Published in final edited form as:

Placenta. 2018 September ; 69: 82–85. doi:10.1016/j.placenta.2018.07.013.

Comparison of diameter-based and image-based measures of surface area from gross placental pathology for use in epidemiologic studies

Alexa A. Freedman^a, Lauren M. Kipling^a, Katie Labgold^a, Carmen J. Marsit^{a,b}, Carol J. Hogue^a, Augustine Rajakumar^c, Alicia K. Smith^c, Halit Pinar^d, Deborah L. Conway^e, Radek Bukowski^f, Michael W. Varner^g, Robert L. Goldenberg^h, Donald J. Dudleyⁱ, and Carolyn Drews-Botsch^a

^aDepartment of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

^bDepartment of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

^cDepartment of Gynecology and Obstetrics, School of Medicine, Emory University, Atlanta, Georgia, USA

^dDepartment of Pathology and Laboratory Medicine, Brown University School of Medicine, Providence, Rhode Island, USA

^eDepartment of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

^fDepartment of Women's Health, Dell Medical School, University of Texas at Austin, Austin, Texas, USA

^gDepartment of Obstetrics and Gynecology, School of Medicine, University of Utah, Salt Lake City, Utah, USA

^hDepartment of Obstetrics and Gynecology, Columbia University Medical Center, New York, New York, USA

ⁱDepartment of Obstetrics and Gynecology, School of Medicine, University of Virginia, Charlottesville, Virginia, USA

Corresponding Author: Alexa A. Freedman, Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road, Atlanta, Georgia, 30322, alexa.freedman@emory.edu.

Contributions:

AAF, LMK, and KL analyzed the placental images. AAF analyzed the data and drafted the manuscript. LMK, KL, CJH, CJM, AR, AKS, HP, DLC, RB, MWV, RLG, DJD, and CDB assisted with data interpretation and reviewing and revising the manuscript. CJH, HP, DLC, RB, MWV, DJD, and RLG designed the study and supervised data acquisition. All authors reviewed and approved the submission of this manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declarations of interest:

None.

Abstract

Placental surface area is often estimated using diameter measurements. However, as many placentas are not elliptical, we were interested in the validity of these estimates. We compared placental surface area from images for 491 singletons from the Stillbirth Collaborative Research Network (SCRN) Study (416 live births, 75 stillbirths) to estimates obtained using diameter measurements. Placental images and diameters were obtained from pathologic assessments conducted for the SCRN Study and images were analyzed using ImageJ software. On average, diameter-based measures underestimated surface area by -5.58% (95% confidence interval: $-30.23, 19.07$); results were consistent for normal and abnormal shapes. The association between surface area and birthweight was similar for both measures. Thus, diameter-based surface area can be used to estimate placental surface area.

Keywords

Placental surface area; validation; assumption

Introduction

Placental surface area has been used as an indicator of placental function and has been associated with mental health in childhood and hypertension and lung cancer in adulthood [1–4]. Such studies require lengthy follow-up to assess long-term health outcomes, which makes existing cohort studies ideal samples to investigate these research questions. Some large cohort studies, such as the Collaborative Perinatal Project, the Helsinki Birth Cohort, the Northern Finland Birth Cohort, and the Dutch Famine Birth Cohort, contain information on gross placental morphology, including placental diameters [1, 5–7]. Calculating surface area from diameters requires the assumption that all placentas are elliptical. Imaging technology offers the capability to calculate exact placental surface area from images taken during pathology examinations, regardless of shape, [8]. However, few existing studies with long-term follow-up have placental images. Therefore, we evaluated the validity of using diameter-based measures of surface area as compared to image-based measures of surface area.

Methods

The Stillbirth Collaborative Research Network (SCRN) Study was a population-based case-control study of stillbirth. Women with stillbirths ($n=663$) and live births ($n=1,932$) were enrolled post-partum from deliveries occurring between March 2006 and September 2008 in five areas of the United States. Details on the study design have been published elsewhere [9]. The study was approved by the Institutional Review Board at each study site and all participants provided written informed consent.

Placentas underwent a standardized examination, which included imaging of the fetal surface. Pathologists captured images using a digital camera with a minimum resolution of 3 megapixels. Peripheral membranes were trimmed prior to imaging and each image included a label with the study identification number and a metric ruler. Three of the five study sites

were able to provide access to stored images. Of the 912 un-fragmented placentas of singletons evaluated at these sites, we obtained images for 491 participants (416 live births, 75 stillbirths). Stillbirths were included in the analysis to increase the power. Further, stillbirths are more likely to have placental abnormalities and be born preterm, which facilitates evaluation of the validity of the measures under a variety of circumstances [10, 11].

