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The efficacy of the placental biopsy

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OBJECTIVE: Our purpose was to determine the sensitivity and specificity of pathologic diagnoses made from a placental biopsy specimen compared with diagnoses made from a complete placental examination.

STUDY DESIGN: Biopsy was performed on 200 singleton placentas with a 16-gauge Rutner biopsy needle shortly after delivery. The biopsy specimens and placentas were evaluated by standard placental pathologic criteria.

RESULTS: The presence of villous edema on the biopsy specimen led to the diagnosis of placental villous edema with a sensitivity of 51% and specificity of 86%, yielding a positive predictive value of 0.97. The sensitivity of the biopsy diagnosis of "increased syncytial knots" was 86%, whereas the specificity was 82%, yielding a positive predictive value of 0.90.

CONCLUSIONS: Because a placental biopsy specimen after delivery is reasonably sensitive for diagnosing villous abnormalities that reflect acute and chronic stresses to the placenta, it may be useful to develop a placental biopsy that can be performed safely during pregnancy. Such a biopsy could be the basis for the rational treatment of some diseases of pregnancy. (*AM J OBSTET GYNECOL* 1995;173:1084-8.)

Key words: Placenta, biopsy, pathologic examination, prenatal diagnosis

The advent of liver biopsy in 1907¹ and kidney biopsy in 1943² ushered in an era of great advances in our understanding of hepatic and renal diseases.³ Before the routine use of biopsy of these organs, physicians could merely follow up these patients until they recovered or died. Only after death could pathologists examine the organs to try to understand the pathologic processes that affected the tissues during life. The biopsy, in contrast, was a window on the disease process,

allowing at first understanding, then determination of prognosis, and finally the foundation for rational treatment. Lack of similar tools for the placental pathologist who assists the obstetrician has hampered our ability to understand fully the clinical course of complicated pregnancies, limited our ability to accurately determine prognosis, and ultimately prevented us from applying rational treatment options.⁴

Before we could suggest performing placental biopsies during pregnancy—which may entail significant risk—we realized that we needed to determine first if a placental biopsy had diagnostic value purely on pathologic grounds. We therefore began evaluating the efficacy of the placental biopsy by performing biopsy on placentas after delivery and comparing the diagnoses made on the specimens with the diagnoses made on the whole placenta.

Examination of 200 biopsy-placenta pairs has sug-

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Presented at the Fifteenth Annual Meeting of the Society of Perinatal Obstetricians, Atlanta, Georgia, January 23-28, 1995.

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Table I. Performance of placental biopsy compared with final pathologic diagnoses

Diagnosis	Sensitivity (%)*	Specificity (%)†	Significance	Correlation coefficient	Positive predictive value
Intervillous fibrin	94 (186/198)	50 (1/2)	$p = 0.012$	0.177	0.99
Calcification of fibrin	17 (11/63)	96 (131/137)	$p = 0.002$	0.218	0.66
Maturation consistent with gestational age	50 (5/10)	93 (177/190)	$p < 0.001$	0.329	0.27
Variable maturation (dysmaturity)	54 (91/169)	61 (19/31)	$p = 0.121$	—	0.88
Accelerated maturation	60 (15/25)	74 (130/175)	$p < 0.001$	0.247	0.25
Increased syncytial knots	86 (114/133)	82 (55/67)	$p < 0.001$	0.663	0.90
Villous edema	51 (91/178)	86 (19/22)	$p = 0.001$	0.235	0.97
Villous agglutination	23 (7/30)	98 (167/170)	$p < 0.001$	0.353	0.67
Chronic villitis	7.1 (1/14)	100 (186/186)	—	—	1.00

Significance is derived from χ^2 nonparametric analysis. —, Statistically invalid calculation. Correlation coefficient is calculated as measure of association between biopsy result and final pathologic diagnosis and is calculated only if χ^2 is significant ($p < 0.05$). Correlation coefficients > 0.25 are considered significant.

