JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE **15** (2004) 651–658

Mechanical failure of human fetal membrane tissues

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Mechanical integrity of the chorioamnion membrane, and the component chorion and amnion layers, was assessed with biaxial puncture testing. Fetal membranes were obtained from term placentas following labored natural delivery or scheduled cesarean section. Preterm specimens were obtained from deliveries prior to 37 weeks gestation. Dividing and peripheral membranes were obtained from multiple gestation pregnancies. Specimens were gripped between parallel plates with circular openings and loaded with an instrumented, hand-held blunt probe until rupture occurred. Peak force was recorded and rupture sites were examined. Defects in multi-layered membranes differed in both size and shape in the individual layers. Compared with chorion and whole chorioamnion, amnion was more mechanically sensitive to different obstetrical conditions. Amnion varied in response at different physical locations within the same patient. Membrane and component puncture force data were used to calculate biaxial failure strength. Membrane stresses arising from amniotic fluid pressure were computed as a function of gestational age, and compared to membrane strength to examine the criterion for membrane failure *in vivo*. Possible mechanical conditions for preterm membrane rupture were examined.

1. Introduction

A normal pregnancy outcome requires physical integrity of the membranes surrounding the fetus until term delivery. Membrane rupture, commonly known as ''water breaking'' due to the release of amniotic fluid, frequently signals the onset of labor. The membranes rupture prior to term in 3–5% of human pregnancies, leading to premature delivery and the associated increase in perinatal mortality and morbidity [1]. Rupture may also occur in pathologic circumstances: when the membranes have prolapsed in cervical insufficiency or when they are over-stretched in polyhydramnios [1]. Pursuing the etiology, treatment, and possible prevention of these abnormalities must be based on an adequate understanding of the mechanics of normal and abnormal membranes.

The physical integrity of the chorioamnion (CA) membrane depends on contributions from the individual component layers, the amnion and chorion. The anatomic relationships and functional aspects of the fetal membranes have been described in detail [2, 3]. The thin, avascular inner amnion layer is passively attached to the thicker, more cellular, chorion layer. Both components have structural, transport, metabolic, and endocrine functions.

In multiple gestation pregnancies a dividing membrane usually separates the fetuses. The dividing membrane consists of two layers of amnion with zero or two layers of intervening chorion [4]. The number of dividing membrane layers depends on whether the fetuses originated from separate fertilized eggs (e.g. dizygotic twins) or from a single fertilized egg (monozygotic). In the case of monozygotic twins, the membrane configuration depends on the timing of the separation [5]. The presence of chorion layers can be detected on ultrasound, and the absence of intervening chorion layers has been correlated with poor perinatal outcome [4, 5].

A common clinical impression is that the amnion is the stronger of the two layers. This impression is reinforced in cases of preterm prolapsed fetal membranes when obviously disrupted chorion is observed, and only the intact amnion is left containing the amniotic fluid. Amnion has indeed been found to be stronger than chorion in controlled uniaxial mechanical tests [6]. However, a uniaxial test does not replicate the *in vivo*

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loading conditions of the membranes, as membranes are loaded biaxially by the amniotic fluid pressure [7].

A number of investigators have considered biaxial CA membrane mechanical behavior [7–11]. Two types of biaxial testing have been used to investigate the chorioamnion: (a) inflation of the membrane with fluid or air pressure until it bursts [7, 8, 11], and (b) puncture of the membrane with an instrumented probe [9, 10]. In puncture tests, failure typically occurs at the location of probe force application, making this test more controlled than burst testing, in which failure can occur at any location in the sample. A recent study examined puncture failure of the CA membrane throughout gestation, and found a significant decrease in strength at full term and a substantial strength decrease in membranes with gross inflammation [10]. Several investigators have studied the effect of labor on the *in vitro* mechanical response of the CA membrane [8, 10–12] but the results are inconsistent across studies using different test techniques. An understanding of the mechanical responses of the fetal membrane layers is a necessary foundation for future investigation of premature membrane rupture, as well as a necessary step in the development of interventions aimed at restoring membrane function following early rupture.

The purpose of the present study was to assess the biaxial puncture failure of intact CA, and of amnion and chorion isolated from the peripheral (''free'') CA. In addition, amnion was stripped from the placental surface and compared to amnion separated from the peripheral CA. The effect of labor and of preterm delivery on biaxial puncture of these four different tissue layers was evaluated. Comparisons were made between peripheral membrane components and their corresponding components in the dividing membranes from multiple gestation pregnancies. Finally, a simple force balance was performed to examine the membrane stress relative to strength, and to model pathological conditions that cause premature membrane failure.