Image-based surface area was determined using ImageJ software [12]. Due to the potential variability in manually evaluating the placental images, three reviewers analyzed each image. Reviewers set the scale of each image by measuring the number of pixels in 1 cm on the included ruler. Following this, reviewers traced the outline of the placental disc to determine the area of the placental surface.

During the standardized placental examination, trained pathologists measured the longest (a) and shortest (b) diameters for all non-fragmented placentas, regardless of shape. Diameter-based surface area was calculated based on the area of an ellipse ($\text{area} = ab\pi/4$). In this analysis, shape was dichotomized by grouping placentas identified by pathologists as round or ellipse as normal and considering all other shapes abnormal [13]. Additional details on the placental examination protocol, including the guidelines for obtaining images and measuring diameters, have been reported elsewhere [14].

We evaluated inter-rater reliability of the image-based measurements by calculating the intra-class correlation coefficient (ICC) for a single measure, two-way random effects model [15–18]. We estimated the validity of the diameter-based measurement relative to the average of the three reviewers' image-based measurement using the Bland-Altman method [19]. We used the percent difference to account for the increased variability associated with increased placental size [20]. In addition to evaluating the total sample, we evaluated the sample stratified by factors that may affect validity (i.e., stillbirth versus live birth, gestational age, and placental shape). To evaluate the impact of measurement type, we estimated the associations between each measure of surface area with birthweight, adjusted for important covariates. We conducted all analyses using SAS version 9.4 (SAS Institute INC., Cary, North Carolina).

Results

There was excellent inter-rater reliability of image-based surface area (ICC = 0.94 among the total sample; Tables S1 & S2) [18]. On average, diameter-based measures underestimated placental surface area by –5.58% (95% confidence interval: –30.23, 19.07) and results were similar in the restricted samples (Figure 1, Table S3). Associations between surface area and birthweight were similar for both measures (Table 1).

Discussion

Our results indicate that, while diameter-based measures slightly underestimate placental surface area, they are an adequate proxy for actual surface area and provide a similar estimate of the association with birthweight. Although the wide confidence interval for

agreement suggests that the relationship between the two measures varies substantially, it is not indicative of systematic measurement error.

There are few previous studies of this question. One study reported that image-based measures of placental morphology explained 14% more of the variation in birth weight as compared to diameter-based measures [21]. However, the measures were obtained from two different samples, which makes direct comparisons challenging.

We believe that our findings from this convenience sample are generalizable to results from the remainder of the SCRn study since the diameter-based estimates in this sample are similar in those with and without available images (Table S4). A limitation of our study is the inherent measurement error in manually outlining the placental surface. Due to the characteristics of the placental images, we were unable to automate this process. However, inter-rater reliability was excellent [18].

Strengths of our study include a large sample size of 491 images and the use of three reviewers to measure image-based surface area. Placental examinations were also conducted by trained pathologists using a standardized protocol. Further, the SCRn Study included a diverse, population-based sample with oversampling of preterm births, which facilitated our ability to estimate agreement in restricted samples (Table S5).

Our findings support the validity of using diameters to estimate placental surface area. This is important given the growing body of research evaluating relationships between placental size and long-term health outcomes and the availability of diameters in some completed cohort studies [1, 5–7]. Additionally, the time and resources necessary to obtain images and use image analysis software may limit the utility of placental images. Further, future studies may be able to provide similar estimates from routine antenatal ultrasound scans [22, 23].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We acknowledge the contribution of the Stillbirth Collaborative Research Network. We also acknowledge the members of the National Institute of Child Health and Human Development Scientific Advisory and Safety Monitoring Board for their review of the study protocol, materials, and progress, as well as all of the other physicians, study coordinators, and research nurses in the Stillbirth Collaborative Research Network.

Members of a study group:

The Stillbirth Collaborative Research Network—University of Texas Health Science Center at San Antonio: Dr. Donald J. Dudley, Dr. Deborah Conway, Josefine Heim-Hall, Karen Aufdemorte, and Angela Rodriguez; University of Utah School of Medicine: Dr. Robert M. Silver, Dr. Michael W. Varner, and Kristi Nelson; Emory University School of Medicine and Rollins School of Public Health: Dr. Carol J. Rowland Hogue, Dr. Barbara J. Stoll, Janice Daniels Tinsley, Dr. Bahig Shehata, and Dr. Carlos Abromowsky; Brown University: Dr. Donald Coustan, Dr. Halit Pinar, Dr. Marshall Carpenter, and Susan Kubaska; University of Texas Medical Branch at Galveston: Dr. George R. Saade, Dr. Radek Bukowski, Jennifer Lee Rollins, Dr. Hal Hawkins, and Elena Sbrana; RTI International: Dr. Corette B. Parker, Dr. Matthew A. Koch, Vanessa R. Thorsten, Holly Franklin, and Pinliang Chen; Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development: Drs. Marian Willinger and Uma M. Reddy; Columbia University Medical Center: Dr. Robert L. Goldenberg.

