranous reabsorption to normalize the amniotic fluid osmolarity after surgery [38, 78, 79, 86, 87]. The complete replacement of the amniotic fluid, after fetoscopy, is expected to take up to 48 hours [38]. Both in vitro and in vivo studies have shown that short-term membrane exposure to low osmolarity solutions induces apoptosis in the amniotic epithelium and may directly weaken amniotic collagen [78, 79, 86]. These changes are likely due to the rapid movement of water from the dilute amniotic fluid into amniotic epithelial cells and between the collagen fibrils. Apoptosis of the amniotic epithelium increases MMP activity which, in combination with weakened collagen, may increase the risk of iPPROM after fetoscopy [65, 79, 80].

Preventing Iatrogenic iPPROM

Efforts to prevent iPPROM after fetoscopy have mainly focused on minimizing membrane damage around the fetoscopic port and preventing chorioamniotic separation. However, more recently, emphasis has been placed on protecting the amniotic epithelium during fetoscopy by heating and humidifying the insufflated CO₂.

Alternative Port Insertion Techniques

The Seldinger technique was adopted from vascular procedures as a way of minimizing local membrane trauma and preventing chorioamniotic separation during fetoscopic port insertion [3, 21, 88, 89]. Instead of directly puncturing the membranes with a large diameter trocar, the port hole is created sequentially using a thin needle, guidewire, and conical dilator. While the Seldinger technique has been shown to reduce postoperative amniorrhexis in small human case series, larger cohort studies have not yet identified any reduction in iPPROM rates [3, 21, 26].

An oblique puncture technique has also been attempted to offset the holes left in the membranes after surgery and prevent chorioamniotic separation. While this technique has shown some success in vitro, it has not been adopted routinely into human fetoscopy [90]. More recently, surgeons have sutured the fetal membranes to the uterine wall during the port insertion to prevent chorioamniotic separation [27]. A similar membrane plication technique has shown success in rabbits [14]. While this technique was associated with lower iPPROM rates in small case series compared to similar procedures, larger cohort studies are still required to confirm this potential benefit [4, 27].

Reducing the Diameter of Fetoscopic Instruments

One large retrospective study identified that the maximum instrument diameter employed during fetoscopy significantly predicted iPPROM [11]. Although this suggests that reducing port diameters could reduce the risk of iPPROM, similar retrospective studies have not identified this association nor a clinical benefit reducing port diameters (i.e., from 10 to 8 French) [3, 26]. Other studies have suggested that factors increasing membrane friction at the port site such as longer surgical durations, more complex procedures, an anterior placenta, and inserting instruments without a port may have a greater impact on the risk of iPPROM than the size of the holes left in the membranes [3, 6, 11].

In addition to reducing the port diameter, there have also been considerable efforts to reduce the number of ports employed during fetoscopy [27]. While procedures

using 2 or 3 ports generally report higher iPPROM rates than single-port procedures, surgical and pathology-specific factors make it difficult to isolate the effect of port number on the risk of iPPROM [11].

Fetal Membrane Plugs, Glues, and Patches

A variety of fetal membrane plugs [6, 12–19], tissue sealants [14, 17, 28, 91–97], adhesive patches [17, 23–25], and membrane welding techniques [98] have been developed in preclinical models to seal punctured or ruptured fetal membranes (summarized in Table 1). Collagen/gelatin plugs are one of the few techniques trialed in humans during fetoscopy; however, there is limited evidence to suggest they reduce the iPPROM compared to leaving the membranes unsealed [20–22]. Despite this limited success, new minimally invasive techniques to apply membrane sealing therapies continue to be developed and show promise in vitro [99].

Heated and Humidified Amniotic Insufflation

Sheep studies have shown that heating and humidifying the CO₂ used for amniotic insufflation reduce inflammatory cell counts in the membranes compared to cold and dry CO₂ [30]. Several fetoscopic centers have recently adopted heated and humidified amniotic insufflation and reported notably lower rates of iPPROM in small case series [4, 27, 29]. Histological studies have also shown similar levels of membrane injury between membranes exposed to heated, humidified CO₂, and noninsufflated controls [29]. However, like many of the factors discussed above, the small number of published cases and variability in surgical technique between centers make it difficult isolating the impact of heated and humidified CO₂ on reducing the risk of iPPROM.

Preclinical Models of iPPROM

Given the vulnerability of human fetuses undergoing fetoscopy, it is essential that studies investigating the mechanisms of iPPROM and developing new therapies are performed in preclinical models. Human fetal membrane explants, rodents, rabbits, sheep, pigs, and nonhuman primates are the most accessible models and have been used extensively for pregnancy-related research (summarized in Table 2) [100]. However, there is considerable variability in the fetal membrane structure and rupture physiology among these models that researchers should be aware of when aiming to translate their findings to human fetoscopy.

