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Reanimating the past: From historical collections of the placenta and uterus to modern imaging, machine learning, and multiscale modeling☆

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ABSTRACT

The placenta and uterus are essential to healthy human pregnancy, yet their complex adaptation and function remain difficult to study, particularly during the second trimester. Historical collections of placenta *in situ* specimens, including the *Boyd, Dixon*, and *Carnegie Collections*, provide rare access to placental and uterine anatomy across developmental stages and pathological conditions. Due to advancements in obstetric care, the preparation and extent of specimens in these collections is uncommon nowadays. They therefore offer a unique window into pregnancy that contemporary imaging cannot fully reproduce. This review article briefly summarizes these historical collections and examines how they can be integrated with modern imaging, machine learning, and multiscale modeling to extend their research utility. Advances in computational methods support the digitization and 3D reconstruction of 2D histological sections, helping to mitigate issues such as tissue deformation, staining variability, and missing sections. In addition, machine learning approaches enable automated segmentation, facilitating more detailed characterization of utero-placental structures and associated physiological functions. Image-based multiscale modeling can link microscale features, such as villous capillary architecture, to organ-scale responses including global perfusion and oxygen transport, while enabling efficient computation when enhanced with physics-informed neural networks or neural operators. These methods preserve the scientific value of legacy specimens while enabling new avenues for studying pregnancy complications such as preeclampsia and fetal growth restriction. By combining legacy resources with contemporary analytical techniques in an interdisciplinary framework, a more thorough understanding of placental biology and maternal-fetal health can be achieved that may inform future research and clinical applications.

1. Introduction

The placenta is a transient organ of remarkable efficiency: small in size, short in life, yet critical to the earliest stages of human existence [1]. Healthy placental development relies on the orchestration of processes across multiple cell types in both the feto-placental and maternal-uterine contexts. Disruptions in these processes can lead to pregnancy complications such as preeclampsia, fetal growth restriction, or stillbirth [2]. Our understanding of placental biology continues to deepen, supported by modern experimental techniques and omics-based approaches. However, studying human pregnancy *in vivo* remains difficult, especially during the second trimester, the *hidden phase* of gestation. Especially in this trimester, marked by rapid placental and fetal development, ethical constraints restrict advanced imaging methods that require radiation or contrast agents and limit tissue sampling, as biopsies are seldom clinically justified.

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To address these shortcomings, *in vitro* models are increasingly developed to more closely replicate *in vivo* conditions by incorporating 3D scaffolds, multicellular systems, and flow-based environments [3]. In parallel, computational models of human pregnancy continue to advance, capturing specific or multiscale features of the maternal-fetal unit *in silico* [4–6]. However, the predictive capability of *in vitro* and *in silico* models relies on accurate *in vivo*-derived imaging, histology, and flow data to realistically capture the underlying (patho)physiology.

Historical utero-placental collections provide rare and irreplaceable insight spanning developmental stages and pathological conditions that are no longer easily accessible, complementing modern approaches. In fact, modern imaging and analytical techniques are needed to re-examine these 2D archival specimens, digitize them, and reconstruct them in 3D, thereby unlocking new structural information that can also support *in silico* modeling. This review article presents several available historical collections and outlines both classical and modern strategies for rendering them in 3D, with particular emphasis on the utero-placental vasculature. Moreover, we discuss how these data, together with contemporary imaging resources, can inform and enhance the predictive power of multiscale models of human pregnancy. In the context of machine learning, such models are becoming increasingly valuable for integrating heterogeneous data and uncovering underlying physiological mechanisms, particularly in settings where data are sparse and noisy.

2. Historical collections and their use in the past

Earlier descriptions of the utero-placental vasculature were primarily derived from historical collections of *in situ* serial placental sections, vascular casts, and X-ray based imaging [7–9]. Although modern *in vivo* imaging methods, such as Doppler ultrasound and magnetic resonance imaging (MRI) [10], as well as *ex vivo* imaging techniques, including micro-computed tomography (CT), light-sheet, and serial block-face scanning electron microscopy (SEM) [11], now complement these data, historical data still form the foundation of our current knowledge. Most available data of *ex vivo* imaging are limited to describing the intervillous space, structures of the placental villi [12–14], or small sections of decidua [15]. Historic placenta *in situ* samples were typically obtained through termination or therapeutic hysterectomies during pregnancy — procedures that, at the time, were commonly the only available treatment option [16]. Consequently, historical collections include specimens of the placenta adjacent to full-thickness uterine tissue across all trimesters. The most prominent examples are the *Boyd and Dixon Collections* (Loke Centre for Trophoblast Research, University of Cambridge, Cambridge, UK) and the *Carnegie Collection* (National Museum of Health and Medicine, Silver Spring, ML, United States).

2.1. The Boyd Collection

The *Boyd Collection* was assembled in the 1950s to 1960s by James Dixon Boyd, who obtained specimens from local pathologists. It includes both uterine samples with placenta *in situ* and isolated placental specimens. Limited clinical information is available for some cases, including crown-rump length of the corresponding embryos or fetuses. All specimens were immersion-fixed, paraffin-embedded, serially sectioned, and stained using various histological methods; selected scans are accessible online: https://www.trophoblast.cam.ac.uk/Resources/boyd-collection.