2. Materials and methods

Fetal membranes from 32 pregnancies were tested within 12 h of delivery. This study was approved by the institutional review board of Abbott–Northwestern Hospital/Allina Health System. Consent for placental evaluation was obtained from each patient. All specimens were from uncomplicated pregnancies without clinical evidence of infection. Unlabored term (gestational age > 37 weeks) fetal membranes (9) were obtained from cesarean sections scheduled for obstetrical reasons prior to the onset of labor. Labored term fetal membranes (9) were obtained from vaginal deliveries. Preterm membranes (6) were obtained from singleton deliveries at gestational ages (GA) less than 37 weeks (average GA 30.8 weeks, range 26–34 weeks). Membranes from (8) multiple gestations (average GA 34.5 weeks, range 32–38 weeks) were obtained from five sets of twins, two sets of triplets, and one set of quadruplets.

For all singleton births, intact free membranes were excised from the placental margin. All samples for testing were obtained away from the clinical rupture site. One piece of each membrane was retained as intact CA, while a second piece was separated into amnion (A) and chorion (C) using gentle traction. (For consistency, all dissections were performed by the same person, SEC.) Finally, the placental amnion reflection (Ap) was separated from the placental margin inward to the base of the umbilical cord and then excised. For multiple gestations, samples of CA and A were obtained from the peripheral membrane as above. Samples of the dividing chorioamnion membrane (DCA) between fetuses were also obtained and tested intact. Finally, a single A layer from the dividing membrane (DA) was stripped from the whole DCA for testing. Specimens were stored in sterile saline prior to testing in air.

Tests were performed on specimens held between parallel flat-plate gripping surfaces with a 2-cm diameter circular opening. A portable testing device was used to test the samples for biaxial puncture strength. The device included a blunt metal probe with an $\frac{1}{8}$ inch (3.2 mm) diameter and a spherical tip. The probe was instrumented with a low-force load cell (Sensotec, Columbus, OH), which was connected through a load cell conditioner to a portable oscilloscope (Fluke, Everett, WA). Force was applied manually at the center of the specimen until membrane rupture occurred (Fig. 1), and the peak force level ($F_{\max}$) was recorded. Each test required a few seconds to perform, minimizing the potential effect of membrane tissues drying in air. Membrane deflection was approximately 10–15 mm at failure, but was not measured in this study. Samples were inspected for failure at locations other than the probe site, and discarded from the analysis if failure occurred at the edges. Two to four puncture tests (depending on amount of available tissue) were performed on independent regions of each membrane component (where available) from each sample, and an average of these tests was taken for each tissue type for each individual specimen.

Averages and standard deviations were computed by group (labored, unlabored, term, preterm) for each membrane component (CA, A, C, Ap). Comparisons were made for each component between labored term (LT) and unlabored term (UT) groups and between the combined set of labored and unlabored term membranes

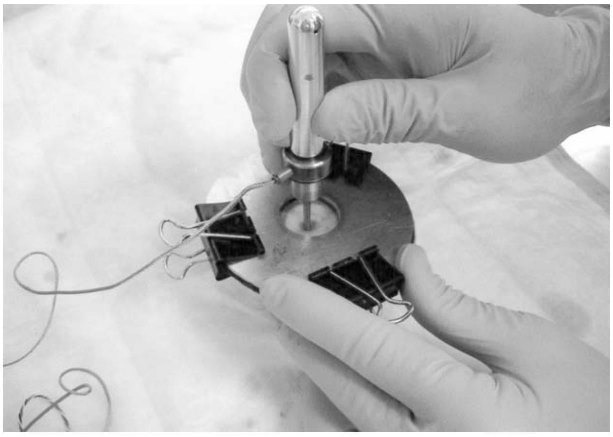

Figure 1 Experimental set-up for the membrane biaxial puncture test. A hand-held 3.2 mm diameter instrumented force probe with a spherical end was used to puncture membrane specimens, which were held between cylindrical disks with fine sandpaper on the gripping surfaces. The circular opening in the grips was 2 cm in diameter.

(T) and the group of preterm membranes (P) by unpaired t-tests at $p < 0.05$. Amnion (A) from the split CA membrane was compared to placental amnion (Ap) for labored and unlabored term membranes and for term vs. preterm membranes.

For the multiple gestation specimens, the ratio of peak forces for dividing membrane vs. peripheral membrane components for both CA and A were computed for each subject and averaged. Finally, in term and preterm singleton gestations where both A and Ap were tested, the ratio Ap/A was computed for each subject and averaged.