*Numbers in parentheses represent number of positive biopsy specimens when placenta is positive ÷ total number of positive placentas.

†Numbers in parentheses represent number of negative biopsy specimens when placenta is negative ÷ total number of negative placentas.

gested that placental biopsy is reasonably sensitive for diagnosing villous abnormalities that reflect acute and chronic stresses to the placenta. A placental biopsy may therefore be a useful tool for determining which gestations should be delivered rapidly because of the danger to the fetus posed by villous abnormalities. Moreover, as safer biopsy techniques become available, biopsies could be the foundation for research into rational treatment during pregnancy. Safer biopsy techniques are bound to be developed as the biopsy is viewed as a valuable component in the array of tools for monitoring complicated pregnancies.

Material and methods

All placentas were delivered at Yale–New Haven Hospital over a 4-month period. Permission to examine this residual pathologic material was approved by the Human Investigation Committee of Yale University School of Medicine. Biopsy was performed on 200 sequential singleton and twin placentas shortly after delivery by use of a 16-gauge Rutner one-handed prostatic biopsy needle (Cook Ob/Gyn, Spencer, Ind.). Biopsies were routinely performed in the middle of the placental parenchyma away from any obvious large fetal vessels, usually in a plane roughly parallel to the chorionic plate. Specimens taken perpendicular to the chorionic plate were equivalent to those taken parallel to the chorionic plate. The biopsy specimens and the placentas were then fixed overnight with formalin, paraffin embedded, sectioned, stained with hematoxylin and eosin, and evaluated by a single investigator (H.J.K.) using standard placental pathologic criteria.⁵ At least three random full-thickness placental sections were collected from each placenta. Chronic villitis was confirmed by T-cell immunohistochemistry with anti-

UCHL-1 at 1:800 (Dako, Santa Barbara, Calif.), avidin-biotin reagents (Vector, Burlingame, California), and diaminobenzidine (Sigma, St. Louis) as the color agent. Villous edema was graded as either none (patchy or diffuse), mild, moderate, or severe. Intervillous fibrin was graded as none, mild, moderate, or severe. Maturation was determined by assessing the age-dependent size of chorionic villous cross-sections. For purposes of statistical analysis, all grades of villous edema or intervillous fibrin were reduced to either *absent* or *present* because insufficient data existed to individually analyze the results for each grade. Placental biopsy specimens were always evaluated before examination of the whole placenta. Sensitivity, specificity, correlation coefficients, and predictive values were determined for the data collected with nonparametric statistical analysis by use of Systat (Systat, Evanston, Ill.).

Results

Only a few diagnoses of the many possible ones that could be made on a full placenta appeared to be routinely discernible in the placental biopsy specimens (Table I). The most frequent diagnoses observed in the placental biopsy specimens related to villous stress (syncytial knots), maturation (villous branching and diameter), and edema. The detailed tabulation of the statistical analysis of the data is shown in Table I.

The data revealed that at least two diagnoses were seen commonly enough and had enough positive predictive value to be potentially useful clinically. The first was villous edema, which represents extravascular fluid accumulation within the mesenchymal cores of chorionic villi of the placenta (Fig. 1, A and B). Although the biopsy specimen identified only 51% of placentas having villous edema, the specificity was 86%