Table 2. Comparative anatomy and physiology of the fetal membranes in humans and domestic species

	Human	Rodent	Rabbit	Sheep	Pigs	Non-human primates
<i>Placental and fetal membrane anatomy</i>						
Placental arrangement	Discoid	Discoid	Discoid	Cotyledonary	Diffuse	Bidiscoid
Amnion	Present	Present	Present	Present	Present	Present
Chorion	Fused with decidua	Fused with decidua	Fused with decidua	Fused with decidua	Fused with decidua	Fused with decidua
Allantois at mid-gestation	Absent	Absent	Small	Large	Large	Absent
<i>Fetal membrane physiology</i>						
Average gestational age, days	266	20-22	30	147	115	168
Number of fetuses	1	5-9	5	1-2	10-14	1-2
Condition of gestational sac at delivery	Partially intact or ruptured	Ruptured	Intact or ruptured	Intact or partially intact	Ruptured	Ruptured
Naturally occurring PPROM	Yes	No	No	No	No	No
Spontaneous membrane healing	No	Yes	Yes	No	Yes	No

Spontaneous Membrane Rupture

Unlike pregnancy complications, such as fetal growth restriction, researchers are yet to develop a preclinical model of iPPROM. This is likely because spontaneous PPROM does not appear to occur naturally in other species [34, 40]. Until recently, this has been attributed to the human's evolution of an upright posture that places unique downward forces on the cervical fetal membranes during pregnancy [40]. However, biomechanical studies have also shown that the human fetal membranes are considerably weaker, and rupture more readily than those of many domestic species, including sheep and pigs [40]. These biomechanical differences mean that only human fetal membrane explants may accurately combine cellular markers of weakening or damage with biomechanical changes that predispose rupture. However, human explants can only be collected after delivery and the composition of these tissues may not be representative of mid-gestation fetal membranes undergoing fetoscopy [34, 101]. This highlights the need to understand the limitations of available animal models in fetal membrane research.

Despite biomechanical differences, the inflammatory responses to injury and membrane weakening cascades involving MMPs are consistent among humans and most domestic species [18, 36, 39, 55-57]. This suggests that preclinical animal studies investigating iPPROM and potential therapies should focus on the biology of membrane injury and weakening rather than changes in mechanical rupture properties [74, 102].

Fetal Membrane Structure and Integrity

There are also anatomical differences between human fetal membranes and those of domestic species. Many mammals have an additional allantoic membrane present at term (summarized in Table 2) [34, 101]. Embryologically, the allantois is an outpouching of the primordial urinary bladder that expands beside the amnion and fuses with the chorion forming the chorioallantois. The allantois is temporary in humans and absent by the time fetal surgery is performed at mid-gestation [34, 101]. However, in sheep and pigs, it persists throughout pregnancy as a large sac filled with fetal urine. A relatively smaller allantois is also seen throughout pregnancy in rabbits [34, 101]. Researchers should be aware of this difference so that interventions, therapies, and tissue collection in preclinical animal studies of iPPROM are performed on combined sections of chorioamnion that are representative of human fetal membranes. The allantois is easily distinguished from the amnion by the presence of clear, dark fetal urine within the allantoic sac compared to the lighter, cloudy amniotic fluid that contains a mixture of urine, mucous, lung liquid, and skin cells [38].

The fetal membranes of many domestic species also contain considerably more blood vessels than human fetal membranes. Membrane vasculature is largely dependent on the anatomical arrangement of the placenta [103, 104]. Primates (including humans), rabbits, and rodents have a discoid placenta that embeds on one side of the uterus (summarized in Table 2) [104]. The small number of blood vessels within the chorion arises from the allantois and drains into the fetal sinus venosus. The placenta of sheep is comprised of multiple smaller placental struc-

tures (cotyledons) randomly distributed within the uterus [104]. Cotyledons are interconnected by a large network of fetal blood vessels running within the chorion, which significantly increases membrane vasculature relative to humans [103]. Increased vasculature is also seen in the fetal membranes of pigs and guinea pigs where the placenta occupies the entire internal surface of the uterus (a diffuse arrangement) [104]. Where possible, preclinical studies investigating mechanisms of iPPROM or aiming to seal membrane defects should use regions away from dense patches of vasculature.

Spontaneous Healing

Unlike humans, the fetal membranes of rodents, rabbits, and pigs show some ability to heal after being punctured at mid-gestation (summarized in Table 2) [6, 12, 16, 18, 25, 105]. In rodent and rabbit membranes, the amniotic epithelium and fibroblasts proliferate around the puncture site and are able to close small defects (<1 cm) within 48–72 hours [6, 12, 16, 18, 105]. Larger defects either heal over longer periods or incompletely [6, 105]. Spontaneous membrane healing in these animal models may exaggerate the efficacy of new techniques aiming to prevent iPPROM in humans.

The fetal membranes of sheep and rhesus monkeys have shown limited healing capacity like humans and may therefore be more appropriate models to test techniques aiming to prevent membrane injury [18]. Sheep also have considerably longer gestations than other animal models and their large size permits invasive monitoring of fetal physiology during pregnancy [100]. These advantages are particularly important as membrane closure techniques should demonstrate efficacy sealing the membranes for several weeks or months and be safe for the fetus when in contact with the amniotic fluid.

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Conclusions

The etiology of iPPROM after fetoscopy is not entirely understood; however, appears multifactorial. Puncturing the membranes with the fetoscopic port, distending the uterus with unconditioned CO₂, and diluting the residual amniotic fluid during fetoscopy potentially weakens the membranes prematurely and increases the risk of iPPROM. Despite multiple attempts to develop novel preventions in preclinical models, iPPROM remains a major concern that limits the benefits of fetoscopy. It is important to consider that the structure and integrity of human fetal membranes are unique and thus promising results from preclinical studies will not always translate into clinical improvements. However, careful combination of large animal studies and human membrane explants may shed light on new ways to reduce iPPROM in the future.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

B.J.A., R.J.H., K.A.R., K.J.C., S.B.H., and P.L.J.D. contributed to the conception and planning of this review. B.J.A. and P.L.J.K. prepared the original manuscript which was then reviewed and approved by R.J.H., K.A.R., K.J.C., and S.B.H. prior to submission.

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