3. Results

Specimen failure is demonstrated in raw force–time (F–t) data for four membrane tissue components from the same subject (Fig. 2) in which a clear drop-off in force indicates membrane rupture. In CA samples, there was on some occasions a discontinuity in the slope of the force–time-trace-prior to final failure. It is likely that this relates to separate failure of the chorion and amnion [6]. This hypothesis is supported by direct observation of the failure site for a CA sample (Fig. 3(a)), in which failure of the amnion and chorion show different patterns. In contrast, the failure for a single membrane component (C, A, Ap) was a single event (Fig. 2), and was associated with a single rupture in the membrane specimen. Interestingly, in some amnion samples, the resulting defect was much larger than the instrumented probe and demonstrated a clear directionality such that the corners of the defect met at a sharp point (Fig. 3(b)).

Force–time data for puncture of dividing membranes (Fig. 4) were similar to that of bilayer chorioamnion, in that there were frequently slope discontinuities in the trace. These features were at times even more pronounced than in the chorioamnion failures, in that the force decreased slightly before increasing again prior to failure (Fig. 4(b)). Direct observation of the failure sites in dividing membranes demonstrated independent failure in three or four independent layers, as shown in Fig. 5.

Amnion specimens were significantly weakened by labor, with average puncture force falling from 3.2 to 2.1 N for peripheral A and from 5.6 to 4.0 N for placental amnion. This weakening was not reflected in either the whole CA membrane or the chorion, both of which demonstrated only slight decreases in failure load following labor (Table I).

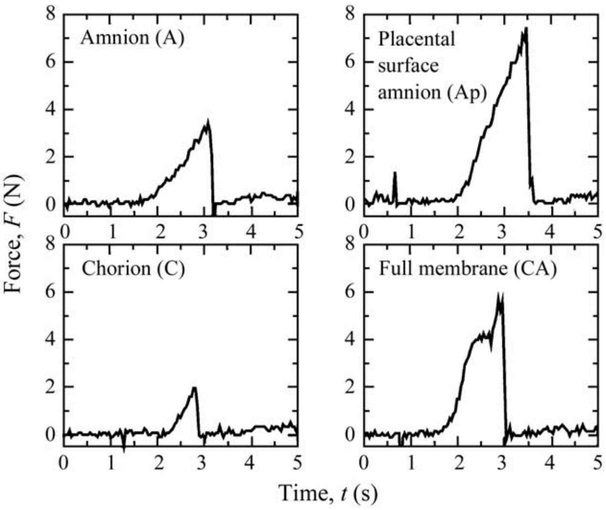

Figure 2 Raw force–time (F–t) data for puncture tests of different membrane components. The maximum force was read from each graph for each test to determine the puncture strength of the tissue. The force data indicates that the chorioamnion specimen failed separately in the amnion and chorion.

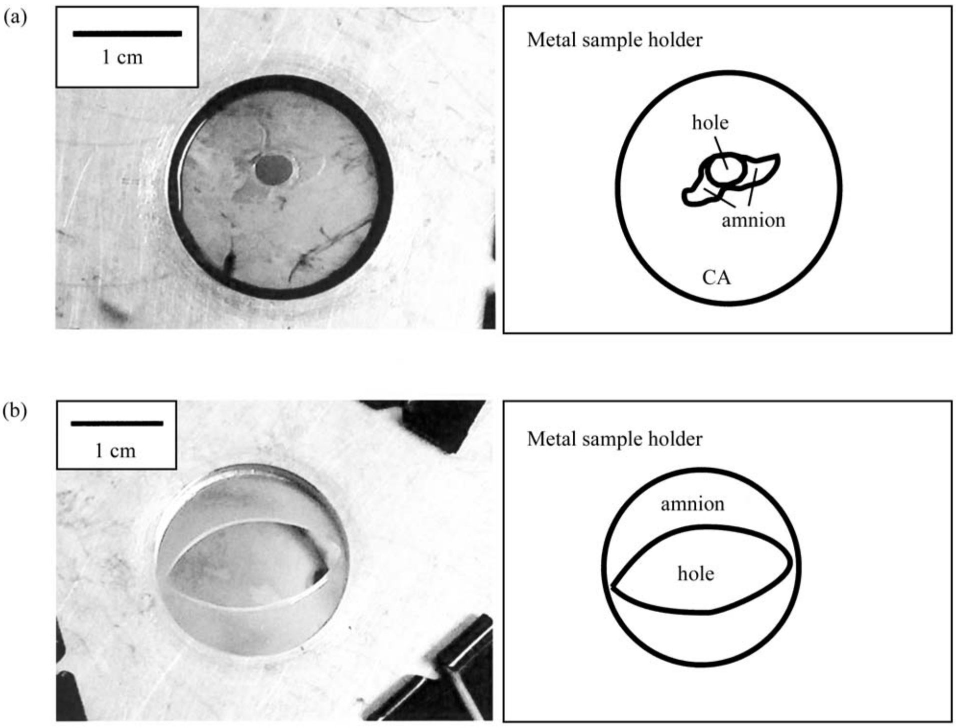

Figure 3 Images of failure sites following biaxial puncture test for (a) whole chorioamnion, showing separate failure of chorion and amnion; and (b) isolated amnion showing an enlarged failure site with directional preference. Schematic representations show the failure sites and identify tissue components for each photograph.