The most extensive description of the collection focuses on first-trimester samples [17]. This work documents the histological development from approximately 11 to 90 days of gestation and discusses changes in the decidua, uterine glands, and trophoblast differentiation. Notably, it includes histological images and, for selected cases, photographs of the uterus, placenta, and embryo *in situ* before sectioning. More recent studies have used this collection to examine the formation of channels within spiral artery trophoblast plugs between 6 and 13 weeks of gestation [18] and, together with material from the *Dixon Collection* (see Section 2.2), to quantify uterine vascular remodeling and trophoblast plugging from 6 to 20 weeks of gestation [19].

2.2. The Dixon Collection

The *Dixon Collection* comprises placenta *in situ* specimens with accompanying clinical data and was assembled between the 1960s and 1980s by Geoffrey Dixon in collaboration with Bill Robertson and Ivo Brosens at Hammersmith Hospital, London, UK, and later at the University of Bristol, Bristol, UK. The collection includes Caesarean hysterectomy samples that were partially fixed, serially sectioned, stained with hematoxylin-eosin, and in some cases injected with Indian ink to improve vascular traceability [20].

The collection was studied extensively by Robert Pijnenborg and Ivo Brosens, whose work provided fundamental insights into trophoblast invasion and spiral artery remodeling. Their analyses, particularly of specimens up to 18 weeks of gestation, established key patterns of trophoblast invasion and form the basis of our current understanding of its relationship to utero-placental arterial remodeling [21–23].

2.3. The Carnegie Collection

The *Carnegie Collection* was initiated by Franklin Mall in the early 1900s and contains human embryos as well as uterine and placental specimens, both healthy and pathological. The specimens were donated by hundreds of physicians across several countries and were used, for example, to create a wax model representing the first 3D reconstruction of a human embryo in the United States (https://embryology.med.unsw.edu.au/embryology/index.php/Carnegie_Collection). The collection is best known for the Carnegie embryos, which continue to define the first eight weeks of human development through the Carnegie staging system, but it also includes placental and uterine specimens that have been examined in past studies. Harris and Ramsey [24] used insights from the collection, supplemented by additional samples, to provide a detailed description of the human utero-placental vasculature from approximately 20 days of gestation to term. Their work includes a range of histological images as well as early attempts to convey 3D context through stereoscopic photographs and anatomical 3D drawings (see also Fig. 1).

2.4. Historical studies using X-ray imaging

Besides the well-curated and still accessible collections of histological specimens, there are also historical studies that used X-ray methods to visualize the utero-placental vasculature. Because X-ray exposure during pregnancy is now avoided, these studies represent valuable legacy data that complement histological findings.

In a comparative study of rhesus monkey and human pregnancies, a radiograph was obtained from a woman at 32 weeks of pregnancy after injecting a radiopaque dye into the femoral artery to visualize the utero-placental vessels. This enabled early characterization of maternal blood entering the intervillous space as *spurts* and offered insight into how the blood disperses and drains through the venous system [25].

Burchell [7] conducted a more extensive study generating serial arteriograms from 30 women between 6.5 and 40 weeks of pregnancy, predominantly in pregnancies with severe complications that prevented continuation. Radiographs were acquired by injecting a radiopaque dye directly at the aortic bifurcation via a femoral-artery catheter. Although the cohort largely represented abnormal pregnancies, the work provided the first quantitative description of adaptations in the arcuate arteries, which branch from the uterine artery and feed the radial arteries upstream of the spiral arteries. It also demonstrated a progressive decrease in perfusion speed across gestation and an increase in the number of maternal *entry sites* into the intervillous space from 6.5 to 12 weeks — an observation now linked to the gradual breakdown of trophoblast plugs [18,19].

Despite limitations in image quality and the absence of computational analysis tools, these studies yielded remarkable insight. Viewed today, their images, and comparable archival data, may offer renewed value, particularly for machine learning methods focused on pattern recognition in medical imaging [26].

2.5. Value of legacy data

The described collections hold special value. With modern, less invasive procedures for elective terminations, placenta *in situ* samples, especially beyond the first trimester, are no longer routinely obtainable. In particular, second- and early-third-trimester placenta *in situ* specimens provide a unique window into the *hidden phase* of pregnancy. Because many samples include associated clinical information, the collections also offer insight into both physiological and pathological placental development. Most studies describing normal placental anatomy and histology from these specimens date to the 1960s to 1980s [17,21–24], and many of these early descriptions have seen little update. They are largely descriptive and include limited quantitative analysis because of the constraints of manual measurements and predominantly 2D methods. Modern computational approaches enabling more accurate 3D reconstructions and higher-throughput analysis can now overcome these limitations.

The use of legacy data collected prior to the establishment of modern informed-consent standards raises important ethical concerns, particularly in the context of contemporary data sharing and global dissemination. Such collections may lack explicit informed consent, thereby challenging patient autonomy and increasing the risk of privacy violations through the disclosure of sensitive medical information, even when the data are pseudonymized. Additional ethical issues arise in relation to the commercialization of findings derived from historical collections, as contributors may not have anticipated subsequent scientific, clinical, or economic uses of their data. Although these samples constitute unique and scientifically valuable resources, their use must remain grounded in respect for the dignity, rights, and privacy of the individuals from whom they originate. Because informed consent cannot be obtained retrospectively, current guidelines require clear ethical justification demonstrating that the research question cannot be addressed with samples collected under contemporary standards. Robust data protection safeguards and strict limitations on access to potentially identifiable information remain essential. Oversight by institutional review boards is therefore necessary to evaluate scientific value, proportionality, and privacy protections, and to ensure transparency about the historical context of the specimens. The *International Ethical Guidelines for Health-related Research Involving Humans* state that the use of historical data collected without explicit consent may be ethically justified when re-contacting participants retrospectively is impracticable, provided that the research has substantial social value and entails no more than minimal risk to the individuals concerned [27]. Such measures balance scientific benefit with the responsible and respectful use of human material collected in earlier eras.

