REBECCA N. BAERGEN
GRAHAM J. BURTON
CYNTHIA G. KAPLAN
EDITORS

Benirschke's Pathology of the Human Placenta

Seventh Edition

Springer

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Editors
Rebecca N. Baergen
Professor of Pathology and Laboratory Medicine
Weill Cornell Medicine, New York Presbyterian Hospital
New York, NY, USA

Graham J. Burton
Centre for Trophoblast Research
University of Cambridge
Cambridge, UK

Cynthia G. Kaplan
Professor Emeritus of Pathology
State University of New York
Stony Brook, NY, USA

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CGK "To my husband Marty and our family"
RNB "To my husband Steve and my family"
GJB "To my wife Hilary and our family"

Preface

It is with great sadness we relate the passing of Kurt Benirschke on September 10, 2014, at the age of 94. In his memory, with the consent of his family, the seventh and all future editions will be titled Benirschke's Pathology of the Human Placenta.

This book had its beginning in 1967 when Shirley G. Driscoll and Kurt Benirschke wrote in English the volume on placental pathology for the *Henke-Lubarsch*, the noted *German Handbook of Pathology.* There seemed to be a need for wider distribution of the text and it was reprinted by Springer Verlag, New York, essentially the only book available devoted just to the human placenta. Dr. Benirschke authored five subsequent editions in collaboration with Peter Kaufmann, Rebecca Baergen, and Graham Burton in 1990 (second edition), 1995 (third edition), 2000 (fourth edition), 2006 (fifth edition), and 2012 (sixth edition). In the early editions, the most important material was in a larger font than the extensive review of exceptions and the discussion in the literature. Since 1967, many other shorter placenta books have been published in English, French, and German. None of these have included the breadth of discussion or the voluminous references which includes details of many historic articles not readily available.

Interest in the placenta has wildly expanded over the intervening more than 50 years with the vast majority of pathologists, obstetricians, and pediatricians recognizing its value, as so well stated by Ballantyne in 1892.

A diseased foetus without its placenta is an imperfect specimen, and a description of a foetal malady, unless accompanied by a notice of the placental condition, is incomplete. Deductions drawn from such a case cannot be considered as conclusive, for in the missing placenta or cord may have existed the cause of the disease and death. During intrauterine life the foetus, the membranes, the cord and the placenta form an organic whole, and disease of any part must react upon and affect the others.

In addition, there are now quite a few new journals, societies, and meetings devoted to the placenta in both clinical and research areas. The interest extends into areas of study well beyond the realm of anatomic pathology.

The seventh edition will, of necessity, differ from the prior editions which Dr. Benirsche wrote largely himself at first, and later with the help of the above noted co-authors. It will now be an international multi-authored book with nearly 40 contributors revising one or more chapters. The explosion of new information necessitated some reordering of chapters and addition of completely new chapters, including Chaps. 31 and 32, "Innovations in Placental Pathology" and "Imaging in Placental Pathology." Dr. Burton's part has been extensively edited, as detailed below. The editors gave the new authors considerable latitude in how to write the new and/or edited chapters. Many of the revised chapters retain much of Dr. Benirschke's anecdotal information as well as the voluminous references. Others are more modern in their approach. All contain substantial new references and current information. It is our hope that *Benirschke's Pathology of the Human Placenta* will remain as a mainstay reference in placental pathology.

For GJB, it was a great honor to take over responsibility for the early chapters covering placental development and structure in the sixth edition from the late Peter Kaufmann, and he

wishes to acknowledge Peter's enormous contribution to the text. In this new seventh edition, the material has been updated, extended, and also significantly rearranged to render the presentation more coherent. In particular, the yolk sac is considered in more detail in Chap. 5 due to recent evidence of its likely importance during the first weeks post-implantation; villous development and maldevelopment are brought together in Chap. 7; there is a new Chap. 8, "The Placental Bed," covering the decidua, extravillous trophoblast, and maternal-fetal immune interactions; considerations of the maternal and fetal circulations to the placenta are integrated in a new Chap. 9; and there is a new Chap. 10, "The Chorionic and Basal Plates," which describes formation of the two plates, the membranes, and deposition of fibrinoid material. It is hoped that this new approach will make it easier for readers to gain a broad understanding of how placental architecture is shaped during normal development, with a view to appreciating how this may be perturbed in complications of pregnancy.

New York, NY, USA — Rebecca N. Baergen
Cambridge, UK — Graham J. Burton
Stony Brook, NY, USA — Cynthia G. Kaplan

Acknowledgments

RNB acknowledges the support of her husband and all the faculty, students, trainees, pathology assistants, and technologists who have assisted her in this endeavor. She would like to give special thanks to her co-editors, Graham Burton and Cynthia Kaplan, for assistance throughout this journey.

GJB is most grateful to his co-authors Eric Jauniaux, Stephen Charnock-Jones, and Ashley Moffett for their valuable authoritative input to the new chapters, and to the many academic colleagues, postdoctoral fellows, and students who have shaped his thinking over the years through inspirational discussions and penetrating questions. Finally, he wishes to express his appreciation of Rebecca Baergen for all her hard work involved in overseeing preparation of this seventh edition in its new format.

CGK is honored to be asked as an editor to the seventh edition and acknowledges the support of her husband and family during the preparation of this edition and in her lifelong devotion to the placenta. Over the years, many faculty, trainees, pathology assistants, and dieners have been immense help in many different ways. She would like to thank Dr. William Bradford, pediatric pathologist at Duke who, in her first year of pathology training, introduced her to the 1967 edition to find what had been described in the placentas of infants born to mothers with scleroderma. Her subsequent years of training at UCSD with Kurt and later interaction at Stony Brook with Lauren Ackerman were irreplaceable experiences.

Contents

Contributors

Susan Arbuckle, MBBS, FRCPA The Children's Hospital at Westmead, Department of Histopathology, Westmead Sydney, Australia

Rebecca N. Baergen, MD Professor of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA

Graham J. Burton, MD, DSc University of Cambridge, Centre for Trophoblast Research, Cambridge, UK

Astrid E. P. Cantineau, MD, PhD University of Groningen, University Medical Center Groningen, Center of Reproductive Medicine, Groningen, The Netherlands

Joanna Sue Yee Chan, MD Jefferson University Hospital, Pathology, Anatomy, and Cell Biology, Philadelphia, PA, USA

Adrian Charles, MA, MD, FRCPath, FRCPA Sidra Medicine, Department of Pathology, Doha, Qatar

D. Stephen Charnock-Jones, BSc, PhD University of Cambridge, Department of Obstetrics and Gynaecology, The Rosie Hospital, Cambridge, UK

Marta C. Cohen, OBE, MD, FRCPath, DMJ Sheffield Children's NHS FT, Department of Histopathology, Western Bank, Sheffield, UK

Jane Esther Dahlstrom, MBBS (Hons), FRCPA, PhD, SFHEA The Canberra Hospital and Australian National University Medical School, Department of Anatomical Pathology, ACT Pathology, Woden, Australia

Gernot Desoye, PhD Medical University of Graz, Graz, Austria

Virginia E. Duncan, MD, MS University of Alabama at Birmingham, Department of Pathology, Birmingham, AL, USA

Margaret J. Evans, BSc. MBChB FRCPath (Paed) LLM Centre for Comparative Pathology, University of Edinburgh, Royal Infirmary of Edinburgh, Department of Pathology, Scotland, UK

Ona Marie Faye-Petersen, MD University of Alabama at Birmingham, Department of Pathology, Birmingham, AL, USA

Sanne Jehanne Gordijn, MD, PhD University Medical Center Groningen, Department of Obstetrics and Gynecology, Groningen, The Netherlands

Amy Heerema-McKenney, MD Cleveland Clinic, Pathology and Laboratory Medicine Institute, Cleveland, OH, USA

Debra S. Heller, MD Department of Pathology, Immunology & Laboratory Medicine, Rutgers-New Jersey Medical School, Newark, NJ, USA

Pei Hui, MD, PhD Department of Pathology, Yale University School of Medicine, New Haven, CT, USA

J. Ciaran Hutchinson, PhD, FRCPath Great Ormond Street Hospital for Children NHS FT, Histopathology. Camelia Botnar Laboratories, London, UK

Eric Jauniaux, MD, PhD EGA Institute for Women's Health at University College London, Obstetrics & Gynaecology, London, UK

Cynthia G. Kaplan, MD Department of Pathology, State University of New York, Stony Brook, NY, USA

Raj P. Kapur, MD, PhD Seattle Children's Hospital, Department of Pathology, Seattle, WA, USA

Philip J. Katzman, MD Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA

Asma Khalil, MBBCh, MD(Res), MRCOG, MSc(Epi) St. George's Hospital, University of London, Fetal Medicine Unit, London, UK

T. Yee Khong, MD Women's and Children's Hospital, Department of Anatomical Pathology, North Adelaide, SA, Australia

Leah M. Lamale-Smith, MD University of California San Diego, Department of Obstetrics, Gynecology and Reproductive Sciences, La Jolla, CA, USA

Louise C. Laurent, MD, PhD University of California San Diego, Department of Obstetrics, Gynecology and Reproductive Sciences, La Jolla, CA, USA

Cathleen Matrai, MD New York Presbyterian Hospital - Weill Cornell Medicine, Department of Pathology and Laboratory Medicine, New York, NY, USA

Ashley Moffett, MD, FRCOG, FMedSci University of Cambridge, Department of Pathology, Cambridge, UK

Christopher James Nolan, BMedSci, MBBS, PhD, FRACP The Canberra Hospital and Australian National University Medical School, Department of Endocrinology, Woden, Australia

Priyadarshini Pantham, PhD University of California San Diego, Department of Obstetrics, Gynecology and Reproductive Sciences, La Jolla, CA, USA

Mana M. Parast, MD, PhD University of California San Diego, Department of Pathology, La Jolla, CA, USA

Jelmer Riemer Prins, MD, PhD University Medical Center Groningen, Department of Obstetrics and Gynecology, Groningen, The Netherlands

Irene Scheimberg, MD, FRCPath Retired Paediatric and Perinatal Pathologist, Barts and the Royal London NHS Trust, London, UK