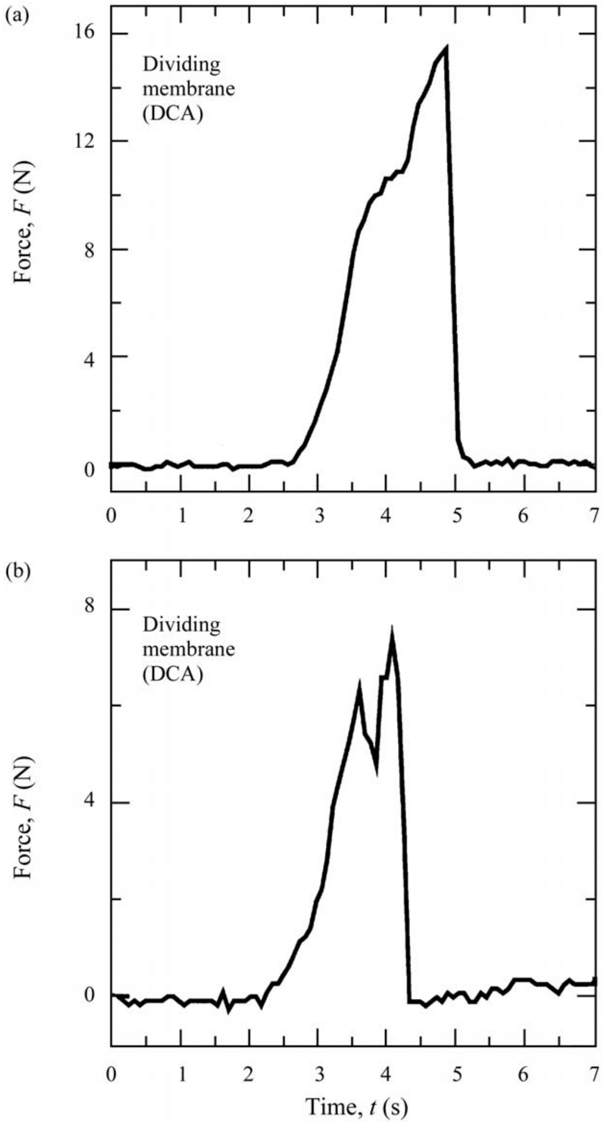

Figure 4 Raw force–time (F–t) plots for puncture tests of dividing membranes from multiple gestations. The force data indicates that the dividing membranes failed in at least two distinct events in both cases, with a more distinct force drop off in trace (b) compared to trace (a).

Membranes obtained from preterm deliveries demonstrated a slightly greater average failure force for the full CA membrane compared to term membranes (5.1 vs. 4.2 N) along with a substantially greater failure force for peripheral amnion (4.3 vs. 2.7 N). Preterm placental amnion was similar to that at term. It was noted that preterm chorion had little integrity as a tissue and was difficult to split from the CA, resulting in only two samples being tested for this group. Both of these samples failed at smaller loads than those typically seen for term deliveries, supporting the observation that preterm chorion was weaker than that at term.

Amnion from the placental surface was substantially stronger than amnion from the free membrane in both term labored (4.0 vs. 2.1 N) and unlabored groups (5.6 vs. 3.2 N). In cases where both placental and peripheral amnion were available from the same specimen, the average force ratio of placental to peripheral amnion (Ap/A) was 2.1 for labored and 1.8 for unlabored term membranes. There was no statistical difference between the two amnion components in preterm membranes, in which the average force ratio was 1.2.

In cases of multiples, failure forces for dividing membranes (DCA), averaging 11.9 N, were more than double those of the peripheral CA membranes from the same pregnancy, which averaged 5.5 N (Table II). In addition, the dividing amnion layer was significantly stronger than the peripheral amnion (6.5 vs. 4.9 N). The average gestational age for the multiples (34.5 weeks) was intermediate between the term and preterm groups, but both the peripheral CA and A from multiples failed at larger loads than the same components from preterm singleton births.

4. Analysis

One issue that has caused persistent confusion in the obstetrics literature is whether the strength of the chorioamnion is exceeded by the amniotic fluid pressure prior to or during labor [13]. We aim to examine this issue by calculating the membrane strength from the failure force, and using simple modeling to compute the stress in the membrane due to amniotic fluid pressure. In making these comparisons between membrane stress and strength, we incorporate data from the current study along with data and observations obtained from the literature.

