Review

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Retinal Vascular Imaging Application in Women's Reproductive Health: Clinical Implications and Future Directions

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Abstract

Over the past two decades, population-based studies employing semiautomatic computer-assisted programs have uncovered associations between retinal microvascular features and various systemic conditions. As the recognition of retinal imaging in cardiometabolic health grows, there is increasing evidence supporting its application in women's health, particularly during the reproductive age. This review aims to summarize the indications of retinal imaging in women's health and intergenerational health, where suboptimal retinal imaging has been found to mirror pathological systemic changes, such as suboptimal hemodynamic circulation, inflammation, endothelial dysfunction, oxidative stress, and hypoxia *in vivo*. Findings from Singapore Growing Up in Singapore Towards Healthy Outcomes and Singapore Preconception Study of Long-Term Maternal and Child Outcomes cohorts have reported serial changes in retinal conventional microvascular features (e.g., retinal arteriolar narrowing, retinal venular widening) and retinal geometric microvascular features (e.g., sparse fractal dimension, enlarged branching angle, and increased curvature tortuosity) during the preconception and antenatal phases. These morphological abnormalities were found to be related to female fertility, maternal antenatal health conditions, postnatal maternal cardiometabolic health, and intergenerational health in the fetus. Given the compelling evidence of the ability to detect microvascular changes through noninvasive methods at an early stage, retinal imaging holds the potential to facilitate timely interventions, mitigate the progression of complications, and prevent adverse pregnancy outcomes. Looking ahead, the convergence of artificial intelligence and advanced imaging techniques heralds a promising era in women's health research and clinical practice.

Keywords: Retinal vascular imaging; Reproductive health

Retinal vascular imaging and its clinical application in the general population

The retina, comprising ten layers of interconnected neurons and a vascular network of arterioles, venules, and capillaries lacks internal elastic lamina, making retinal vessels prompt and sensitive to systemic regulation and inflammation.[1,2] Over the past two decades, population-based studies employing semiautomatic computer-assisted programs revealed associations between retinal microvascular features (arteriolar and venular caliber, tortuosity, branching angle, and fractal dimension) and various systemic conditions. Narrower arterioles predict incident hypertension[1,3,4] and chronic kidney disease,[5–8] while wider venules predict type 2 diabetes,[9,10] stroke,[11,12] and cardiovascular disease.[13,14] Novel geometric features like curvature tortuosity, branching angle, and fractal dimension reflect vascular health,[15,16] inflammation,[17] and systemic disease,[18–20] including arterial stiffness.[21]

With the increasing recognition of retinal imaging in the realm of cardiometabolic health, there is a growing body of evidence supporting its application in women's health, particularly during the reproductive age. Understanding the roots of systemic diseases in adulthood often leads back to preclinical vascular and metabolic disorders in early life,[22,23] involving both mothers and fetuses. This review seeks to introduce the utilization of retinal imaging in the context of women's reproductive health, with a specific focus on the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) and Singapore Preconception Study of Long-Term Maternal and Child Outcomes (S-PRESTO) cohorts, both conducted in Singapore (Figure 1).

Retinal imaging and its application in women's reproductive health

Women's fertility

Derived from the S-PRESTO preconception cohort, a longitudinal study on prepregnancy influences in multiethnic Asian women planning spontaneous conception within the

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next 12 months, the study team investigated the relationship between retinal microvasculature and various fertility outcomes.[24] Women with longer time-to-pregnancy exhibited a sparser arteriolar fractal dimension and wider venular branching angle during the pregravid phase.[25] In ensuing pregnancies, individuals with higher preconception and greater arteriolar and venular curvature tortuosity encountered a 25–34% increased risk of spontaneous abortion before 20 weeks' gestation.[26] The underlying pathophysiology, characterized by vascular inflammation,[27,28] hypoxia,[15,16] oxidative stress,[29] endothelial dysfunction,[30–32] and impaired uterine perfusion,[33,34] contributes to both reduced fecundability and spontaneous abortion, in addition to common risk factors like advanced maternal age,[35,36] stress,[37] cigarette smoking,[38] medication or substance use,[39,40] medical conditions,[41–43] and environmental pollution.[44]