Bart's NHS Trust, Department of Histopathology, London, UK

Neil Sebire, FCRPath Great Ormond Street Hospital, London, UK

Francesca Soncin, PhD University of California San Diego, Department of Pathology, La Jolla, CA, USA

Srimeenakshi Srinivasan, PhD University of California San Diego, Department of Obstetrics, Gynecology and Reproductive Sciences, La Jolla, CA, USA

Akila Subramaniam, MD, MPH University of Alabama at Birmingham Hospital, Obstetrics and Gynecology/Maternal-Fetal Medicine, Birmingham, AL, USA

Aafke P. A. van Montfoort, PhD Maastricht University Medical Center, Department of Obstetrics and Gynaecology, Maastricht, The Netherlands

Cato J. Vrouwenraets, MD, MSc Maastricht University Medical Center, Department of Obstetrics and Gynaecology, Maastricht, The Netherlands

Kathy Zhang-Rutledge, MD University of California San Diego, Department of Obstetrics, Gynecology and Reproductive Sciences, La Jolla, CA, USA

Examination of the Placenta

1

Rebecca N. Baergen

Storage

Some have advocated storing placentas. The practice of saving unexamined placentas for a week will enable examination of most of the placentas likely to show pathology and allow for examination in neonates who develop problems after delivery [3]. To do this, storage is required so that placentas are available when needed. The American College of Obstetricians and Gynecologists, on the other hand, has suggested, surprisingly, that the routine study of the placenta is not warranted [1], a decision with which we strongly disagree. Placentas should *not* be frozen prior to examination, as this obliterates the most useful histological characteristics and makes even macroscopic examination more difficult. We believe that formalin fixation has similar unwanted effects. It is best to store the delivered placentas in plastic containers, labeled, in a refrigerator at 4 °C. In this state, the placenta is preserved allowing meaningful examination for many days. Autolysis is minimal. We cannot agree with the opinion of Naeye [36] that this storage causes significant artifacts at the gross level that render a subsequent examination difficult. Indeed, the immediate fixation of the organ in formalin, recommended by others [6] as a good means to evaluate the extent of infarction, makes the placenta more difficult to evaluate critically, aside from the storage problems, expense, odor, and hazardous material exposure. Prior fixation, of course, makes tissue culture, bacteriologic examination, and other procedures more difficult or impossible. For maximal convenience, it is a good idea to have a refrigerator with seven shelves, labeled Monday through Sunday, and to discard the normal placentas from one shelf when the next similar weekday arrives. In this way, all placentas from problem births will be available for study.

R. N. Baergen (✉)
Professor of Pathology and Laboratory Medicine,
Weill Cornell Medicine, New York Presbyterian Hospital,
New York, NY, USA
e-mail: rbaergen@med.cornell.edu

The placenta loses some weight during storage. In part, the loss is due to evaporation, but most weight is lost by leakage of blood and serum occasioned by the mass of placental tissue resting on other portions. The amount of weight loss depends on the length of storage and the degree of edema, but it is not great in the normal placenta. It is most significant in the edematous placentas of hydrops. We have observed a 180-g fluid extravasation from a 740-g placenta within 1 day from a hydropic placenta. The freshly examined placenta is thus softer, bloodier, and thicker than one that has been stored. On the other hand, it must be noted that the placenta gains weight when it is stored in formalin, particularly during the first day of fixation. Not all organs increase in weight uniformly after such fixation, as the detailed report by Schremmer [44] specified. The placenta, according to this author, gains between 0.7% and 23.0%, with an average of +9.9%. It is among the organs with the largest deviations in weight gain after fixation [25]. Our own findings are summarized in the graph shown in Fig. 1.1.

Photography

A photographic record is often desirable and is useful for many purposes. Nowadays, of course, digital photography has become a routine and storage of the digital image is easy. This suggests that much more photography of specimens is desirable and should be done. This task is generally quickly accomplished. Friends have often been amused by this recommendation, but they agree that a good picture is worth a lot of words, especially when it comes to litigation.

Examination

Detailed protocols for the examination of the placenta have been presented in the past [3, 8, 9, 15, 21]. Some protocols were designed to allow an unbiased examination of the placenta and record keeping by the many different medical

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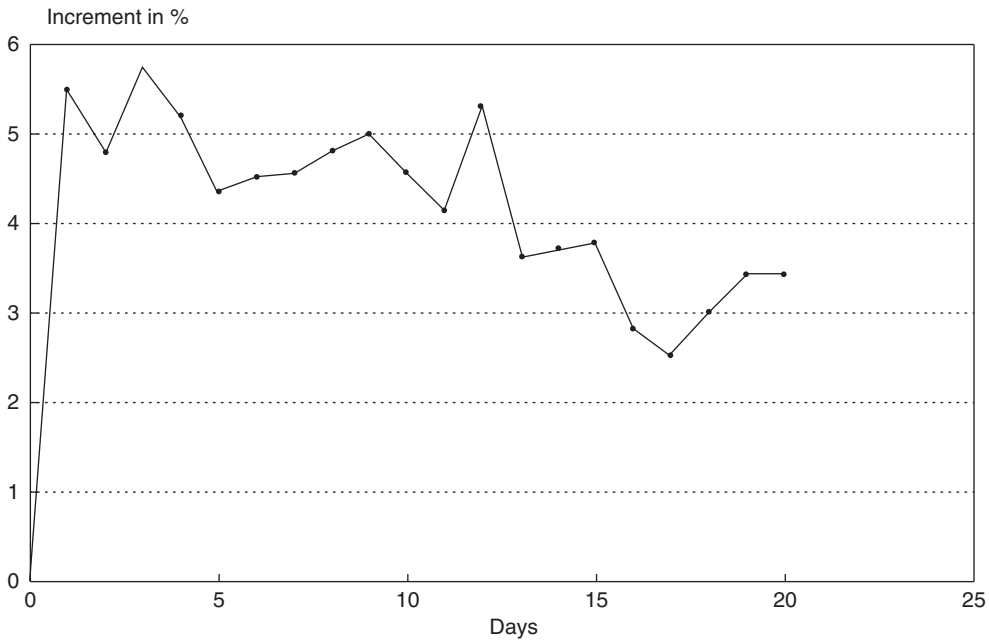

Fig. 1.1 Weight gain of placenta (trimmed, without cord or membranes) after formalin fixation

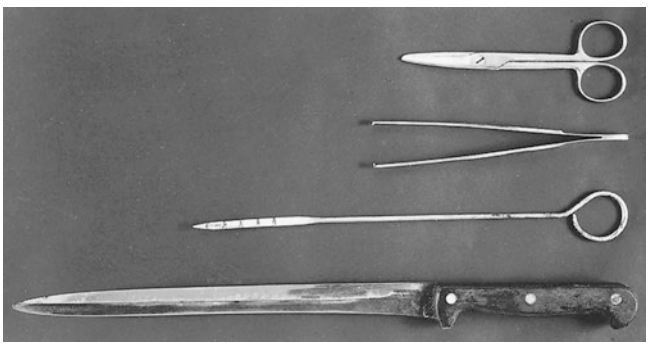

Fig. 1.2 Instruments found to be most practical for the placental examination: scissors, forceps, "dipstick" to measure the thickness of placental tissue, and a long, stiff knife

centers of the "Collaborative Study" so that, ultimately, correlations could be made regarding fetal outcome. Our routine procedure now is to select for histological study those that appear abnormal or whose perinatal circumstances demand such an examination. The selection and storage process just outlined has been helpful, and we have rarely missed a placenta that was of importance [26, 27, 48].

The tools for the examination are simple (Fig. 1.2). They consist of a ruler, a long and sharp knife, toothed forceps, a pair of scissors, and a scale. Our ruler is permanently mounted over the cutting board, thus enabling rapid measurement of the length of the umbilical cord and the placental diameter. A butcher's scale with removable bucket that weighs items up to 2 kg is also available. The long knife, best obtained from a butcher supply house, is sharpened just before examination.

When the placenta is removed from its container, one often perceives rather characteristic odors. In infected placentas, the fetid smell of *Escherichia coli* and the rather sweeter smell of *Listeria monocytogenes* can be distinguished by an experienced pathologist. Storage in the refrigerator enhances the growth of *Listeria* and hence the recognition of these organisms.

The shape of the placenta is then ascertained by stretching it flat on the cutting board. Is it round or oval? This may be assessed by measuring the length of the longest axis and then the longest length of the axis perpendicular to the first, or by taking multiple measurements of the radius from the site of cord insertion [39, 43]. Depending on the methodology used, different conclusions are sometimes reached. Interest in placental shape has been revitalized by the recent observation that ellipticity is related to developmental programming of the fetus [4, 5]. The mechanisms underlying this association are unknown at present, but the shape of the placenta may reflect the site of implantation and hence, potentially, its maternal vascular supply or some other aspect of uteroplacental physiology that impacts on placental efficiency.

Another feature to note is the presence of accessory (succenturiate) lobes. One finds that usually during the delivery, the membranes have inverted over the maternal surface (shiny "Schultze" position) and rarely are they found in the configuration they held in utero (dirty "Duncan") [42]. Membranes are then positioned by the examiner so that they assume their in utero configuration. One next ascertains the completeness of the membranes. It is also noted at this time if the tear that allowed the infant to escape from its membranous enclosure extends to the edge of the placenta or if free membranes extend beyond the closest edge. If there is any margin of intact membranes, this placenta could not have been a placenta previa, provided it was from a vaginal deliv-

ery. If the edge of the membranous tear is far from the placental border, a fundal position can be deduced. Torpin and Hart [47] made the point that when the minimally disturbed sac is immersed in a bucket of water, the sac assumes the configuration of the uterus and that its position before birth can be reasonably accurately determined by this study. It is now prudent to inspect the color and appearance of the fetal surface of the placenta. Normally, it is shiny and the subjacent blood is seen as a clear blue hue, particularly in the immature organ. When chorioamnionitis is present, the membranes become opaque by the interposition of leukocytes, and the surface usually loses its sheen. Greenish discoloration betrays either meconium (slimy) or hemosiderin deposition.