Values for peak force at puncture from the current study were converted to strengths using previously published values of membrane component thickness (h) [12] and values of peak tangent modulus (E) from uniaxial membrane testing [12, 14]. Biaxial puncture strength σ_F^B, defined as the maximum radial stress at failure, for labored and unlabored amnion, chorion, and chorioamnion was computed using the following expression [15]:

$$\sigma_F^B = \sigma_{RR}^{MAX} = \frac{1}{h}\sqrt{\frac{F_{MAX}Eh}{6\pi R}} \qquad (1)$$

TABLE I Puncture force at failure (F_{max}) for fetal chorioamnion membrane tissues

$F_{max}(N)$	Unlabored term (UT)	Labored term (LT)	All term (T)	Preterm (P)
Chorioamnion (CA)	4.26 ± 1.09 ($n = 9$)	4.04 ± 1.52 ($n = 8$)	4.16 ± 1.27 ($n = 17$)	5.09 ± 1.30 ($n = 6$)
Chorion (C)	1.78 ± 0.49 ($n = 5$)	1.72 ± 0.44 ($n = 9$)	1.75 ± 0.44 ($n = 14$)	1.19 ± 0.00 ($n = 2$)
Amnion (A)	3.18 ± 0.37 ($n = 8$)	2.10 ± 0.68^1 ($n = 7$)	2.68 ± 0.76 ($n = 15$)	4.30 ± 0.71^2 ($n = 5$)
Placental amnion (Ap)	5.62 ± 1.33^3 ($n = 9$)	$4.01 \pm 0.64^{1,3}$ ($n = 7$)	4.92 ± 1.34 ($n = 16$)	4.85 ± 0.22 ($n = 6$)

Data are presented as mean ± standard deviation with the number (n) of individual specimens given for each group. Term was defined as gestational age > 37 weeks.

[1] Labored (LT) significantly different from unlabored (UT) by unpaired t-test, $p < 0.05$.

[2] Preterm (P) significantly different from term (T) by unpaired t-test, $p < 0.05$.

[3] Placental amnion (Ap) significantly different from amnion (A) by unpaired t-test, $p < 0.05$.

TABLE II Puncture force at failure ($F_{\max}$) for fetal chorioamnion membrane tissues from the dividing membrane or the peripheral membranes in multiple gestations

	Dividing membrane $F_{\max}(N)$	Peripheral membrane $F_{\max}(N)$	Force ratio, dividing/peripheral
Chorioamnion (DCA or CA)	11.89 ± 2.95 ($n = 8$)	5.54 ± 2.30 ($n = 8$)	DCA/CA $= 2.45 \pm 1.11$
Amnion (DA or A)	6.49 ± 1.38 ($n = 8$)	4.90 ± 1.58[4] ($n = 8$)	DA/A $= 1.44 \pm 0.60$

[4] Dividing amnion (DA) significantly different from peripheral amnion (A) by paired t-test, $p < 0.05$.

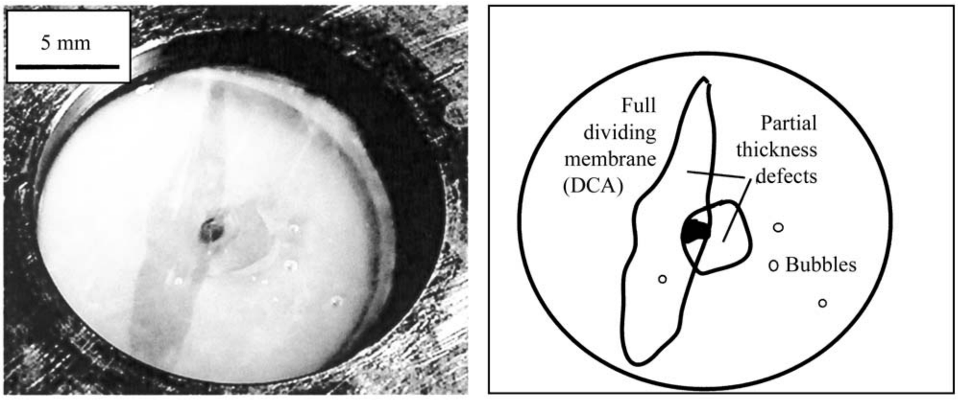

Figure 5 Images of failure sites following the biaxial puncture test for a dividing membrane. Schematic representation illustrates the failure sites and identifies a single full-thickness defect and two distinct partial-thickness defects.

where R is the probe radius and an incompressible neo-Hookian material is assumed. These biaxial failure strength values along with their ranges are plotted against the uniaxial failure strength values σ_F^U previously published [12, 14] for the same tissue components (Fig. 6). There is a direct correlation between the mean values of strength for uniaxial and biaxial testing conditions for all three tissue components (CA, C, A) on both labored and unlabored conditions. Interestingly, the ranges of strengths are much larger for the uniaxial studies compared to the current biaxial study, related to the fact that the flaws are generated in a controlled manner at the probe contact site in biaxial testing while any edge flaw can cause failure in uniaxial testing.