Women's antenatal health

The GUSTO study, initiated with the aim of delving into the repercussions of pregnancy conditions on antenatal maternal health, meticulously selected women with singleton pregnancies during their initial trimester, spanning since June 2000.[45] These outcomes encompassed high-fat diet patterns,[46] maternal obesity,[47] elevated gestational blood pressure,[48] psychosocial disorders,[49] and the development of gestational diabetes mellitus (GDM).[50]

Exploring the intricate domain of retinal morphological changes revealed a consistent pattern during the 26–28 weeks of gestation. Noteworthy alterations in retinal characteristics, namely, venular widening,[46,47] increased venular branching angle,[50] and greater venular curvature tortuosity,[47] were identified. These alterations were distinctly linked to maternal nutritional and metabolic conditions, illustrating the profound interplay between retinal microvasculature and the underlying metabolism during pregnancy. Interestingly, anomalies in retinal arterioles—characterized by narrowing[47,48,50] or widening of caliber,[49] sparser fractal dimensions,[48,50] and reduced branching angles[48]—were identified in correlation with circulatory and psychological disorders experienced by pregnant women.

These observed microvascular morphological changes in retinal characteristics alluded to potential systemic microcirculation pathology in pregnant women grappling with suboptimal hemodynamic circulation,[51] inflammation,[52] and endothelial dysfunction[53] *in vivo*. However, it is essential to acknowledge the inherent limitations of drawing definitive conclusions from these findings due to the cross-sectional nature of the study. While providing valuable insights, further longitudinal investigations are imperative to comprehensively understand the dynamics of these associations over the course of pregnancy and beyond.

Women's postpartum cardiometabolic health

Therefore, in the GUSTO postpartum follow-up study, the team selected 142 mothers diagnosed with GDM during index pregnancy and 136 cohort-nested controls matched by age, ethnicity, and body mass index, extending its investigation to assess the long-term implications on maternal health 5 years after delivery. The study involved retinal photography conducted during the 26–28 weeks gestation period,[45] with subsequent metabolic outcomes evaluated at the 5-year postpartum follow-up.[54] This in-depth analysis aimed to establish a potential correlation between abnormal antenatal retinal microvasculature and adverse postpartum cardiometabolic health.

Notably, antenatal retinal venular widening emerged as a significant factor, showing a direct association with a 60% increased risk of maternal metabolic syndrome[54] and a 20% increased risk of abnormal glucose metabolism (i.e., prediabetes and type 2 diabetes),[55] at the 5-year mark among women with GDM. This finding illuminated the possibility that changes in microvascular structure during pregnancy could mirror subclinical alterations that contribute to the postpartum development of cardiometabolic disorders. Furthermore, both studies emphasized the significance of incorporating retinal microvascular assessments during pregnancy as valuable indicators for identifying individuals at risk of adverse postpartum cardiometabolic health. This approach facilitates timely intervention and preventive measures.

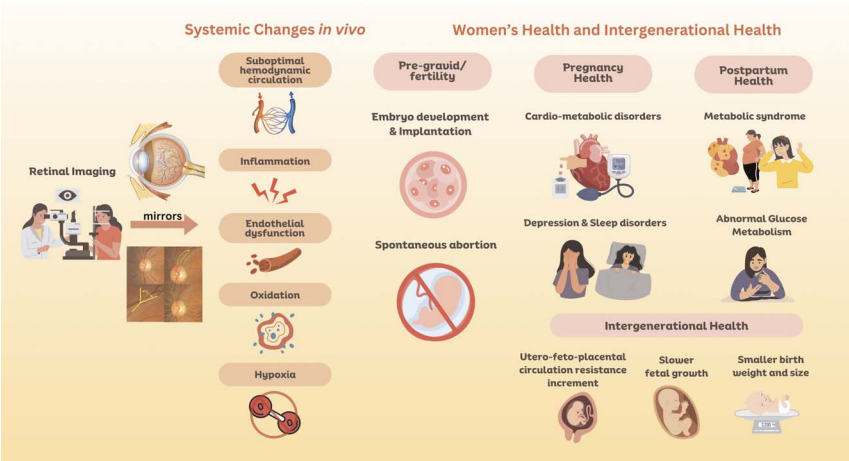

Figure 1. Retinal vascular imaging application in women's reproductive health.