Next, the membranes are cut off the edge of the placenta with the knife. If one anticipates making sections of the placenta for histological study, it is wise to follow a routine protocol for doing so, as it enhances subsequent interpretation. It is preferable to cut the membranes off in such a manner that one knows the point of rupture; then, when sections are made, the membrane roll is prepared in such a fashion that the point of rupture is in the center of the roll with the amnion inward (Fig. 1.3). This method of preparing a roll of membranes (the "jelly roll"), in order to obtain a maximum amount of membranes with decidua capsularis, was first described by Zeek and Assali [50]. In immature placentas, there may be a large amount of decidua, and it is often ragged. In more mature organs, the decidua atrophies and often degenerates. Occasionally, one finds an intrauterine device in this decidua capsularis, usually at the edge of the placenta and associated with old clot and debris (Figs. 1.4 and 1.5). Frequently, there are areas of brown to green discoloration in the membranes that are from former hemorrhages, or they may have been induced by amniocentesis.

In many placentas, the amnion is disrupted or sheared off the underlying chorion. In fact, the amnion may be totally detached. Milky, white vernix caseosa occasionally dissects underneath the amnion; it is readily removed and has no significance. The membranes near the edge of the placenta frequently contain the remnant of the yolk sac, a small white to yellow oval disk that is located underneath the amnion. The yolk sac in early stages of development can now be visualized ultrasonographically. Occasionally, one sees remnants of tiny vessels traversing from it to the insertion of the cord, or even within the cord.

The color of the membranes is noted, as are the surface characteristics. A slimy feeling is often the result of meco-

Fig. 1.4 Edge of the placenta (*right*) with an intrauterine device embedded in degenerating decidua (partly removed) and old blood clot

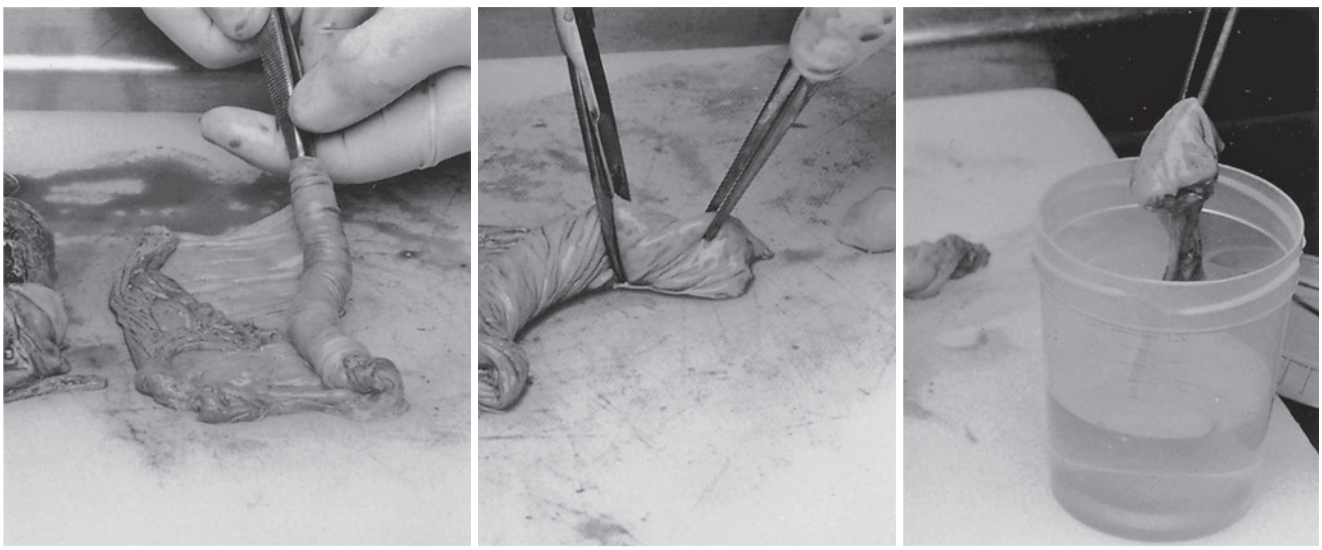

Fig. 1.3 Rolling of membranes for fixation and later sectioning. It is best to prepare them in a standardized fashion, e.g., amnion inside, starting at the site of rupture and proceeding toward the edge of the placenta, as shown at *left*. A segment is then taken from a well-rolled portion (*center*) and is fixed for a day (*right*) before trimming

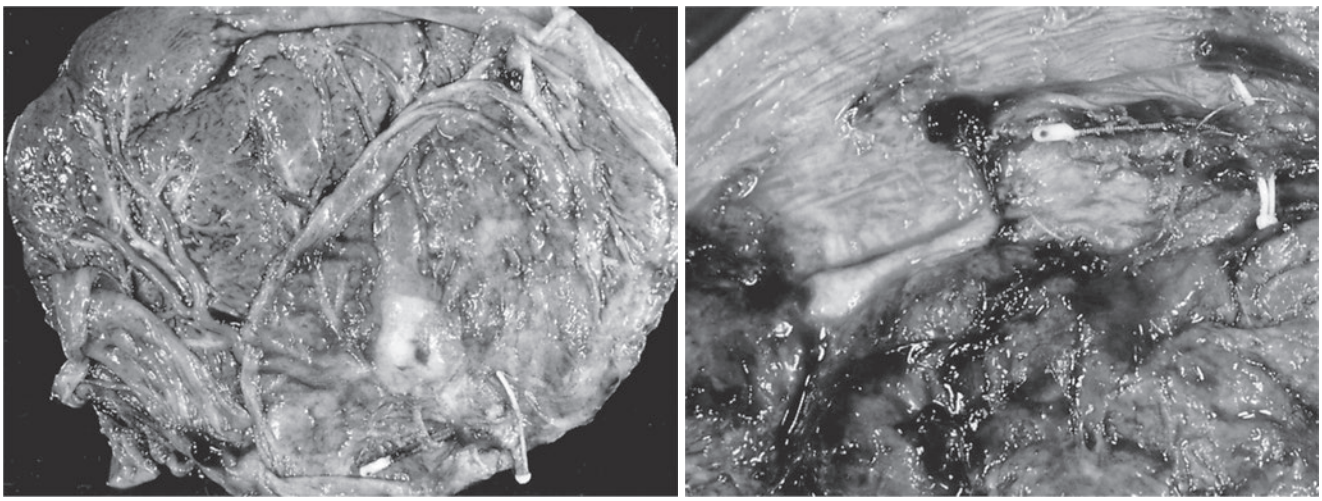

Fig. 1.5 Intrauterine devices at the placental margin at term (*left*) and in a slightly immature (*right*) pregnancy. Note the attending hemorrhagic degeneration of the adjacent tissues

nium discharge, as is of course a green color. The length of time of meconium discharge can be estimated by the presence of green discoloration in different layers. When it is only in the amnion, this suggests a short-time interval; when meconium is found also in the chorion after the amnion is stripped off, a longer interval has passed since discharge [32]. According to this study, after 1 h, the meconium macrophages are visible within the amnion; after 3 h, they may be seen in the chorionic tissue. At even later times, it reaches the decidua capsularis. Subsequent studies have produced different results suggesting that the time interval may be longer for pigment to be seen in the membranes, from 24 to 48 hours prior to delivery [18]. Greenish or brownish discolorations in immature placentas are more often due to blood breakdown products (hematoidin, hemosiderin) following hemolysis, rather than from meconium. Hemosiderin, of course, can be stained with the Prussian blue method for iron; however, the bilirubin of meconium stains rather poorly with bile stains. The very immature fetus cannot discharge meconium, lacking the hormonal maturation for intestinal propulsion [28]. Meconium is quite common at term and even more common post-term. The surface layer of the membranes, the amnion, is normally shiny. Around the insertion of the cord, one may find squamous metaplasia in the form of concentric nodules that are hydrophobic (Fig. 1.6). They are normal features. Amnion nodosum, usually represented by a finely granular, dull appearance of the amnionic surface, correlates with oligohydramnios. One must, of course, be cognizant of whether the amnion is present at all and, if not, whether amnionic bands exist. Often, some blood dissects underneath the amnion during placental delivery or if fetal blood has been aspirated for diagnostic tests from the fetal surface blood vessels.

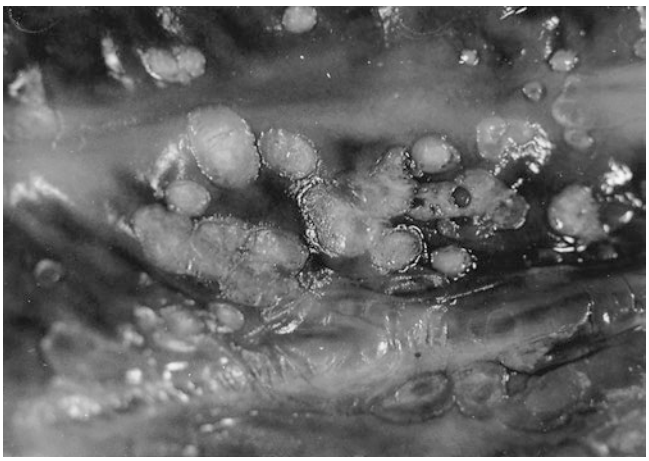

Fig. 1.6 Squamous metaplasia of amnion in concentric patches, usually found near the insertion of the umbilical cord. The plaques are water repellent

Next, the cord is examined; is it central, eccentric, marginal, or membranous (velamentous) in its insertion? What is its length, and is it coiled to the right or left, hypercoiled or hypocoiled? We now believe that the length of the umbilical cord is determined primarily by fetal movements and that excessive coiling implies unusual fetal motions [33]. There may be a genetic component to the spiraling and the length, as the umbilical cords of some animals have different and consistent lengths, but this characteristic is so far unknown for human umbilical cords. Are there knots, thrombi, or discolorations? Can any other unusual features be detected? The cord is then severed from the bulk of the placenta, and its cut surface is studied at several locations. The most important observation to be made here is whether there are three vessels and if other unusual features are present. Single

umbilical artery (SUA) is the commonest abnormality. One must also appreciate that there is almost always an anastomosis ("Hyrtl's anastomosis") between the two umbilical arteries which is usually found near the point of insertion on the placental surface but may extend up to 10 cm from the point of insertion [41]. Thus, counting the number of vessels is best done farther away from the insertion. When a velamentous insertion of the cord is found, the examiner must pursue the ramifications of the fetal vessels after they leave the site of cord insertion, at times finding thrombi, particularly in membranous vessels. These vessels may be disrupted, as in vasa previa, and acute exsanguination of the fetus is common in such circumstances.