3. From 2D to 3D

3.1. Digital access to historical specimens in 3D

One example of providing digital access to anatomical details from a historical collection is *The Multi-Dimensional Human Embryo* project. This collaboration released a subset of formalin-fixed Carnegie embryos as the first distributable 3D reference of human embryonic stages, using a combination of photography, magnetic resonance microscopy, and MRI. For each embryo, fully registered T1-, T2-, and diffusion-weighted datasets are provided side by side to maximize anatomical detail, complemented by volume-rendered surface images, pseudo-time-lapse growth animations, and segmentations of major organs (https://humanembryo.embryo.brsimage.com/index.html). This project illustrates how fixed and preserved historical specimens can be made globally accessible through modern imaging and segmentation techniques.

In contrast, the placenta *in situ* samples in the historical collections were not preserved as intact organs or larger blocks but only as histological slides. As a result, alternative methods are required to reconstruct these materials in a 3D anatomical context. However, efforts are also in place to make digital images from the *Boyd and Dixon Collections*, with a number of images now available online (https://www.trophoblast.cam.ac.uk/Resources/boyd-collection).

3.2. Reconstruction challenges

One major limitation of using historical collections of histological samples is that the fixation method cannot be altered retrospectively. All collections discussed here were preserved by immersion fixation, meaning the tissue was cut, washed, and then immersed in a fixative. As a result, and unlike the *in vivo* situation, blood vessels and the intervillous space are no longer pressurized at the time of fixation. Moreover, fixatives such as formaldehyde extract water from the tissue, causing sample shrinkage. Burton et al. [28] directly compared several morphological metrics in placentae fixed by immersion versus fixation under a 50 mmHg perfusion pressure. Immersion fixation produced significantly smaller estimates for structures strongly affected by *in vivo* perfusion, including the fraction of capillary lumina, number of vessels per villous profile, vessel diameter, and villous diameter. By contrast, estimates of trophoblast fraction and barrier thickness were higher with immersion fixation. These findings provide a useful indication of how immersion fixation may systematically under- or overestimate placental morphological features — an important consideration when developing computational methods to quantify morphometry in such samples today.

A further challenge arises when reconstructing 2D serial sections into 3D volumes. Even when tissue is collected specifically for 3D reconstruction with standardized staining, consecutive sections often differ due to tearing, artifacts, poor-quality cuts, or slight misalignment. For legacy datasets, additional complications occur, such as inconsistent staining protocols and missing slides. To obtain a coherent 3D volume, these variations must be corrected by aligning corresponding features across neighboring sections. This *image alignment* can be performed using commercial or custom alignment algorithms, which should be evaluated to determine the best fit for each dataset [29]; see also Section 3.5.

After 3D reconstruction, the next step is typically structure segmentation. In similar datasets, this has mostly been performed manually [30,31]. Automated segmentation is particularly challenging in historical collections because immunohistochemical staining — which would help distinguish structures — is generally unavailable. Most sections are stained with hematoxylin-eosin, which offers limited contrast between neighboring utero-placental cell types. While deep learning models have been used to segment intervillous space from placental tissue [32] and to classify healthy versus diseased placental vessels in 2D slides [33], no automated method currently exists to segment the main utero-placental tissues (stroma, vessels, glands, and intervillous space) without relying on immunohistochemistry.

3.3. A historic example: 3D reconstruction of the Carnegie Collection

A striking early example of the labor-intensive manual reconstruction of histological sections into 3D anatomical models is the work of Harris and Ramsey [24]. Using *in situ* serial sections from the *Carnegie Collection*, supplemented with hysterectomy samples injected with India ink, they traced the full length and thickness of uterine spiral and partially radial arteries. Each section was projected to scale and redrawn on paper, capturing the vessels and surrounding structures. These drawings were then transferred onto cellulose acetate sheets using specialized ink and assembled into calibrated stacks. The resulting stacked sheets formed a 3D model of the tissue, which served as a template for detailed anatomical visualization by drawing on paper. Fig. 1 shows two examples of these acetate stacks and their corresponding drawings, kindly provided by the Loke Centre for Trophoblast Research, University of Cambridge, Cambridge, UK.