The consistency in strength data across both investigators and testing techniques motivates closer examination of membrane failure based on these available strength measurements. The criterion for membrane failure *in vivo* is when the membrane stress exceeds the membrane strength. We test the idea that the amniotic fluid pressure provides a sufficient membrane stress to meet this failure criterion. By a simple balance of forces, treating the amniotic sac as a spherical pressure vessel, we can relate the membrane stress, σ to the internal amniotic fluid pressure, p by:

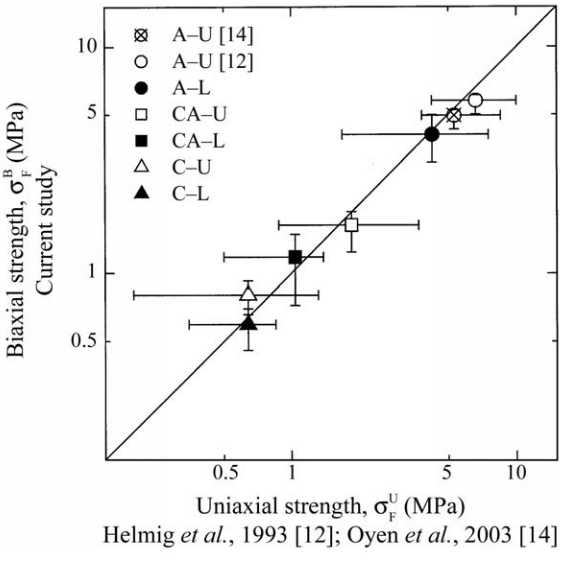

Figure 6 Comparison between fetal membrane strength σ_F measurements obtained in biaxial testing (current study) and uniaxial tension measurements [12, 14]. The average strength values correlate directly but the range of experimental values is substantially smaller in the biaxial tests.

$$\pi r^2 p = 2\pi r h \sigma \tag{2}$$

where r is the amniotic sac radius. The bilayer membrane is modeled as a uniform monolayer for this simple calculation. We can rearrange this to give an expression for the stress on the membrane as a function of the internal amniotic fluid pressure,

$$\sigma = p\frac{r}{2h} \tag{3}$$

Amniotic fluid pressure measurements have been reported as a function of gestational age [16] and pressure was found to increase linearly with gestational age. We use these data (Fig. 3 in [16]) to estimate the average pressure at any timepoint along with approximate upper and lower bounds. In addition, we approximate the radius of the sac and allow it to increase linearly with gestational age based on bounding values of 7 cm at 20 weeks, 10 cm at 30 weeks, and 13 cm at 40 weeks from the clinical experiences of one of us (SEC). The membrane thickness was estimated to be fixed at its term value of 191 μm [12], a reasonable approximation as the collagen content of the amnion does not change after the second trimester [8]. A set of curves (average and bounds) for membrane stress as a function of gestational age is constructed using Equation 3, and plotted in Fig. 7. The membrane stress increases quadratically as a function of gestational age, due to

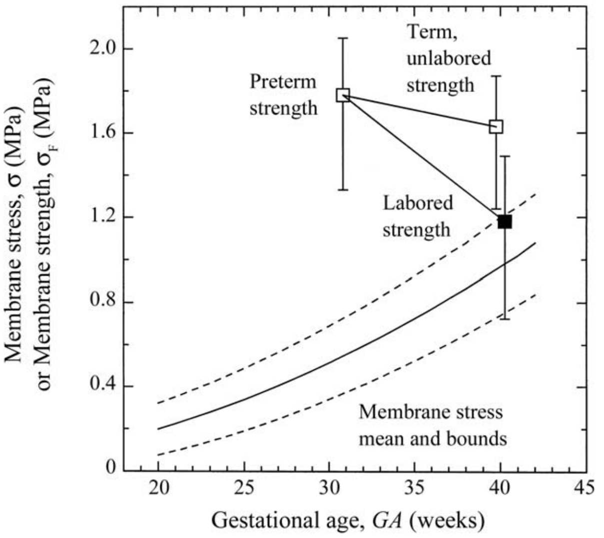

Figure 7 Plots of the calculated membrane stress σ as a function of gestational age (Equation 3) along with experimental measurements of biaxial membrane strength σ_F for different membrane conditions. The membrane failure criterion of stress equals strength is met at full-term for labored chorioamnion membranes but not for preterm or unlabored membranes.

linear increases in both the amniotic fluid pressure and the radius of the amniotic sac.

To compare the estimated membrane stress to the membrane strength, we plot the means and ranges for chorioamnion membrane biaxial strength, as calculated above for full term (both labored and unlabored) membranes in Fig. 7. For preterm membranes, we estimate the strength from peak force data using E and h for unlabored term CA, and place this data point at the mean GA of 30.8 weeks.