The weight of the remaining disk is now ascertained. It is generally useless to know the weight of the entire organ, including cord and membranes [29]. Correlations with fetal weight and development can be made only by knowing the "net" weight of placental tissue [22, 49]. Excessive amounts of maternal, retroplacental clots must, of course, also have been removed before weighing. Note again that the weight of formalin-fixed placentas is greater than that of fresh organs (Fig. 1.1) [44]. Variations in normal placental weight are common. They reflect mostly length of storage and amount of fetal blood content.

When studying the fetal surface of the placenta, one notes its color and the possible presence of granular excrescences. Most importantly, however, one must carefully inspect the fetal vessels, which are carried in the chorion; the amnion has no blood vessels. In nearly all placentas, one can recognize the fetal arteries as those vessels that cross over the veins [10, 12]. It will be observed that the terminal branches of arteries dip singly into a lobule; next to it, a vein emerges to return the blood to the cord (Fig. 1.7). One often finds thrombi in these vessels in placentas of abnormal newborns.

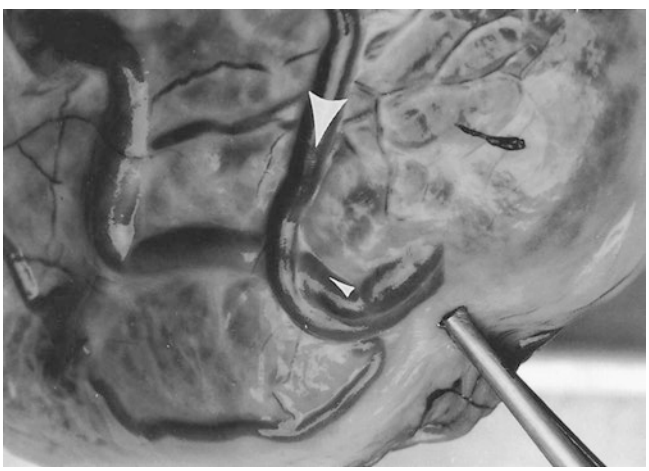

Fig. 1.7 Entrance of fetal vessels on the chorionic plate into the cotyledon. One artery (*large arrowhead*) brings the fetal blood; the vein (*small arrowhead*) next to it returns it to the fetus

They appear as white-yellow streaks on the vessel's surface and are usually not completely occlusive. When they are, an area of hemolysis is often seen adjacent to the thrombosis. Thrombi may also calcify. They must be sampled for histological study.

The fetal surface of the mature placenta is often described as being "bosselated" or "tessellated," meaning that tiny white elevations are present underneath the chorion, giving the surface a mosaic, irregular pattern. These protrusions represent accumulations of fibrin in the intervillous space, and they increase in number with advancing maturity. Larger patches of fibrin also exist; at times they have a liquefied center, but they are assumed to be of little significance [19]. In our experience, however, larger subchorionic thrombi are abnormal and occasionally associated with fetal growth restriction. Cysts from the subchorionic extravillous trophoblast cells ("X-cells") may bulge on the surface and contain a clear, slightly viscid mucoid substance. At times it is discolored with blood. Finally, the insertion of the membranes is observed. Is it at the edge, or is there a ring of "circummargination" or "circumvallation?"

When the placenta is next turned over, thus exposing the maternal surface, the first step is to identify possible areas of retroplacental hemorrhage, often clinical abruptio placentae. When a separation is fresh, one may not be able to differentiate it from the normally present postpartum maternal blood clot that adheres. Within a few hours, though, the blood dries and becomes firmer and more stringy with better adherence to the maternal surface. Over time it changes color to brown, and eventually it may become greenish. In such cases, the placenta underneath the clot is usually infarcted, or at least compressed. Retroplacental hemorrhages are common, and most are clinically silent. The majority are located at the margin of the placenta; and, on occasion, one finds an old clot behind the membranes. Calcification on the maternal surface is then observed as small yellow-white granules in the decidua basalis and septa. Calcifications vary a good deal in quantity; they are usually found only in mature organs. The quantity has no clinically important correlations [16, 17, 24], but clinicians have paid much attention to the recognition of calcification. It may be detected by sonography and has served as a method to "grade" (age) the placenta [14, 20]. This is rarely done now as it has not been found to be helpful. At this point, one also observes the cotyledons, the major subdivisions of the placental tissue. They increase in size and differentiation with advancing gestation, being absent early. One needs to try to ascertain now whether all of the placental "floor" is present or whether there are missing cotyledons. If no cotyledonary subdivisions exist in the mature placenta, then the floor is often too thick and may be infiltrated with an excess amount of fibrin. This condition is known as "maternal floor infarction" (MFI) or massive perivillous fibrin deposition and is best noted at this time [35].

Long, parallel cuts are now made with the knife, and, most importantly, the color, texture, and other features of the villous tissue are observed. The red color of the villous tissue is almost wholly determined by its content of fetal blood. Thus, a congested placenta (as in maternal diabetes, for instance) is dark. The placenta of an anemic, hydropic, exsanguinated, or erythroblastotic fetus is pale, and it is usually also much more friable. Such a placenta is also commonly thicker, 3–5 cm, in contrast to the normal placenta that averages 2.0–2.5 cm at term.

It is normal to find "holes" in the center of many placental cotyledons [45]. Such holes were filled, in vivo, with maternal blood and represent the areas of first blood distribution into the intervillous space from the maternal injection jet. Intervillous thrombi, often located in these spaces, may be dark when fresh; alternatively, they are composed of layered white fibrin when older. The intervillous thrombi differ from infarcts in that they displace villous tissue, showing a shiny texture, often with striations. Infarcts tend to be based on the maternal surface. Furthermore, infarcts are more rectangular or, at the margin, triangular and granular in texture, because they are composed of dead villous tissue. Fresh infarcts are red, and older ones are yellow to white. When sectioning the placenta, one also finds that the intercotyledonary septa contain some calcium, and often they contain some cystic spaces filled with trophoblastic secretion, the same clear mucoid material as contained in surface cysts. They too arise from extravillous trophoblast cells. Occasionally, one encounters round tumors of a solid nature, chorioangiomas. It is a good practice to estimate the total amount of infarction or any other lesion and to record the percentage of involvement. In fact, it is ultimately of some importance and may have medicolegal implications in infants with growth restriction. Single marginal infarcts are common at term and do not correlate with either fetal or maternal conditions. Other lesions are occasionally seen and rarely grossly noted "infarcts" turn out to be choriocarcinoma on histological study [13].

Placentas of Multiple Births

Placentas of multiple births are important records for the infants and pediatrician alike, and they are routinely examined. A recording of the membrane relation between the twins, triplets, and so on is mandatory. Of course, for meaningful analysis, it is necessary that the umbilical cords be labeled with sutures or clamps by the obstetrician, in the order of births. The most important decisions to be made in examining placentas of multiple births are (1) the number of membranes that divide the sacs (two or four or none) and (2) the types of vascular anastomoses that are present, generally only in monochorionic twin placentas. Fraternal (dizygotic) twins essentially *always* have diamnionic/dichorionic (DiDi) placentas. Fused placentas, however, are not always monochorionic. They may be DiDi, and they may be diamnionic/monochorionic (DiMo). Finally, there may be no "dividing membranes" between the fetuses, as in the monoamnionic/monochorionic twin placenta (MoMo). All monochorionic twin placentas belong to monozygotic (MZ, "identical") twins. The time at which MZ twins separated one from another during the early embryonic stages presumably determines the type of placentation that ultimately develops, and this can thus be estimated from an examination of the membrane relation. The diagnosis of a DiDi twin placenta is made by ascertaining that the dividing membranes are opaque and contain remnants of old vessels or other debris (old decidua, degenerated villi) which appear as white streaks. Also, in DiDi placentas, one usually finds a ridge at the site where the membranes meet over the placenta. It is caused by the buckling of tissues from the collision of the two expanding placental tissue masses. The dividing membranes of DiMo placentas, in contrast, are transparent consisting only of amnion. The diagnosis of membrane relationship is, of course, easiest and most permanently established by a histological section of a membrane roll of this tissue, or by a "T section" that includes the junctional area (Fig. 1.8).

After the membrane relation is established, the "vascular equator," i.e., the area where the two chorionic vascular districts meet, is examined. This is generally *not* in the same location as the dividing membranes and can be found by identifying the chorionic plate vessels that branch from each umbilical cord insertion. In DiDi placentas, there is never confluence of fetal blood vessels; if one were found, it would be exceptional and would be the basis for the exceedingly rare blood chimerism in fraternal twins. It must be cautioned here that ascertainment of a DiDi relation does *not* make the diagnosis of fraternal twins. Approximately one third of monozygotic twins have this placentation. In monochorionic placentas (DiMo, MoMo), there are almost always some anastomoses, particularly in the prematurely delivered pla-

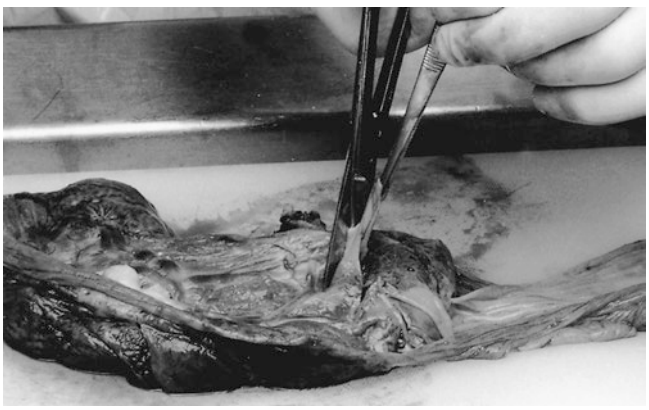

Fig. 1.8 Preparation of a "T section" of the meeting point of the dividing membranes in twin placentas

centas. These anastomoses have a great influence on the well-being of the developing fetus [7, 9]. They take three forms: artery to artery (AA), vein to vein (VV), and artery to vein (AV). The last of these is doubtless the most important and is the basis for the "twin-to-twin transfusion syndrome (TTTS)." It must be remembered that arteries lie on top of veins and that they are thus readily identified macroscopically. An AV anastomosis carries the blood of one twin, through a cotyledon in a one-way direction, from one twin to the other. Often the various types of anastomoses coexist, and the consequences for fetal development may be different depending on the arrangements that are present. When in doubt, one may inject the vessels in question with water or other liquid but in practice this is rarely necessary [37]. AA and VV anastomoses are easily identifiable by their direct connection. AV anastomoses may be identified by the presence of unpaired vessels in the chorionic plate, i.e., one twin will show an artery without a paired vein.