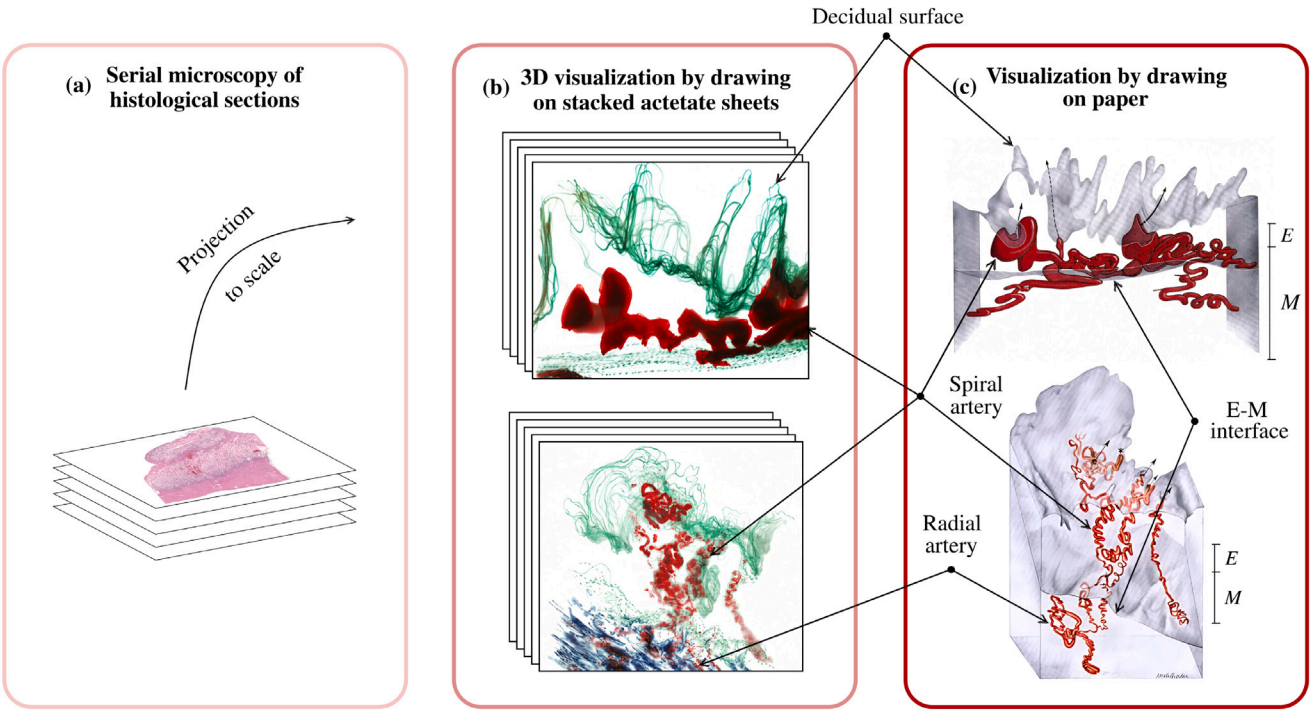

Fig. 1. 3D reconstruction of serial histological sections by Harris and Ramsey [24]. (a) Serial sections of the placenta *in situ* were projected and enlarged to scale, and a representative histological section is shown. (b) The projections were drawn onto acetate sheets and stacked to form 3D reconstructions, with green outlines marking the decidual surface facing the intervillous space, red shapes marking arteries, green dotted lines indicating the endometrial-myometrial interface, and blue shading marking the myometrium. (c) Anatomical drawings were created based on each corresponding acetate-sheet stack, as previously published [24]. Top panel shows a sample at 20 weeks of gestation, bottom panel shows a sample at 63 days of gestation. The scale indicates the relative thickness of the decidua basalis/endometrium (E) and the myometrium (M).

3.4. A modern example: Computational 3D reconstruction of the Boyd Collection

Histological serial sections have been reconstructed into 3D representations of tissue anatomy in various contexts [34], including visualization of spiral artery and intervillous space architecture [35]. Fig. 2 illustrates how 3D reconstructions can be generated from 2D sections of the *Boyd Collection* [17,36], imaged using whole-slide scanning [19] and downsampled to obtain computationally manageable file sizes (Fig. 2(a)). In this case, the sample consisted of 158 serial sections of 15 μm-thick sections with 37 sections missing at various positions. After downsampling, the image background was removed by thresholding.

For digital image processing, normalized color is essential because it strongly affects feature detection [34]. In case of the used sample, serial sections were treated with different histological stains and the uterine arteries had been infused with Indian ink. The tissue images were therefore color-normalized to match the color distribution of a target image, preparing them for registration (Fig. 2(b)). Even with consistent staining (e.g., hematoxylin-eosin), some degree of normalization is still required.

Image registration was performed in two steps: rigid (Fig. 2(c) to (d)) and non-rigid registration (Fig. 2(e) to (f). Rigid registration identifies biologically meaningful landmarks between adjacent slices and aligns them to a common orientation. Non-rigid registration then uses spatially invariant features — identified using a scale-invariant feature transform (SIFT) [37] — to correct local distortions that are not biologically plausible, such as abrupt changes in vessel direction. SIFT detects distinctive local image features, such as corners, edges, and texture patterns, that remain stable under changes in scale, rotation, and illumination. These mathematically described features can then be matched across serial sections to align neighboring images [38].

Following registration, the final step is segmentation and 3D reconstruction of the relevant biological structures (Fig. 2(g)), here performed using a supervised machine learning approach implemented in *PyTorch* based on a VGG16 model.

3.5. From computational reconstruction to segmentation

The serial slide reconstruction method presented here was tailored to the characteristics of the *Boyd Collection* samples — including the number of slides, section thickness, staining protocols, and file formats. Other groups have reconstructed serial sections from different tissues and with varying imaging properties. A recent review by Kurz et al. [39] provides an overview of comparable 3D reconstructions generated from histopathological slides. As in our approach (Fig. 2), the first and most critical step in these workflows is spatial alignment of the scanned sections. In addition to custom-written code, several free or commercial software packages have been used for this purpose, including *Fiji*, *Amira*, *HiD*, *Imaris*, *Voloom*, and *WinSurf*. Because each tool uses distinct algorithms for alignment and reconstruction, their performance can differ notably.