Intergenerational impact on placental circulation, fetal growth, and neonatal anthropometry

In 1986, Emanuel defined intergenerational influences as "those factors, conditions, exposures, and environments experienced by one generation that relate to the health, growth, and development of the next generation."[56] Among various hypotheses, one posits that adverse in-utero experiences may modify maternal metabolism, creating an unfavorable environment for the fetus.[57] Utilizing the S-PRESTO cohort, the team investigated the potential mechanisms underlying the connection between pre-conception conditions and subsequent fetal health.

As elucidated in earlier hypotheses, numerous pregnancy conditions are intricately linked to suboptimal uterine-fetoplacental circulation.[58,59] Recognizing the significance of this crucial yet previously overlooked link, the investigation into the relationship between preconception maternal retinal vasculature and utero-fetoplacental circulation assumed paramount importance, being rigorously examined within the SPRESTO cohort subsequently. In this study, the team revealed that maternal preconception retinal venular widening was associated with elevated pre-gravid inflammation *in vivo*, and steeper resistance increments in maternal uterine and fetal umbilical arteries from the second to third trimester in the ensuing pregnancy, leading to a twofold risk of developing notching and extremely high umbilical artery resistance.[60] In addition, the S-PRESTO cohort identified a strong link between maternal preconception generalized retinal arteriolar narrowing and reduced fetal growth trajectory, as indicated by decreased z-score changes in fetal abdominal circumference and length between 24–28 and 32–34 weeks of gestation.[61] These findings were substantiated by the antenatal GUSTO cohort study, where a narrower retinal arteriolar caliber and sparser fractal dimension in 26–28 weeks of gestation were associated with slower fetal growth from 26–28 weeks to 32–34 weeks of pregnancy, and even birth weight and size at delivery.[62] These findings could suggest a reduction in villous surface and placental size, potentially leading to restricted or slowed fetal growth throughout pregnancy. This implication was put forth by the research team from the Generation R study,[63,64] which revealed that retinal arteriolar narrowing in the second trimester correlated with lower levels of pIGF and VEGF biomarkers. This correlation points to suboptimal circulation, which may hinder placental synthesis of nitric oxide (a major vasodilator and angiogenesis factor) and polyamines (key regulators of DNA and protein synthesis).

Future development: Prediction model using retinal vascular features and retinal images, by using artificial intelligence technology

The landscape of clinical practice is poised for significant advancements with the burgeoning integration of artificial intelligence (AI) into retinal imaging. The widespread development of AI has revolutionized the detection of retinal vascular characteristics, markedly reducing the time required for manual grading.[65] Embracing the wave of digital health innovations,[66,67] our research endeavors extended to include multiple machine learning projects within the GUSTO/S-PRESTO cohorts.

These projects unveiled a remarkable finding—the machine learning methodology, alongside traditional statistical prediction methods, exhibited superior predictive performance compared to conventional maternal risk factors. This underscores the immense potential of machine learning applications in the realm of women's health research, particularly in leveraging retinal vascular parameters and intrauterine growth restriction biomarkers. Moreover, the future of retinal imaging ventures into more sophisticated techniques, such as Optical Coherence Tomography-Angiography and ultrawide field retinal imaging. This noninvasive method enables the assessment of functional retinal vascular networks without the need for contrast dyes, boasting high repeatability in vessel caliber measurements.[68]

Conclusion

In summary, our study provides robust evidence affirming the efficacy of retinal vascular imaging as a valuable tool for predicting adverse maternal and fetal outcomes, starting as early as the preconception phase. The ability to detect microvascular changes through noninvasive methods at an early stage paves the way for timely interventions, offering the potential to mitigate the progression of complications and prevent adverse pregnancy outcomes. The convergence of AI, machine learning, and advanced imaging techniques heralds a promising era in women's health research and clinical practice.

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Conflicts of Interest

None.

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