Examination of the maternal surface and other parameters of the placentas of twins follow that of the regular protocol. It must be borne in mind that when the blood content of twins differs considerably, it may be reflected in the macroscopic placental examination as well. One portion of such a twin placenta may be severely congested and larger, with the other being pale and smaller. This condition is most commonly seen when only one AV anastomosis exists. Here, in the classical mechanism of the transfusion syndrome, one twin constantly loses blood through this one-way AV shunt, whereas the other becomes plethoric. Usually, it leads to hydramnios, premature birth, and disparate birth weights of these "identical twins." It must be recognized, however, that differences in neonatal hemoglobin content of monochorionic twins may also occur acutely, when large AA and VV anastomoses exist. Thus, after the delivery of one twin, the other twin may "bleed" through anastomoses if the cord of the delivered twin is not promptly clamped. Likewise, when one of such twins dies in utero, significant shifts of blood may occur from the live twin through such large anastomoses into the relaxed vascular bed of the deceased twin. Finally, it is our practice to dissect the two halves of the twin placenta at the site of the vascular equator in order to determine the placental weight of each twin. Higher multiple births are handled the same way.

Sections

It is the recommended practice to save at least two sections of umbilical cord, one or two sections of the membrane roll, and three pieces of placental tissue for histological examination. Of course, having more sections of umbilical cord available for histological study is ideal, as an inflammatory response, thrombi, and other features are not always uniformly distributed throughout the length of the umbilical cord. Preparing more than one piece of placental tissue for histological study is also desirable because so many areas of the placenta show histological variations. Thus, one can much better determine the existence of inflammatory lesions and is less apt to overlook changes that are not ascertained macroscopically. Moreover, one must obtain sections from the more normal portions of the placenta as well. Although the pathologist is used to sampling abnormal areas for histological study, it is not desirable to take only abnormal areas of the placenta. Indeed, almost all infarcts are histologically alike, and since they also have a typical macroscopic appearance, they are rarely worth the trouble of histological study, except that the sections provide verifiable evidence of the existence of infarcts. It is much more important to save normal appearing placental tissue for microscopy. One must sample both the fetal and maternal surfaces in order to include some fetal surface blood vessels. Because it is generally impossible to anticipate from macroscopic inspection whether chronic villitis and many other lesions exist, it is better to preserve too much than too little in the fixative. It goes without saying that unusual-appearing areas must also be sampled.

For histological examination, we prefer the hematoxylin and eosin (H&E) stain. On some occasions, however, it is useful to employ special stains, such as those that demonstrate elastic fibers, bacterial and spirochete stains, periodic acid-Schiff (PAS) preparations, and specific immunohistochemical stains that disclose the presence of viruses, e.g., cytomegalovirus and herpes antigens. Specific proteins can also be immunostained, e.g., human chorionic gonadotropin (hCG), human placental lactogen (hPL), major basic protein (MBP), cytokeratin, vimentin, fibrin, and proliferation markers. While these tests have given much insight into the distribution of various placental tissue components, the sites of hormone production, and the involvement by organisms as well as other pathological processes, they are generally not necessary for routine diagnosis. The report form used by us during placental examination is reproduced at the end of the chapter for the benefit of the reader.

mRNA and Microarray Analyses

Studies of gene expression have been used to investigate the pathophysiology of various placental disorders. The advent of commercially available microarray platforms allows thousands of transcripts to be analyzed at once, and for gene networks to be identified. However, special collection procedures are required if the data are to be representative of the in vivo state. These start with the mode of delivery. Placentas subjected to labor display higher levels of oxidative stress compared to nonlabored placentas delivered by Cesarean section,

and this is associated with changes in the endocrine and cytokine profile. Many of the changes reported in preeclampsia are observed in normal placentas following labor [11]. Ideally, therefore, analysis should be restricted to placentas delivered by Cesarean section. mRNA degrades rapidly following delivery, and tissue samples need to be frozen rapidly, preferably within 10 min. After this time, metabolic and oxidative changes are detectable [46]. Multiple small samples should be taken in a systematic random uniform fashion [30] from at least ten placentas in each group, as studies have shown that there is large intra- and interplacental variability in gene expression [2, 40]. The samples should be washed thoroughly in buffered saline to remove maternal contaminants, frozen rapidly in liquid nitrogen, and then stored in a minus 80 °C freezer for subsequent analysis. A suitable protocol has been described by Pasupathy et al. [38].

Results from microarray studies should be confirmed by qRT-PCR techniques, and the general consensus is that three housekeeping genes should be used to increase the accuracy of normalization. Suitable housekeeping genes have been identified [31, 34].

Special Procedures

The placenta can serve as a good source of tissue for *chromosome analysis*. This is especially true when the fetus is macerated. One proceeds best by disinfecting the amnion with some alcohol and then stripping the amnion off a portion of placental surface. Sterile instruments are recommended for taking the biopsy from chorion. A small piece of chorion, ideally with a bit of fetal surface vessel, is best for the purpose of establishing a tissue culture. The biopsies are placed into tissue culture medium with antibiotics and transferred to the laboratory. It is of parenthetic interest that Jauniaux and Campbell [23] showed that many structural abnormalities of the placenta can be anticipated from sonography.

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Macroscopic Features of the Delivered Placenta

2

Rebecca N. Baergen

Fetal Surface

The full-term, delivered placenta is, in more than 90% of the cases, a disklike, flat, round to oval organ. In nearly 10%, it has abnormal shapes, such as placenta bilobata, placenta duplex, placenta succenturiata, and placenta membranacea Torpin [10], (see Chap. 17). The average diameter is 22 cm, the average thickness in the center of the delivered organ 2.5 cm, and the average weight 470 g (see Appendix A.1). The respective measurements show considerable interindividual variation and strongly depend on such factors as the mode of birth, timing of cord clamping (see Appendix A.1), and time elapsed between delivery and examination. The fetal (chorionic) surface, facing the amniotic cavity, has a glossy appearance because of the intact epithelial surface of the amnion. This avascular membrane covers the chorionic plate, including the chorionic vessels, and extends over the free membranes (chorion laeve) and the umbilical cord. The chorionic plate vessels branch in a starlike pattern centrifugally from the cord insertion over the fetal surface (Fig. 2.1). Where arteries and veins cross, the arterial branches are usually superficial; they cross over the veins on their amniotic aspect. Wentworth [11] reported that only about 3% show the opposite condition. According to Boyd and Hamilton [1], the superficial position of one or more venous branches at points of arteriovenous crossing is not unusual.

In the vicinity of the larger chorionic vessels, the chorionic plate normally has an opaque appearance because an increased number of collagen fibers accompany the vessels. Those areas of the chorionic plate located between the chorionic vessels are mostly transparent and are dark lilac to black because of the maternal blood in the intervillous space below. Opaque spots (bosselations) or large opaque areas independent of chorionic vessels usually point to large subchorionic deposits of fibrin/fibrinoid.

Near the placental margin, where the most peripheral branches of the chorionic vessels curve vertically down toward the villous trees, the transparency of the chorionic plate decreases, resulting in a largely incomplete, opaque, subchorial closing ring that is a result of increased amounts of cytotrophoblast and collagen fibers. It connects the placenta with the membranes. A circumvallate or circummarginate placenta is formed when the closing ring is peripherally overgrown by villous trees. In such cases, it does not represent the outermost margin of the placenta; rather, the membranes insert superficially from the fetal surface of the placenta.

Placental shape and cord insertion are sometimes regarded as structurally impressive but functionally unimportant parameters. Whether the normal placenta is considered round or elliptical depends heavily on the algorithms used to derive a shape index. Taking multiple radial markers leads to the conclusion that the placenta is round [8], whereas taking the longest and shortest dimensions perpendicular to each other results in the conclusion that it is elliptical [6]. Increased variability in shape is related to a decreased efficiency of the placenta, as assessed by the ratio of placental and fetal weights, which may reflect either maternal uteroplacental or fetoplacental pathology [7, 8]. Due to the orientation of the blastocyst at the time of implantation, with the animal pole associated with the inner cell mass adhering to the uterine epithelium, the cord is normally inserted near the center of the disk. A recent large study in fact revealed that the site of insertion is most commonly off-center [6]. Variations may therefore reflect aberrations in the initial process of attachment. Alternatively, it has been suggested that excessive villus regression, secondary to limitation of the maternal arterial circulation toward the end of the first trimester, results in the cord being attached toward the margin of the remaining placental mass [2]. Whatever the cause, eccentric insertion is associated with a lower fetoplacental weight ratio, again suggesting a less efficient placenta [12]. Whether this reflects

R. N. Baergen (✉)
Professor of Pathology and Laboratory Medicine,
Weill Cornell Medicine, New York Presbyterian Hospital,
New York, NY, USA
e-mail: rbaergen@med.cornell.edu

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compromise of the maternal vascular supply or a reduced exchange capacity on the fetal side is not known, but eccentric cord insertion is generally associated with a higher resistance in the umbilical circulation [5].

Maternal Surface

The uterine (maternal) surface of the placenta is slightly opaque, as it is an artificial surface originating from laminar degenerative processes within the junctional zone that led to the separation of the organ. This separation process subdivides the junctional zone between the placenta and uterine wall into:

- The basal plate which is attached to the placenta and represents the maternal, uterine surface of the organ.
- The placental bed which remains in utero.