Kartasalo et al. [29] bench-marked a range of available algorithms using two datasets (slide images) with different tissue types, fixation methods, section numbers, and resolutions. They compared metrics such as registration accuracy, tissue shrinkage, accumulated errors, and reconstruction smoothness. While the algorithms displayed varying strengths and weaknesses, the *ElasticStackAlignment* (https://imagej.net/plugins/elastic-alignment-and-montage) plugin for *Fiji* emerged as the only method that matched or outperformed all others across every metric in both datasets. This plugin combines SIFT with optimization strategies.

The value of 3D reconstruction becomes fully apparent when accurate tissue segmentation is integrated with the reconstructed volume, enabling thorough analysis of tissue architecture. Manual segmentation

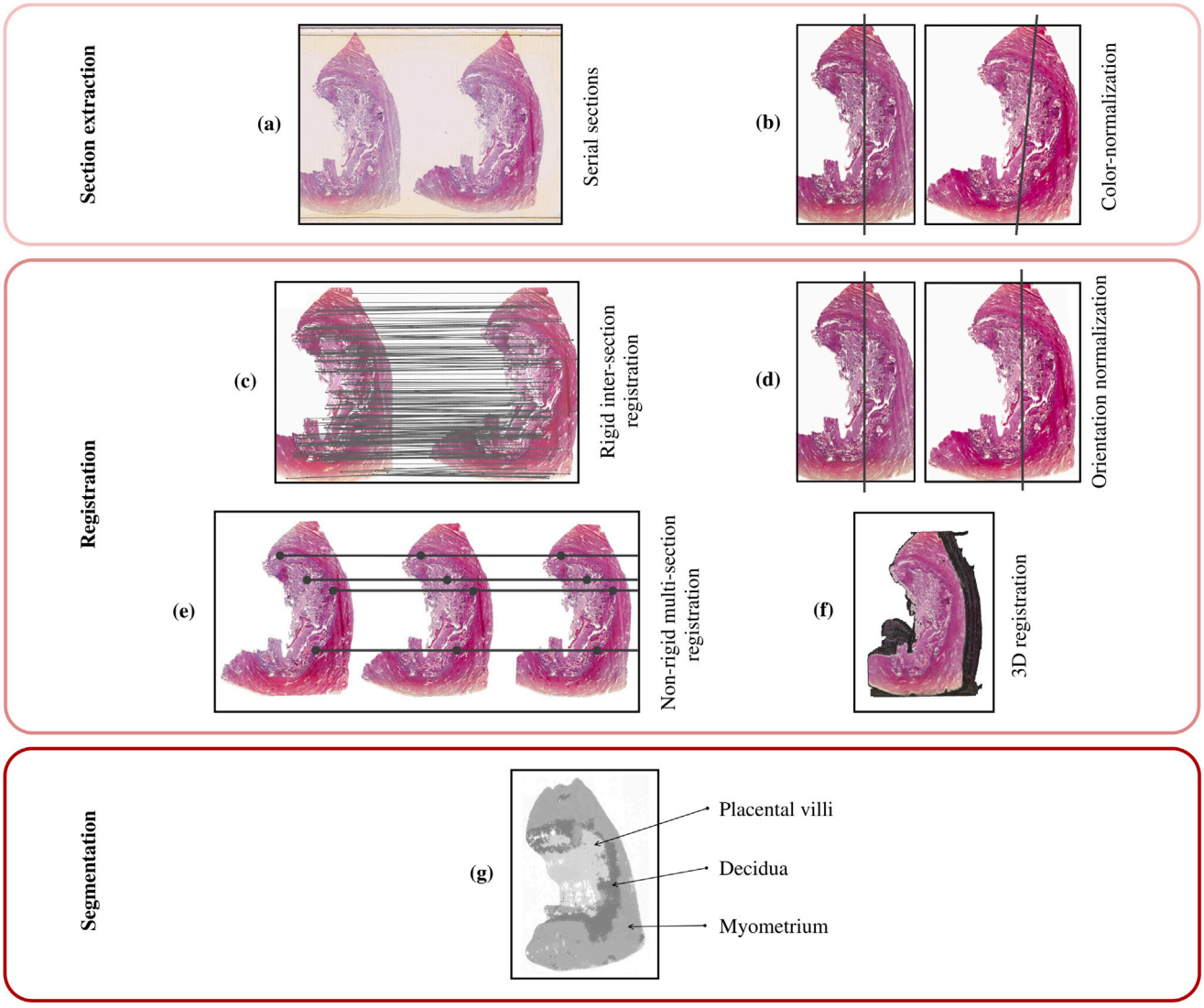

Fig. 2. Computational 3D reconstruction and segmentation of a representative sample of the Boyd Collection. (a) 158 serial sections of a placenta *in situ* sample (11^{+3} weeks of gestation) were imaged with a slide scanner. (b) Slides after background removal and color normalization. (c) Rigid registration of adjacent slides with lines showing the connection between identified biologically meaningful landmarks. (d) Adjusted slide orientation after rigid registration. (e) Non-rigid registration across multiple slides with circles and lines showing connections between spatially invariant features. (f) All serial sections reconstructed into a 3D stack after successful registration. (g) Exemplary segmentation of the 3D reconstruction into placental villi (light gray), decidua (dark gray), and myometrium (mid gray).

is possible [35], but it is labor-intensive for large datasets and requires expert knowledge. McCarthy et al. [30] demonstrated a notable example: they reconstructed and segmented 200 hematoxylin-eosin-stained serial sections from formalin-fixed placentae to compare morphological features between normal and complicated pregnancies (preeclampsia, fetal growth restriction, and gestational diabetes). Registration was performed using custom software, and 3D visualization, segmentation of components (chorionic plate, decidua basalis, stem villi, and lower-order villi), and the creation of microanatomical reconstructions of smaller sub-volumes were carried out with *Volume Viewer*. This approach enabled qualitative identification of differences in villous size, distribution, and branching patterns. However, the study relied on manual segmentation and visual comparison rather than quantitative analysis — limitations that can be overcome with machine learning methods [32].