The Stillbirth Collaborative Research Network Writing Group—Dr. Carol J. R. Hogue (Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia); Dr. Robert L. Goldenberg (Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, New York); Drs. Radek Bukowski and George R. Saade (Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, Texas); Dr. Barbara J. Stoll (McGovern Medical School, University of Texas Health Science Center, Houston, Texas); Drs. Marshall Carpenter, Donald Coustan, and Halit Pinar (Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Brown University School of Medicine, Providence, Rhode Island); Dr. Deborah Conway (Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, San Antonio, Texas); Dr. Donald J. Dudley (Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, Virginia); Drs. Robert M. Silver and Michael W. Varner (Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Utah School of Medicine, and Maternal Fetal Medicine Unit, Intermountain Healthcare, Salt Lake City, Utah); Drs. Uma M. Reddy and Marian Willinger (Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland); and Drs. Matthew A. Koch and Corette B. Parker (Statistics and Epidemiology Unit, Health Sciences Division, RTI International, Research Triangle Park, North Carolina).

Funding:

The Stillbirth Collaborative Research Network was supported by grant funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (grants U10-HD045953 (Brown University), U10-HD045925 (Emory University), U10-HD045952 (University of Texas Medical Branch at Galveston), U10-HD045955 (University of Texas Health Sciences Center at San Antonio), U10-HD045944 (University of Utah Health Sciences Center), U10-HD045954 and HHSN275201400001C (RTI International)). AAF was supported by grant funding from the NICHD (grants F31HD092025 and T32HD052460) and the Maternal and Child Health Bureau, Health Resources and Services Administration (grant T03MC07651).

Abbreviations:

CI	confidence interval
ICC	intra-class correlation coefficient
SCRN	Stillbirth Collaborative Research Network
SE	standard error

References:

- [1]. Barker DJ, Thornburg KL, Osmond C, Kajantie E, Eriksson JG, The surface area of the placenta and hypertension in the offspring in later life, *Int J Dev Biol* 54(2–3) (2010) 525–30. [PubMed: 19876839]
- [2]. Khalife N, Glover V, Hartikainen AL, Taanila A, Ebeling H, Jarvelin MR, Rodriguez A, Placental size is associated with mental health in children and adolescents, *PLoS One* 7(7) (2012) e40534. [PubMed: 22792364]
- [3]. Barker DJ, Thornburg KL, Osmond C, Kajantie E, Eriksson JG, The prenatal origins of lung cancer. II. The placenta, *Am J Hum Biol* 22(4) (2010) 512–6. [PubMed: 20309992]
- [4]. Barker DJP, Eriksson JG, Kajantie E, Alwasel SH, Fall CHD, Roseboom TJ, Osmond C, Chapter 2: The maternal and placental origins of chronic disease, in: Burton G, Barker DJP, Moffett A, Thornburg KL (Eds.), *The Placenta and Human Developmental Programming*, Cambridge University Press, Cambridge ; New York, NY, 2011, pp. 5–16.
- [5]. Niswander KR, Gordon M, National Institute of Neurological Diseases and Stroke., The women and their pregnancies; the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke, National Institute of Health; for sale by the Supt. of Docs, U.S. Govt. Print. Off., Washington, 1972.
- [6]. Ravelli AC, van der Meulen JH, Michels RP, Osmond C, Barker DJ, Hales CN, Bleker OP, Glucose tolerance in adults after prenatal exposure to famine, *Lancet* 351(9097) (1998) 173–7. [PubMed: 9449872]