The basal plate and the maternal surface of the placenta cannot be identified before placental separation of the in situ specimen. It is composed of a heterogeneous mixture of trophoblastic and decidual cells embedded into prevailing amounts of extracellular debris, fibrinoid, and blood clot.

An incomplete system of grooves subdivides the basal surface of the placenta into 10–40 slightly elevated areas called maternal lobes or cotyledons (Figs. 2.1 and 2.2). Internally, these grooves correspond to the placental septa, folds of the basal plate which project into the intervillous space. In histological sections, the septa can often be seen to be indented at their basal surfaces. It is likely that these grooves and the respective basal indentations of the septa are the postpartal results of tearing at sites of minor mechanical resistance, as the basal central parts of the septa are often characterized by necrotic zones, clefts, and local pseudocysts. Despite their possibly artifactual genesis, the grooves

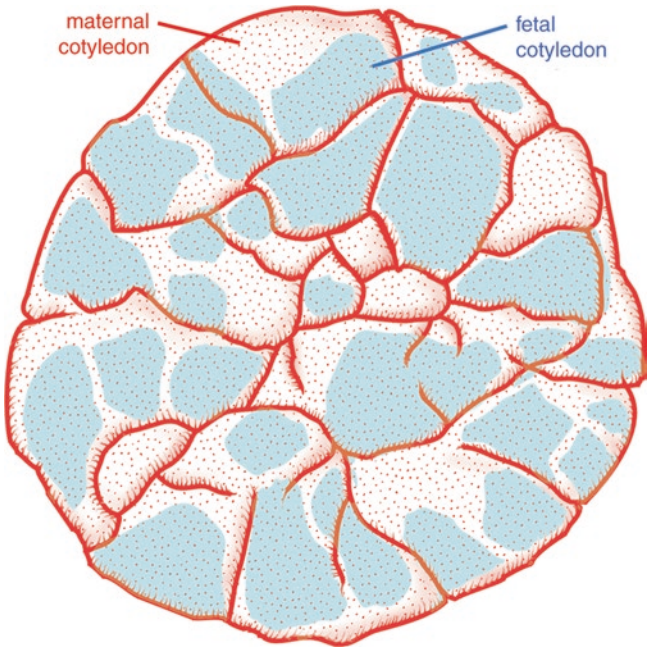

Fig. 2.2 Maternal view of the placenta, drawn in combination with a radiograph of the same placenta after injection of a radiopaque medium into the fetal vessels. The borderlines of the placental lobules (maternal cotyledons, *red stippled*) are marked by *red lines* corresponding to the grooves. The radiographic projections of 29 villous trees are represented *by blue stippled areas*. This combination demonstrates a fairly good harmony of villous trees and maternal lobes. One to three villous trees (fetal cotyledons) are projected on one lobe (maternal cotyledon) (From Kaufmann and Scheffen [4], with permission; based on photographs by Boyd and Hamilton [1])

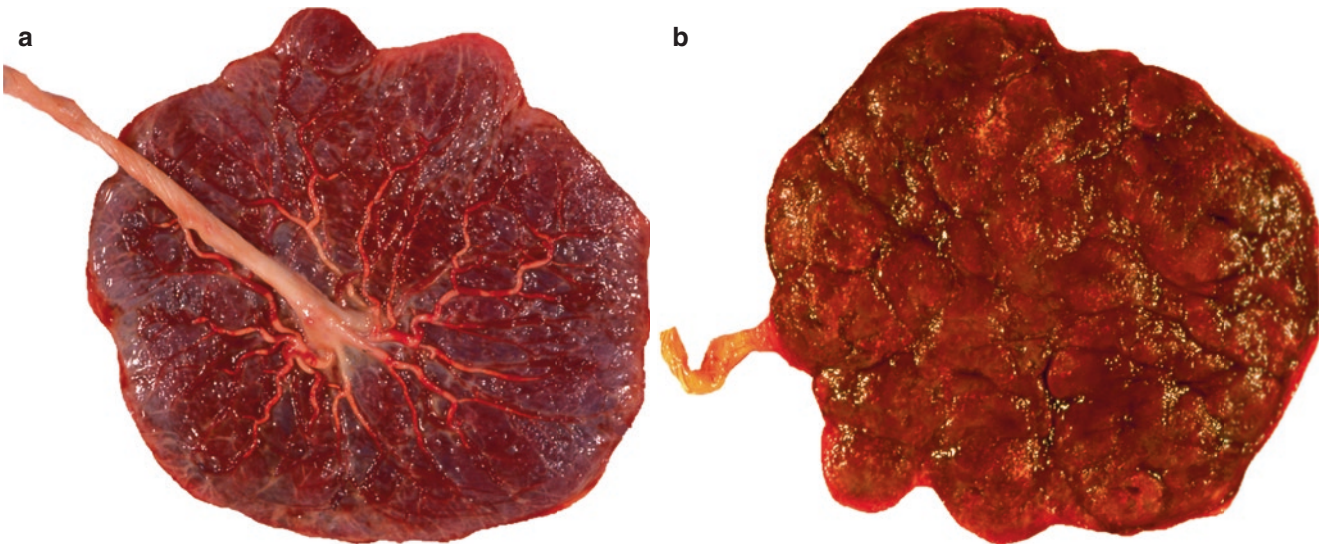

Fig. 2.1 Fetal (**a**) and maternal (**b**) views of a freshly delivered, mature human placenta. Note the slightly eccentric insertion of the umbilical cord, which is the most usual location. The chorionic arteries (*white* because of postpartum injection of milk) cross over the corresponding veins (*dark*). The basal (maternal) surface (**b**) is subdivided into placental lobules of varying size by an interrupted net of dark grooves ×0.4

delineate the lobes and mark the position of the septa. The septa must not be misunderstood as structures that subdivide the intervillous space into chambers; rather, they are irregular pillars or short sails that only trace the lobar borders and do not extend all the way to the chorionic plate.

The lobes show fairly good harmony with the position of the fetal lobules or cotyledons. From the chorionic plate at term, 60–70 villous stems arise, each branching into one villous tree (or lobule) (see Figs. 4.6 and 7.18). Thus, according to Boyd and Hamilton [1] and Kaufmann [3], each lobe is occupied by one or several villous trees. When a radioangiograph of the villous trees is projected onto a basal view of the same placenta (Fig. 2.2), the borderlines of the lobes usually coincide with the borderlines of single villous trees or small groups of trees. Small marginal lobes are likely to be occupied by only a single villous tree and thus correspond to what Schuhmann [9] and his group described as representing a placentone.

The Terms "Fetal Placenta" and "Maternal Placenta"

When describing human placentation, terms such as "fetal placenta" and "maternal placenta" must be avoided because they are misleading and often cause misinterpretation. The terms originate from study of the noninvasive placentas of many domestic species, where a fetal component interacts with a clearly defined maternal component, and the two can be cleanly separated at delivery. Such a separation cannot be achieved in the invasive form of human placentation. This point becomes important as soon as morphologically inexperienced biochemists, endocrinologists, and others isolate respective parts of the organ and draw incorrect functional conclusions.

- A typical example is that of the basal plate, often erroneously referred to as "maternal placenta." It is not exclusively composed of maternal cells but rather represents a colorful mixture of trophoblastic (fetal) and endometrium-derived (maternal) cells.
- A corresponding warning is necessary regarding the placental bed. It is often thought to represent only the maternal remains of the placental site after separation of the placenta. Trophoblastic cells deeply invade the endometrium, however, and even penetrate the myometrium. They remain in utero long after delivery and can be found as fetal admixtures in the placental bed.
- The term "fetal placenta" is also inappropriate. With the possible exception of the central parts of the chorionic plate, there are no placental structures for which the pure fetal composition can be ensured. The marginal zone of the chorionic plate contains decidua, and the same is true for parts of the cell islands and septa. Because the latter may be attached to the villous trees, one is never certain that preparations of it are devoid of maternal tissues, even if we disregard maternal blood and fibrinoid deposits that are partly maternal blood clot products.

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Microscopic Survey

3

Graham J. Burton

Histological sections of placental samples contain a broad variety of different structures, both villous and non-villous. The aim of this chapter is to provide a brief introduction into those features that help to provide points of orientation. For this purpose, a collection of conventional photographs from routine histological sections has been selected. Labeling of the figures is explained in the text. For further reading concerning the features, references are made to later chapters. Quantitative data are provided in Table A.1.

Ideally, the routine histological examination of the human placenta requires vertically oriented sections that cover the entirety of the placenta from the chorionic plate, via the intervillous space down to the basal plate (Figs. 3.1 and 3.2). Such sections are easily obtained from most second and third trimester placentas, as well as from the rare in situ specimens obtained by hysterectomy in the first trimester (Fig. 3.1). Tissue samples from terminations of pregnancy are generally not good for survey pictures, as usually the basal plate and neighboring tissues such as septa, anchoring villi, and cell columns are either absent or difficult to identify because they are destroyed or mixed up among the villi.

Typical Histological Features of the First Trimester Placenta

Complete and well-preserved survey sections of the first trimester placenta, such as this vertical section of an in situ specimen from the sixth week post-menstruation (p.m.) (Fig. 3.1a), cover the following structures: chorionic plate (b), intervillous space surrounding the placental villi (c-f), cell islands (g), and the basal plate (j-m) from which the beginnings of a septum (h) protrudes into the intervillous space; some anchoring villi are connected via cell columns to the septum (h) or to the basal plate (i).

G. J. Burton (✉)
University of Cambridge, Centre for Trophoblast Research, Cambridge, UK
e-mail: gjb2@cam.ac.uk

The intervillous space is the space bounded by the chorionic plate on the fetal side and the basal plate on the maternal side (Fig. 3.1a). Up to the 12th week p.m., the intervillous space is filled with a clear fluid, formed of maternal plasma supplemented by secretions from the endometrial glands (see Chap. 5). The fluid passes around the villous trees and drains into openings of the uterine veins. In early pregnancy, development of the villous trees is relatively sparse, and the mean width of the intervillous pores between neighboring villi is several hundred micrometers.

Histological specimens of the first trimester chorionic plate (Fig. 3.1b) (see Chap. 10) are usually devoid of amnion as for most of this period the amniotic sac has not expanded sufficiently to reach the chorionic plate. Instead, the extraembryonic coelom is still interposed between the two.