Machine learning-based segmentation relies on detecting patterns in smaller image regions called convolutions [40] and requires training on labeled tissue data. Segmentation may be performed on individual 2D sections prior to reconstruction or directly on the 3D volume, the latter being advantageous when features with 3D morphology (e.g., *vesselness*) are relevant [36]. In the *Boyd Collection* example, color normalization is a critical preprocessing step. The hematoxylin-eosin stain, which colors nuclei blue and cytoplasm/extracellular matrix pink, helps distinguish structures such as myometrium, decidua, and vasculature by morphology — but it cannot reliably differentiate arteries from veins. When available, immunohistochemical markers provide much clearer discrimination. For example, combining CD31 (endothelial marker) with smooth muscle actin (vascular smooth muscle marker) helps distinguish arteries (with muscular walls) from arterioles (without), enabling reconstruction of specific vessel types.

4. Image-based multiscale modeling of the utero-placental unit

Like other organs, the utero-placental unit is inherently complex, governed by multiphysical processes — including blood flow, tissue deformation, tissue growth and remodeling, solute transport, and oxygen exchange — that act across multiple spatial and temporal scales.

Imaging data quantifying these processes remain however sparse, particularly *in vivo*, because ethical constraints limit high-resolution or invasive measurements during pregnancy, as discussed earlier.

In the utero-placental vasculature, for example, the organ-scale captures global uterine and placental perfusion. The macrovascular scale includes the uterine, arcuate, radial, and spiral arteries (from ~2–6 mm to ~200–500 μm) on the maternal side, as well as the umbilical, chorionic plate, and stem villous arteries (from ~2–4 mm to ~50–500 μm) on the fetal side. The microvascular scale resolves the intermediate (80–150 μm) and terminal villous arterioles (50–80 μm), as well as the terminal capillaries (5–10 μm), which are responsible for maternal-fetal exchange and operate with a diffusion distance of approximately 2–5 μm.

This highlights that, while single-scale models provide valuable insights, image-based multiscale modeling is essential for linking biologically relevant microscale mechanisms to organ-scale behavior and utero-placental unit dynamics, thereby enabling causal, mechanistically grounded, and predictive simulations [41,42]. Notably, their predictive capability relies on realistic *in vivo* boundary conditions and image-based geometrical models, which are critical for advancing clinically translational understanding of utero-placental function. Because imaging data remain sparse — particularly for second- and early-third-trimester as well as for longitudinal datasets — histological data such as 3D reconstructions from serial tissue sections can offer unique information that can rarely be obtained from utero-placental tissue today.

4.1. Available imaging modalities for different scales

Imaging of the utero-placental unit relies on complementary modalities that differ in spatial resolution, availability, acquisition window, noise characteristics, and suitability for computational modeling [43]. *Ex vivo* techniques typically provide nanometer- to micrometer-scale structural detail but may distort geometry and vascular caliber relative to the *in vivo* perfused state of the utero-placental unit and are often limited by sample availability, which rarely encompasses the whole unit. In contrast, *in vivo* modalities generally operate at organ- or millimeter-scale spatial resolution and exhibit greater uncertainty.

Among *ex vivo* imaging techniques, electron microscopy comprises transmission electron microscopy (TEM) and SEM, both destructive modalities achieving nanometer-scale resolution [44]. TEM provides high-resolution 2D images of internal ultrastructure from ultrathin sections, enabling detailed characterization of trophoblast and utero-placental capillary ultrastructure, whereas SEM scans the specimen surface to generate 2D images of 3D surface morphology, revealing features of the intervillous space. In both cases, 3D reconstructions can be obtained, making these techniques particularly useful for capillary-scale modeling. Confocal microscopy enables high-contrast 3D imaging of terminal villi and microvascular networks around them (maternal) and within them (fetal) [12], with effective submicron-to-micron spatial resolution over an acquisition volume on the order of ~1 mm^3. While this supports microvascular flow and oxygen exchange modeling, limited penetration depth restricts access to deeper intraplacental regions. Additional optical techniques such as optical coherence tomography [45] and multiphoton microscopy [46] enable 3D imaging of villous architecture at micron and submicron-to-micron spatial resolution, respectively, extending volumetric characterization of placental microstructure beyond the penetration limits of confocal microscopy. Light-sheet microscopy extends volumetric imaging to both micro- and macrovascular structures at micrometer-scale spatial resolution [47], typically requiring optical clearing, contrast agents, or antibody labeling; however, imaging windows remain constrained and are generally limited to excised tissue samples. Histology remains a foundational tool for precise 2D quantification via stereology at submicron spatial resolution; however, reconstructing 3D geometries from serial sections is labor-intensive and prone to sectioning artifacts, complicating its use for computational modeling. Bridging scales, micro-CT provides non-destructive 3D imaging of vascular branching across larger tissue volumes at micrometer-scale spatial resolution, making it especially valuable for whole-vascular-tree reconstruction and computational fluid dynamics simulations [48,49], albeit with unavoidable trade-offs between field of view and spatial resolution.

While these *ex vivo* modalities offer unmatched resolution, integrating them with *in vivo* imaging — which provides functional, organ-scale information — is essential for building physiologically grounded multiscale models that both reflect the native configuration of the utero-placental unit and link detailed anatomy to realistic, physiologically meaningful boundary conditions.