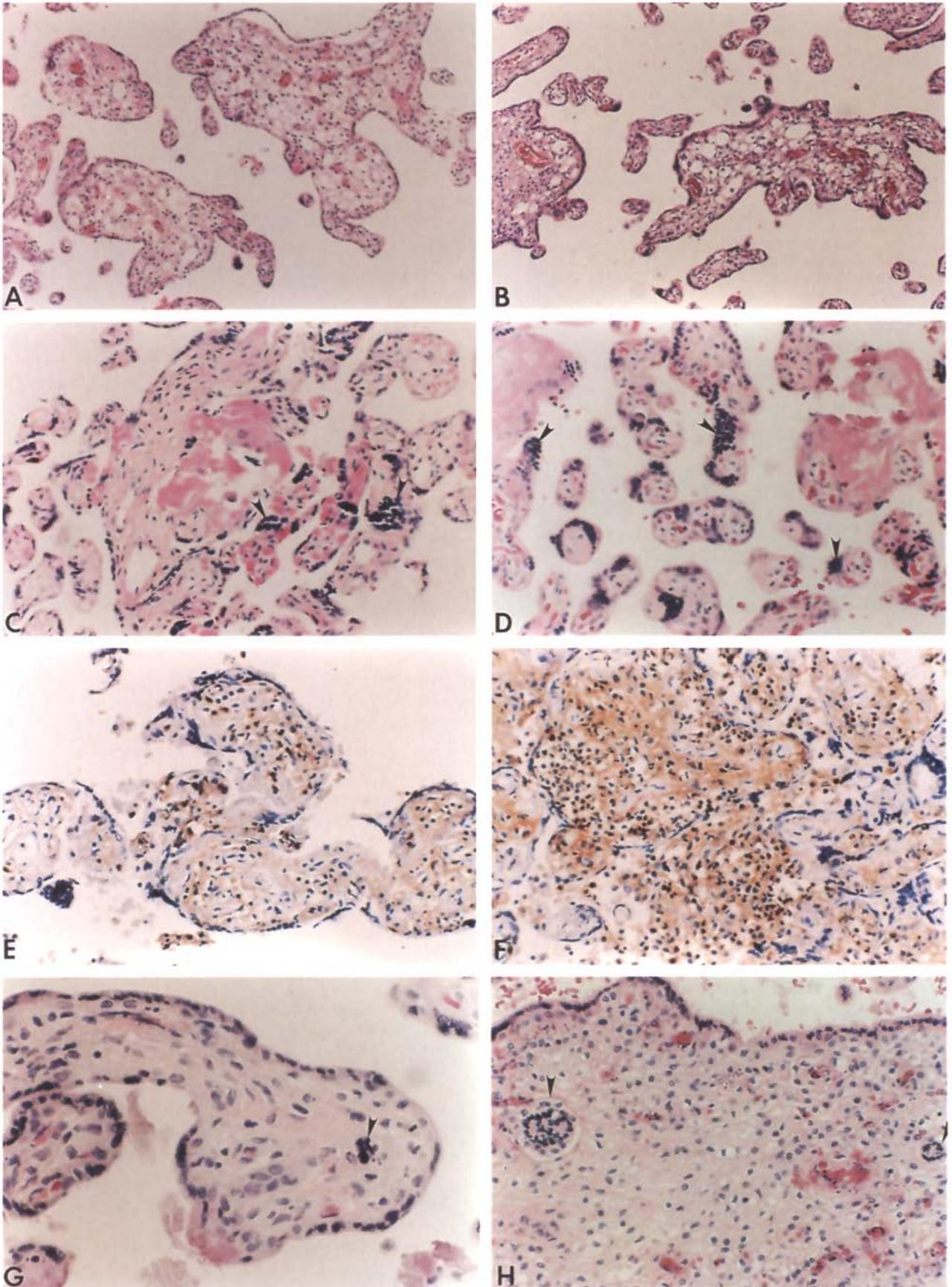


Fig. 1. For legend see opposite page.