If the amnion is missing, as in this case, the surface of the chorionic plate toward the fetus is covered by an inconspicuous, incomplete layer of mesothelium. The mesothelium covers a thick layer of chorionic mesoderm in which the chorionic branches of the umbilical vessels are embedded. Toward the intervillous space, the surface is formed in the early stages by a layer of syncytiotrophoblast, which as pregnancy advances is replaced by fibrinoid (Fig. 3.2c).

The treelike placental villi arise from the chorionic plate and are suspended in the intervillous space, the villous trophoblastic surface being bathed directly by maternal plasma or limited amounts of blood (Fig. 3.1c). The trophoblastic surface of the villi is composed of an outer continuous layer of syncytiotrophoblast beneath which is an almost continuous layer of villous cytotrophoblast (Langhans' cells) (see Chap. 6). Syncytiotrophoblast is a terminally differentiated tissue that has lost the capacity to replicate. Instead, the villous cytotrophoblast represents proliferating stem cells that fuse with the syncytiotrophoblast to enlarge its mass. The syncytiotrophoblast forms the all-important maternal-fetal transport epithelium and immunological barrier for the placenta. It is a continuous tissue, not interrupted by intercellular spaces, and composed of neither individual cells nor individual syncytial units. Plural terms such as "syncytial

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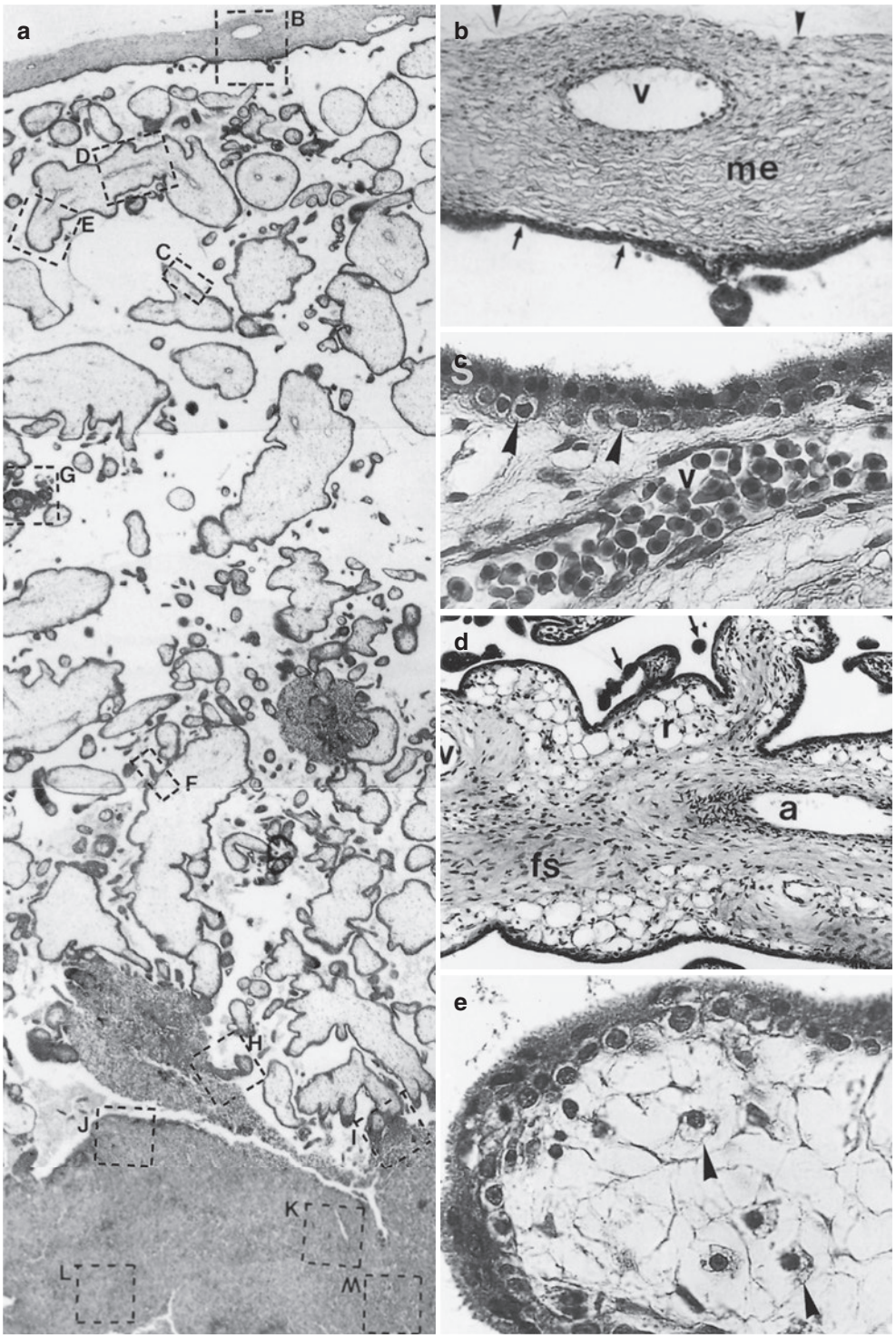

Fig. 3.1 Typical features of the first trimester placenta as seen in paraffin sections following H&E staining. All specimens are from the sixth week p.m., except when otherwise stated. For details, see the text. (**a**) Vertical survey section of an in situ specimen, sixth week p.m. The marked frames refer to the following detailed pictures. ×20. (**b**) Chorionic plate. *v* vein; *arrowheads* mesothelium; *me* chorionic mesoderm; *arrows* incomplete layer of syncytiotrophoblast. ×100. (**c**) Surface of an immature intermediate villus with trophoblast and a fetal vessel (*v*) containing nucleated red blood cells. *s* syncytiotrophoblast; *arrowheads* cytotrophoblast. ×400. (**d**) Transitional form between an immature intermediate villus and a stem villus (18th week p.m.). *a* artery; *v* vein; *r* reticular stroma; *fs* fibrous stroma; *arrows* sprouts. ×100. (**e**) Immature intermediate villus showing characteristic reticular stroma with macrophages (arrowheads). ×400. (**f**) Mesenchymal villus (*m*) arising from an immature intermediate villus (*i*) and extending into syncytial sprouts (ss). ×400. (**g**) Cell island (*ce*) attached to some villi. ×100. (**h**) Placental septum (*ps*) connected to a villus (*av*) by a cell column (*cc*). ×200. (**i**) Anchoring villus (*av*) connected to the basal plate by a cell column (*cc*). ×200. (**j**) Surface of the basal plate showing extravillous trophoblast cells (*arrowheads*) embedded in fibrinoid (tenth week *p.m.*). ×100. (**k**) Deep part of the basal plate showing a uteroplacental vein (*uv*) surrounded by extravillous cytotrophoblast (*ec*) and decidua (*dc*) (37th week p.m., similar to the first trimester situation). ×140. (**l**) Multiple cross sections of a spiral artery (*sa*), the wall of which is replaced by fibrinoid (*arrowheads*). ×100. (**m**) Endometrial glands (*eg*) of the junctional zone embedded in endometrial stroma (*es*). ×200. For further details, see the text

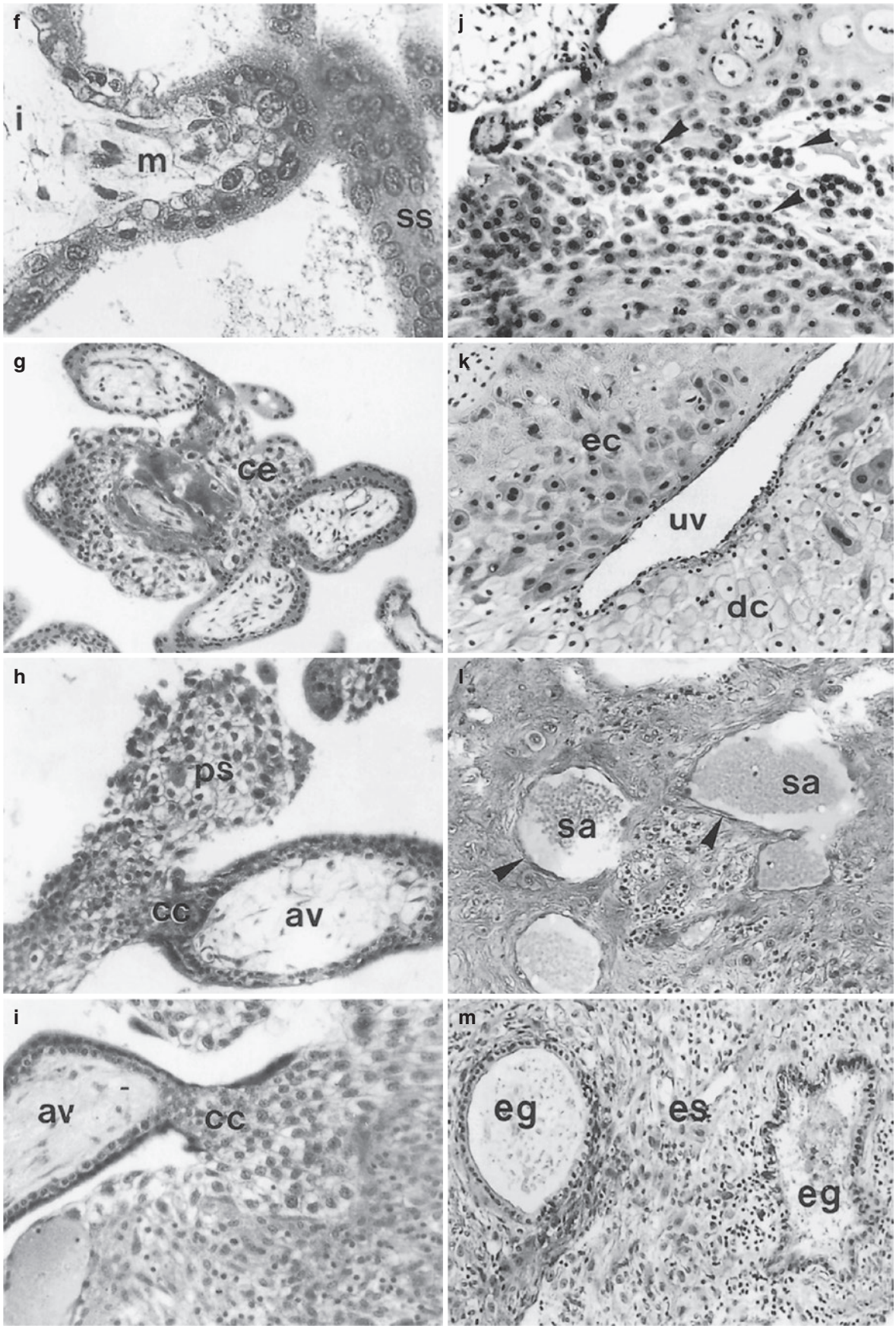

Fig. 3.1 (continued)