MRI techniques, including diffusion-weighted imaging and blood oxygenation level dependent (BOLD) MRI, enable non-invasive assessment of placental perfusion, diffusion, and oxygenation at millimeter-scale spatial resolution [50]. These approaches provide indirect valuable metrics suitable for validating whole-organ hemodynamic models but remain unable to resolve intraplacental vascular architecture or flow at the villous or capillary scale, and are further affected by motion sensitivity and acquisition constraints. Ultrasonography remains the cornerstone of clinical surveillance, providing real-time flow velocity measurements in major uterine and umbilical vessels at millimeter-scale spatial resolution. When combined with advanced algorithms such as Slow*flow*HD, it can now even enable visualization and characterization of flow in the intraplacental microvasculature, down to the level of tertiary villi [51]. Notably, results may vary depending on insonation angle, fetal and maternal motion, and operator variability. Emerging tools such as ultrasound elastography, which operates at millimeter-scale spatial resolution, enable inverse quantification of bulk tissue stiffness and offer opportunities to detect pathological remodeling and incorporate changes in mechanical properties into multiscale simulations of the utero-placental unit, despite limited sensitivity to microscale structure [52].

Selected imaging data from the techniques discussed in this section are shown in Fig. 3(b).

4.2. Bridging scales with machine learning models

Over the last decade, numerous multiscale physics-based models have been developed to link micro- and macroscopic vascular structures and to examine the effects of vascular resistance on hemodynamics [49,53]. Other models focus on oxygen transport within the villous tree, from terminal villi to larger villous branches, thereby accounting for multiple spatial scales [54]; others examine hemodynamics in the intervillous space using anatomical images and villus representations derived from SEM images to quantify hemodynamic metrics, such as local wall shear stress, that are relevant to maternal-fetal exchange [55,56]; still others model the maternal vasculature supplying and draining the placentone to assess how anatomical variability influences utero-placental blood flow and circulation within the intervillous space [57]. For detailed overviews, see, e.g., [4,6,58]. Overall, although these models aim to capture multiple scales, they struggle to efficiently bridge them while accounting for multiphysical phenomena and consistently transferring physical fields or quantities across scales. This may be partly due to the high computational cost of image-based single-scale models, which increases substantially when multiple scales are coupled, often rendering full-organ simulations impractical.

As an illustrative example within a multiscale view on preeclampsia, maternal hypertension propagates through the maternal-fetal unit via a series of tightly coupled biophysical processes, as shown in Fig. 3(a). Insufficient spiral artery remodeling together with elevated systemic blood pressure and increased utero-placental resistance can lead to reduced maternal perfusion of the intervillous space. These altered boundary conditions generate altered wall shear stress and pressure fields around the villous trees, which may impair oxygen transfer at the terminal villi and ultimately reduce fetal oxygen delivery. Reduced