($p = 0.001$), yielding a positive predictive value of 97%. Therefore, although negative results did not rule out the presence of villous edema, specimens that did show villous edema were strongly predictive of finding villous edema in the placenta. The second was the presence of increased numbers of syncytial knots. Syncytial knots are collections of multiple syncytial trophoblast nuclei that form buds on the chorionic villous surface (Fig. 1, C and D). The sensitivity of the biopsy specimen to identify increased syncytial knots was 86%, whereas the specificity was 82% ($p < 0.001$), resulting in a positive predictive value of 90%. The diagnoses of calcification of fibrin and villous agglutination may have some clinical significance in spite of lower positive predictive values. The remaining diagnoses did not appear to have clinical utility because they occurred either virtually all the time (intervillous fibrin) or too infrequently (maturation consistent with gestational age, chronic villitis, trophoblast inclusions), they did not show significance (variable maturation), or they did not have sufficient positive predictive value (accelerated maturation). Occasionally examination of the placental biopsy specimens revealed pathologic findings that were only seen rarely and could not be evaluated statistically—for example, the presence of T-cell-positive chronic villitis (Fig. 1, E and F) and trophoblast inclusions (Fig. 1, G and H).

Comment

Fortuitously, two critical diagnoses in the evaluation of a placenta were accurately predicted by examination of a placental biopsy specimen: villous edema and increased syncytial knots. Both of these diagnoses can be associated with significant clinical findings. Villous edema has been associated with antenatal hypoxia,⁶⁻⁹ and its early appearance after the initiation of chorioamnionitis may be associated with significant fetal hypoxia.¹⁰ Syncytial knots are not normally seen until ~35 weeks of gestation and are generally considered to relate to the “maturity” of the placenta. Significantly increased numbers of syncytial knots for a particular gestational age can be seen in cases of acute stress (e.g., chorioamnionitis) and chronic stress (e.g., chronic uteroplacental insufficiency).^{11, 12} Coincidentally, Emanuel et al.¹³ have recently shown that maternal blood and amniotic fluid corticotropin-releasing hormone levels do not begin to rise significantly until after the thirty-third week—a rise that is associated with fetal cortisol production and lung maturation. Furthermore, these

workers showed that pregnancy-induced hypertension is associated with increased corticotropin-releasing hormone production, again coincident with the finding of increased syncytial knots in this clinical setting. Therefore the presence of increased syncytial knots in a placental biopsy specimen could be correlated with early and increased levels of corticotropin-releasing hormone production, which appears to be a sign of uteroplacental ischemia.

Although somewhat less predictive, the findings of fibrin calcification or villous agglutination in biopsy specimens may be sufficiently predictive to merit clinical consideration. Fibrin deposition and its subsequent calcification suggests chronically decreased or slowed maternal intervillous blood flow and thus may be indicative of chronic uteroplacental ischemia.¹⁴ Villous agglutination has been associated with maternal viral infections,¹⁵ and therefore its presence in a placental biopsy specimen may be useful in the intrauterine assessment of the fetus. Finally, the diagnosis of chronic villitis in a biopsy specimen, although rare, appears to be highly predictive of finding this pathologic process in the placenta itself.

Observations of the placenta *in utero* may lead not only to diagnoses of diseases of pregnancy but also to the development of rational treatments. If the efficacy of these biopsies is established in clinical practice, their safety will likely increase in direct proportion to their utilization. With the advent of highly refined techniques that make placental and decidual blood flow visible and thus make inadvertent damage to major blood vessels less likely,¹⁶⁻¹⁸ we appear to be closer to the time when, like the liver and renal pathologists before us, we may be able to suggest responsibly that placental biopsy during gestation can be an effective and safe tool to diagnose diseases of pregnancy.

We thank Erika Meaddough for assisting in data entry, the pathology assistant students of Quinnipac College for processing the placental tissues, Dr. David L. Olive for reviewing the statistical analysis, and Dr. Joshua A. Copel for helpful advice.

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Fig. 1. Pathologic findings in placental biopsy specimens compared with whole placenta. Representative photomicrograph from placental biopsy specimens (A, C, E, G) and paired whole placentas (B, D, F, H) showing villous edema (A, B), increased syncytial knots (arrowheads) (C, D), chronic villitis immunohistochemically stained for T cells (brown-stained cells are maternal T cells) (E, F), and trophoblast inclusions (arrowheads) (G, H) in both placental biopsy specimen and whole placenta. (Original magnifications $\times 275$; except G, $\times 550$.)

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