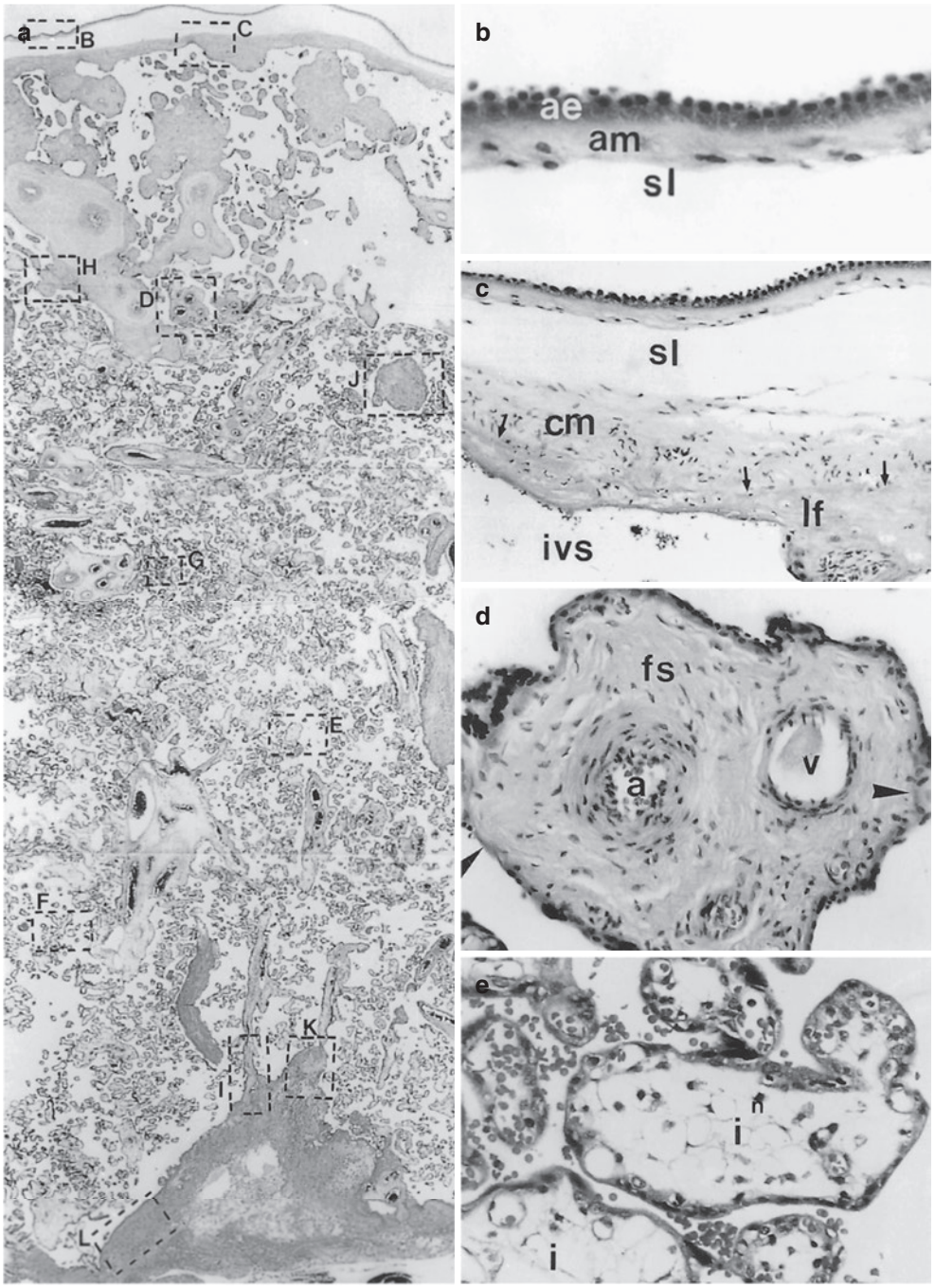

Fig. 3.2 Typical features of the third trimester placenta as seen in paraffin sections following H&E staining. All specimens are from the 40th week p.m. For details, see the text. (**a**) Vertical survey section. The marked frames refer to the following detailed pictures. ×10. (**b**) Amnion. *ae* amniotic epithelium; *am* amniotic mesoderm; *sl* spongy layer. ×120. (**c**) Chorionic plate, covered by the amnion. *lf* Langhans' fibrinoid stria; *arrows* basement membrane; *cm* chorionic mesoderm; *ivs* intervillous space. ×60. (**d**) Peripheral stem villus. *fs* fibrous stroma; *a* artery; *v* vein; *arrowheads* syncytiotrophoblast. ×180. (**e**) Two immature intermediate villi (*i*) surrounded by some mature intermediate and terminal villi. ×180. (**f**) A longitudinally sectioned mature intermediate villus (*mv*) together with some terminal villi and some villous fibrinoid necrosis (*if*). ×180. (**g**) A group of terminal villi (*t*) showing considerable syncytial knotting (*k*). ×360. (**h**) A small stem villus, the trophoblastic cover of which is partly replaced by a thick plug of perivillous fibrinoid (*f*). ×180. (**i**) An anchoring villus (*av*), connected to the basal plate by fibrinoid (*rf*) as the original cell column is no longer present. ×180. (**j**) Cell island. *mf* matrix-type fibrinoid. ×90. (k) Tip of a placental septum. ×90. (**l**) Basal plate with obvious layering. *rf* Rohr's fibrinoid; *nf* Nitabuch's fibrinoid; *dc* decidual cells; *ec* extravillous trophoblast; *v* vein. ×90. For further details, see the text

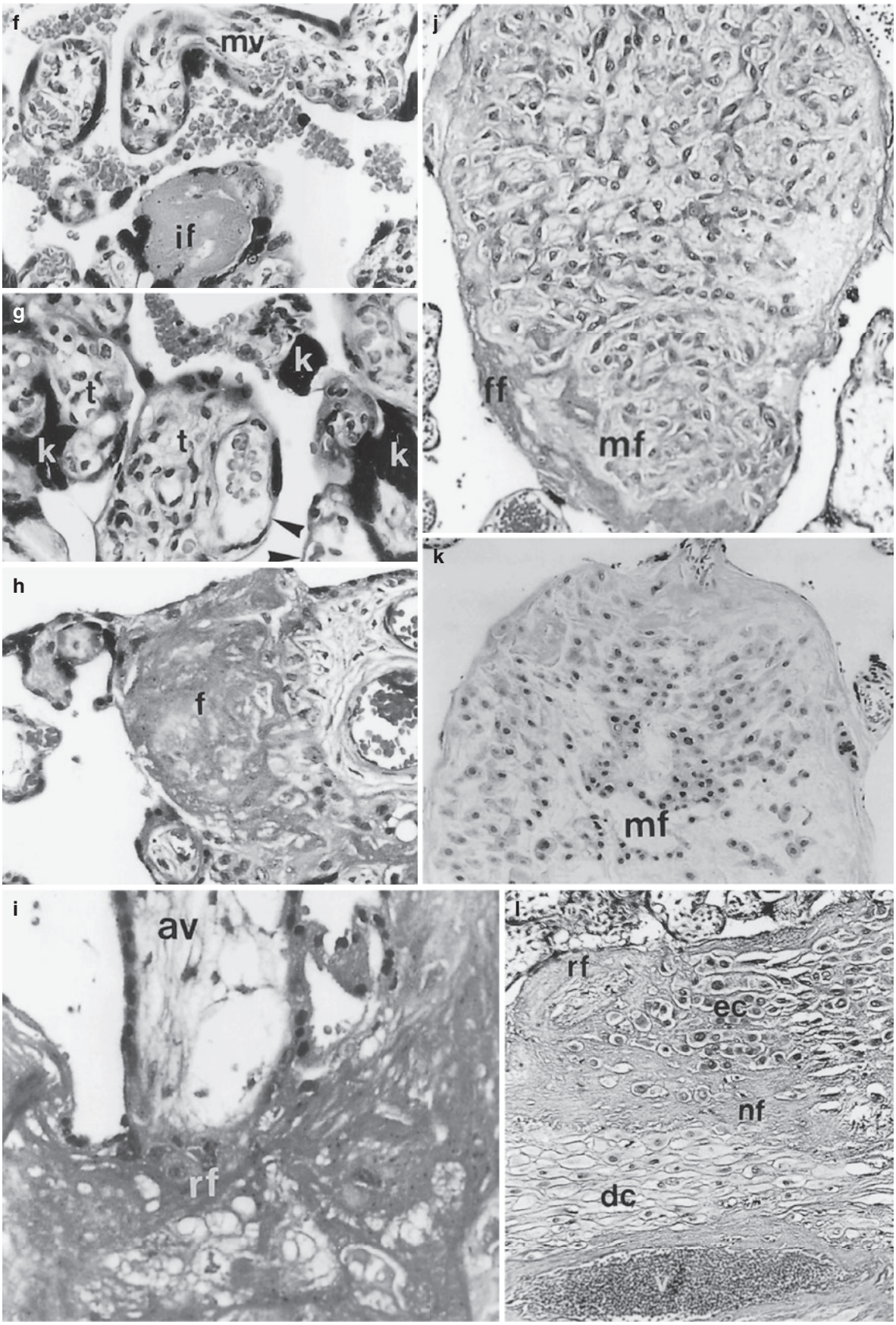

Fig. 3.2 (continued)