For preterm membranes, there is a large difference between the membrane stress and membrane strength, consistent with the fact that most membranes do not rupture at this early GA. For unlabored term membranes, there is a moderate difference between the stress and strength, again consistent with the integrity of membranes in unlabored patients, for whom the membrane is cut by the delivering physician. For labored term membranes, however, the membrane stress and strength are comparable. The stress and strength directly cross over, demonstrating that the failure criterion is met for labored membranes at full term. These results, indicating that in some cases the stress due to amniotic fluid pressurization is sufficient to rupture the membrane, are consistent with the observation that membrane rupture is associated with decreases in barometric pressure [17]. This combination of evidence supports the idea that small pressure changes across the membrane can lead to the force associated with membrane failure, and provide clear motivation for more detailed modeling work to investigate membrane failure.

5. Discussion

The membrane puncture test for obtaining peak force measurements is easy to perform and quick, and the results from testing are remarkably consistent. The current study used a hand-held probe and thus membrane deflection was not measured directly in the current study; the results in Pressman *et al.* [10] demonstrated that force was a more sensitive indicator of membrane integrity than deflection. As a similarly-sized force probe was used, it can be noted that the numerical results for CA strength (3.8 N for GA 20–38 weeks and 2.5 N for GA > 38 weeks) obtained by Pressman *et al.* [10] are comparable to those obtained in the current study, although a slightly different definition for ''term'' gestation was used. An additional investigation from a third different group [13], also using the same approximate probe size as the current study, obtained nearly identical peak force measurements for unlabored, > 37-week membranes (4.1 N) as in the current study (4.3 N). Conversion of the puncture loads from the current study to puncture strengths demonstrates remarkable agreement with uniaxial measurements previously published [12, 14] for both labored and unlabored membranes and membrane components. However, there was substantially less test-to-test variability in the puncture strength data than in that obtained from uniaxial tensile tests.

There is clear potential for membrane repair in the event of preterm rupture. A recent *in vitro* study explored the use of fibrin glue for sealing chorioamnion, demonstrating some restoration of mechanical integrity in repaired membranes under tests in uniaxial tension [18]. The future success of any membrane repair technique will be determined by the restoration of the mechanical function of the amnion along with the development of a water-tight seal for amniotic fluid containment. Biaxial mechanical testing will be the best way to determine the efficacy of membrane repair techniques in replicating the mechanical functionality of natural membranes.

In the present study, a large number of different tissue types from different obstetrical groups were tested for puncture resistance. The common theme in the results is that the thin collagenous amnion, the primary strength-bearing layer in the chorioamnion, was responsible for most of the differences between obstetric conditions. The amnion was most puncture-resistant preterm, was weaker at full term in the absence of labor, and was further weakened by labor. The amnion on the placental surface was weakened by labor in approximately the same proportion as that harvested from the free CA membrane, which suggests a chemical membrane alteration, rather than a mechanical effect. One potential chemical weakening agent is matrix metalloproteinase-9, which has been shown to correlate with a decrease in membrane strength [19].

In two different aspects of the current study, amnion from different locations in the same patients was found to differ substantially in puncture force, even though the chemical environment would have been similar. Term amnion covering the fetal surface of the placenta was dramatically stronger, by nearly a factor of two, than amnion obtained from the peripheral membranes for both labored and unlabored groups. In addition, amnion from the dividing membrane in multiples was about one and a half times stronger than that from the periphery. One possible explanation for the strength variability is that different amnion components are placed under different external mechanical loading conditions during gestation. Peripheral amnion is under fluid pressure on one side but is essentially free on the other side, butted against the uterus but not solidly attached. Placental amnion is constrained by attachment to the fixed fetal surface of the placenta, while dividing amnion has only fluid pressure loading the membrane on both sides. Thus there is greatest force difference across the peripheral amnion, and almost no force difference around the other amnion components. This lack of force may reduce mechanical weakening of the membrane in the placental and dividing amnion. The most obvious mechanical weakening mechanism would be through localized membrane straining. There is also a potential for localized membrane thinning, which was not measured in the current study but should be examined in future investigations. The addition of displacement-measurement capability to the current set-up would allow for direct measurement of pre-failure membrane mechanical properties, such as elastic modulus, as the analytical background for probe-based testing of thin membranes has recently been explored in detail [15].

The average puncture force was more than doubled for dividing membranes compared to peripheral chorioamnion. This result is surprising given that the dividing membrane contains two amnion layers and up to two chorion layers, and is therefore at most a doubled chorioamnion. Detailed examination of the conformation of the dividing membrane structure was not performed for the membranes examined in the current study, and presents an opportunity for future examination. However, the observation that dividing membranes are substantially stronger than their peripheral counterparts is in agreement with the clinical observation that dividing membranes are not known to rupture spontaneously.