- [7]. Rantakallio P, The longitudinal study of the northern Finland birth cohort of 1966, *Paediatr Perinat Epidemiol* 2(1) (1988) 59–88. [PubMed: 2976931]
- [8]. Salafia CM, Yampolsky M, Misra DP, Shlakhter O, Haas D, Eucker B, Thorp J, Placental surface shape, function, and effects of maternal and fetal vascular pathology, *Placenta* 31(11) (2010) 958–62. [PubMed: 20933281]
- [9]. Parker CB, Hogue CJ, Koch MA, Willinger M, Reddy UM, Thorsten VR, Dudley DJ, Silver RM, Coustan D, Saade GR, Conway D, Varner MW, Stoll B, Pinar H, Bukowski R, Carpenter M, Goldenberg R, Stillbirth Collaborative Research N, Stillbirth Collaborative Research Network: design, methods and recruitment experience, *Paediatric and Perinatal Epidemiology* 25(5) (2011) 425–35. [PubMed: 21819424]
- [10]. Pinar H, Goldenberg RL, Koch MA, Heim-Hall J, Hawkins HK, Shehata B, Abramowsky C, Parker CB, Dudley DJ, Silver RM, Stoll B, Carpenter M, Saade G, Moore J, Conway D, Varner MW, Hogue CJ, Coustan DR, Sbrana E, Thorsten V, Willinger M, Reddy UM, Placental findings in singleton stillbirths, *Obstet Gynecol* 123(2 Pt 1) (2014) 325–36. [PubMed: 24402599]
- [11]. MacDorman MF, Reddy UM, Silver RM, Trends in Stillbirth by Gestational Age in the United States, 2006–2012, *Obstet Gynecol* 126(6) (2015) 1146–50. [PubMed: 26551188]
- [12]. Schneider CA, Rasband WS, Eliceiri KW, NIH Image to ImageJ: 25 years of image analysis, *Nat Methods* 9(7) (2012) 671–5. [PubMed: 22930834]
- [13]. Kaplan CG, Gross pathology of the placenta: weight, shape, size, colour, *J. Clin. Pathol* 61(12) (2008) 1285–95. [PubMed: 18708423]
- [14]. Pinar H, Koch MA, Hawkins H, Heim-Hall J, Shehata B, Thorsten VR, Carpenter M, Lowichik A, Reddy UM, The Stillbirth Collaborative Research Network (SCRN) placental and umbilical cord examination protocol, *American Journal of Perinatology* 28(10) (2011) 781–92. [PubMed: 21717387]
- [15]. Koo TK, Li MY, A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research, *J Chiropr Med* 15(2) (2016) 155–63. [PubMed: 27330520]
- [16]. Shrout PE, Fleiss JL, Intraclass correlations: uses in assessing rater reliability, *Psychol Bull* 86(2) (1979) 420–8. [PubMed: 18839484]
- [17]. Hammer RM, Compute six intraclass correlation measures, 2000 <http://support.sas.com/kb/25/031.html>.
- [18]. Hallgren KA, Computing Inter-Rater Reliability for Observational Data: An Overview and Tutorial, *Tutor Quant Methods Psychol* 8(1) (2012) 23–34. [PubMed: 22833776]
- [19]. Bland JM, Altman DG, Measuring agreement in method comparison studies, *Stat Methods Med Res* 8(2) (1999) 135–60. [PubMed: 10501650]
- [20]. Giavarina D, Understanding Bland Altman analysis, *Biochem Med (Zagreb)* 25(2) (2015) 141–51. [PubMed: 26110027]
- [21]. Salafia CM, Maas E, Thorp JM, Eucker B, Pezzullo JC, Savitz DA, Measures of placental growth in relation to birth weight and gestational age, *Am J Epidemiol* 162(10) (2005) 991–8. [PubMed: 16192346]
- [22]. Higgins LE, Simcox L, Sibley CP, Heazell AE, Johnstone ED, Third trimester placental volume and biometry measurement: A method-development study, *Placenta* 42 (2016) 51–8. [PubMed: 27238714]
- [23]. Viero S, Chaddha V, Alkazaleh F, Simchen MJ, Malik A, Kelly E, Windrim R, Kingdom JC, Prognostic value of placental ultrasound in pregnancies complicated by absent end diastolic flow velocity in the umbilical arteries, *Placenta* 25(8–9) (2004) 735–41. [PubMed: 15450392]

HIGHLIGHTS:

- We compared placental surface area from images to area estimated using diameters
- Manual outlines of placental area from images have excellent inter-rater reliability
- Placental diameters are an adequate proxy for estimating surface area

Figure 1.

Results for agreement between image-based and diameter-based measures for the total sample (n=491).

Abbreviations: CI – confidence interval

Table 1.

Estimates of the association between birthweight and placental surface area modeling image-based and diameter-based measures separately.

	β^a	95% CI	Change in R^2 ^b
Image-based area ^c	3.65	3.00, 4.31	0.032
Diameter-based area ^c	3.81	3.13, 4.49	0.033

^aEstimates reflect a 1 cm² increase in surface area

^bChange in R^2 reflects the contribution of the surface area measure to the R^2 of the adjusted model

^cBoth models adjust for stillbirth/live birth status, gestational age, race/ethnicity, maternal education, maternal smoking, maternal height, maternal weight, preeclampsia, gestational diabetes, parity, sex, placental shape, and placental thickness