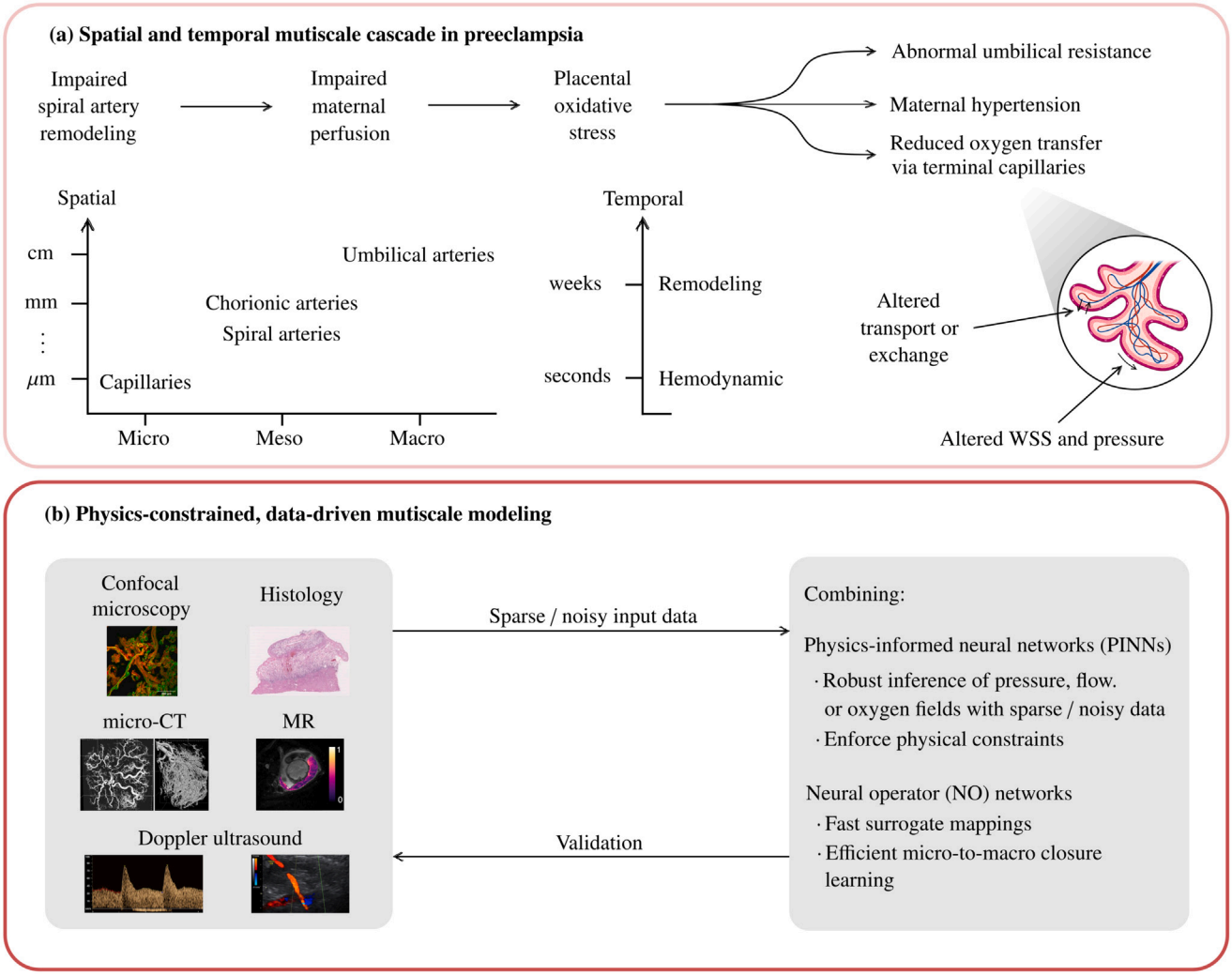

Fig. 3. Multiscale cascade in preeclampsia and physics-constrained, data-driven modeling. (a) Simplified spatial and temporal multiscale cascade underlying placental dysfunction in preeclampsia, linking impaired spiral artery remodeling at the microscale to changes across scales, such as abnormal umbilical resistance or maternal hypertension at the macroscale, and reduced oxygen transfer via terminal capillaries at the microscale (WSS: wall shear stress). (b) Motivation for a physics-constrained, data-driven multiscale modeling framework integrating sparse and noisy clinical and imaging data including confocal microscopy (from [12], licensed under CC-BY), histology, micro-computed tomography (CT) (from [48], licensed under CC-BY), magnetic resonance (MR) (from [50], licensed under CC-BY), and Doppler ultrasound (from [10], licensed under CC-BY) imaging, with physics-informed neural networks (PINNs) for robust inference under physical constraints and neural operators (NOs) for fast surrogate modeling and efficient micro-to-macro closure learning.

fetal growth, known as fetal growth restriction, either in combination with preeclampsia or as an independent pregnancy disorder, is often characterized by an increase in umbilical vascular resistance. Clinically this can manifest at the organ scale as abnormal umbilical artery Doppler waveforms.

Capturing this cascade requires bridging spatial scales from micrometer-scale villous capillaries to the centimeter-scale, or full-organ-scale, placenta, as well as temporal scales spanning seconds (hemodynamics) to weeks (tissue and geometric remodeling). At the same time, different imaging modalities may need to be incorporated, which can be challenging with currently available data; longitudinal data or data from the second trimester may be missing, in which case historical data could come into play. Additionally, many parameters or boundary conditions cannot be measured, or can only be measured imprecisely, making this task even more difficult. Here, the application of modern machine learning tools is of high relevance [41].

In fact, physics-informed neural networks (PINNs) [59] enable this multiscale integration by inferring unmeasured pressure or diffusion processes from sparse imaging data — such as Doppler ultrasound or MRI — while implicitly satisfying the underlying physical flow, transport, or mechanical equations, see Fig. 3(b). Moreover, neural operator (NO) [60,61] networks complement this by learning mappings between functions, allowing for scale bridging, for example by translating microscale villous geometry into effective vascular flow resistances or oxygen-transfer coefficients that can be embedded in organ-scale models. By combining physics-based constraints (requiring a machine learning model to obey physics) with data-driven surrogates (machine learning models that learn from a suite of physics based simulations), PINNs and (physics-informed) NOs [62] make it computationally feasible to simulate how maternal blood pressure disturbances cascade through vascular remodeling, intervillous hemodynamics, villous exchange, and fetal circulatory responses in pregnancy complications such as preeclampsia and/or fetal growth restriction.

5. Conclusion

Integrating historical collections of utero-placental samples with modern imaging, machine learning, and multiscale modeling offers unique opportunities to advance placental research. Revisiting legacy resources can provide additional insight into placental and uterine

development across pregnancy, particularly during the ethically constrained second trimester. Digitization and 3D reconstruction of these specimens help preserve their scientific value while enabling analyses that were not previously possible. The use of machine learning and multiscale modeling can further connect historical datasets with contemporary research questions, supporting investigations of physiological processes such as utero-placental blood flow, vascular remodeling, and oxygen exchange by capturing small-scale phenomena and embedding their mechanisms in a computationally efficient manner into organ-scale models to capture utero-placental system dynamics. As imaging and computational approaches continue to develop, combining historical and modern data is likely to contribute to a more comprehensive understanding of pregnancy-related conditions and maternal-fetal health. This interdisciplinary approach exemplifies how the past can inform the future and how historical data can provide value for current research.

CRediT authorship contribution statement

Malte Rolf: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Sahan Jayatissa:** Writing – original draft, Visualization, Resources. **Jonathan Reshef:** Visualization, Methodology. **Stefan Posch:** Writing – review & editing. **Ellen Kuhl:** Writing – review & editing, Funding acquisition. **Joanna L. James:** Writing – review & editing, Supervision, Funding acquisition. **Alys R. Clark:** Writing – review & editing, Supervision, Funding acquisition, Data curation. **Hanna H. Allerkamp:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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