A simple balance-of-forces model was constructed to explore the relationship between membrane mechanical strength and amniotic fluid pressurization as a function of gestational age. We find that it is quite plausible that the amniotic fluid pressure causes localized membrane failure at term, particularly in the case of labored membranes, which presumably have been weakened chemically. We can exploit this simple model further to examine two types of clinically-recognized premature membrane failure: (1) preterm premature rupture of membranes (PPROM), and (2) polyhydramnios leading to membrane rupture. In some clinical cases of PPROM, the intrinsic strength of the membrane is decreased, due to biochemical degradation of the membrane from infection, inflammation, or both. As such, the lines for membrane strength would be shifted downward (Fig. 8(a)), such that failure could occur at an earlier timepoint and a lower strength for fixed membrane stress. In the case of polyhydramnios, the amniotic fluid pressure is higher at any given gestational age [16] and the effective radius is larger, as there is a large increase in amniotic fluid volume as well. Thus, for fixed membrane strength, the fluid pressure is shifted higher (Fig. 8(b)) causing the cross-over point between stress and strength to occur at an earlier gestational age. In these schematic diagrams (Fig. 8) the cross-over point where stress equals strength shifts to about 36 weeks instead of 40 weeks, and the membrane failure criterion is met prior to term gestation.

There is clear potential for further exploration of the mechanics of *in vivo* membrane rupture using simple modeling techniques, as were employed in the current study, in conjunction with careful mechanical examination of membranes from normal and pathological obstetric conditions. The development of interventions for preterm membrane rupture, including membrane repair techniques utilizing patches or adhesives, requires continued exploration of the *in vivo* mechanical loading and mechanical strength of fetal membranes.

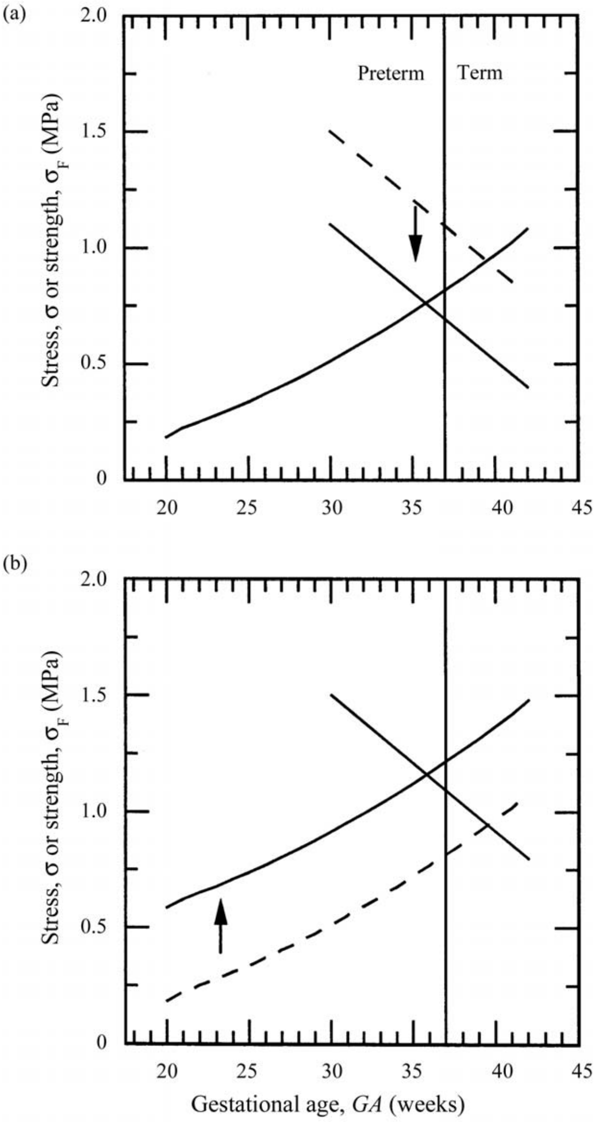

Figure 8 Schematic representations of the alterations in membrane stress, σ, and strength, σ_F, for clinical conditions associated with preterm deliveries: (a) in PPROM the stress is invariant while the strength decreases, and (b) in polyhydramnios the strength is invariant but membrane stress increases. The dashed lines in each figure are the baselines from Fig. 7, strength in (a) and stress in (b). The vertical line in each figure represents the preterm–term boundary of 37 weeks, which is crossed in both scenarios.

Acknowledgments

This work was supported by Allina Health System and through a grant from the Women's Health Fund at the Department of Obstetrics, Gynecology, and Women's Health, University of Minnesota.

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Received 29 December 2003
and accepted 5 February 2004