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The assessment of fetal brain growth in diabetic pregnancy using in utero magnetic resonance imaging

--Manuscript Draft--

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Corresponding Author:	Michael Paddock University of Sheffield Sheffield, South Yorkshire UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Sheffield
Corresponding Author's Secondary Institution:	
First Author:	Michael Paddock
First Author Secondary Information:	
Order of Authors:	Michael Paddock
	Rahim Akram
	Deborah A Jarvis
	Paul Armitage
	Soon Song
	Priya Madhuvrata
	Paul D Griffiths
Order of Authors Secondary Information:	
Abstract:	Aim: To assess fetal brain growth over the third trimester in pregnant women with diabetes using in utero magnetic resonance imaging (iuMR) to determine if greater brain growth occurs in type 1 (T1DM) when compared to gestational (GDM) diabetes. Materials and Methods: Each consented participant was scanned at three fixed times during the third trimester using iuMR. 157 patients were approached, 48 participants were recruited and 36 complete data sets were analysed. 3D iuMR volume data sets were manually segmented using software to construct models of the fetal brain from which brain volumes could be calculated. Inter-rater analysis was performed, and volume differences and growth rates were compared between T1DM and GDM. Results: Recruitment proved difficult with low uptake and high attrition rates (77.1%). Inter-rater analysis revealed excellent correlation (intraclass correlation coefficient=0.93, $p<0.001$) and agreement with no significant difference between operators ($p=0.194$). There was no evidence of increased brain volume in the T1DM group. Growth rates between visit 1 and 3 for T1DM and GDM were not significantly different ($p=0.095$). Conclusion: T1DM brain volumes were not significantly larger than GDM volumes and there was no significant divergence of brain growth over the third trimester. Constructing volume models from 3D iuMR acquisitions is a novel technique that can be used to assess fetal brain growth. No specialist software or knowledge is required. Larger studies attempting to recruit pregnant women in the later stages of pregnancy should employ multicentre recruitment to over-come recruitment difficulties and high attrition rates.

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The assessment of fetal brain growth in diabetic pregnancy using *in utero* magnetic resonance imaging

Michael Paddock [a,*], Rahim Akram [b], Deborah A Jarvis [a], Paul Armitage [a], Soon Song [c], Priya Madhuvrata [d], Paul D Griffiths [a]

[a] Academic Unit of Radiology, University of Sheffield, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK
[b] The Medical School, The University of Sheffield, Beech Hill Road, Sheffield, S10 2RX, UK
[c] Department of Diabetes and Endocrinology, Northern General Hospital, Sheffield, S5 7AU, UK
[d] Department of Obstetrics & Gynaecology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, S10 2JF, UK

*__Guarantor and correspondent__: Dr Michael Paddock, Academic Unit of Radiology, University of Sheffield, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK
Telephone: +44 114 271 1643. Facsimile: +44 114 271 1714
E-mail: michael.paddock@doctors.org.uk

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Conflict of interest

The authors declare no conflict of interest.

Submission declaration

This article has not been published previously and is not under consideration elsewhere. Its publication is approved by all authors and explicitly by the responsible authorities where the work was carried out, and if accepted, will not be published elsewhere.

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Author contributions

1. guarantor of integrity of the entire study – MP
2. study concepts and design – MP, SS, PA, PDG
3. literature research – MP, RA
4. clinical studies – PDG
5. experimental studies / data analysis – MP, PDG
6. statistical analysis – MP, RA, DJA, PDG
7. manuscript preparation – MP
8. manuscript editing – MP, RA, DJA, PA, SS, PM, PDG

ABSTRACT

Aim: To assess fetal brain growth over the third trimester in pregnant women with diabetes using *in utero* magnetic resonance imaging (*iu*MR) to determine if greater brain growth occurs in type 1 (T1DM) when compared to gestational (GDM) diabetes.

Materials and Methods: Each consented participant was scanned at three fixed times during the third trimester using *iu*MR. 157 patients were approached, 48 participants were recruited and 36 complete data sets were analysed. 3D *iu*MR volume data sets were manually segmented using software to construct models of the fetal brain from which brain volumes could be calculated. Inter-rater analysis was performed, and volume differences and growth rates were compared between T1DM and GDM.

Results: Recruitment proved difficult with low uptake and high attrition rates (77.1%). Inter-rater analysis revealed excellent correlation (intraclass correlation coefficient=0.93, $p<0.001$) and agreement with no significant difference between operators ($p=0.194$). There was no evidence of increased brain volume in the T1DM group. Growth rates between visit 1 and 3 for T1DM and GDM were not significantly different ($p=0.095$).

Conclusion: T1DM brain volumes were not significantly larger than GDM volumes and there was no significant divergence of brain growth over the third trimester. Constructing volume models from 3D iuMR acquisitions is a novel technique that can be used to assess fetal brain growth. No specialist software or knowledge is required. Larger studies attempting to recruit pregnant women in the later stages of pregnancy should employ multicentre recruitment to over-come recruitment difficulties and high attrition rates.

Introduction

Diabetes mellitus (DM) occurs in 2–5% of pregnant women in England and Wales[1] of which approximately 87% have gestational diabetes (GDM), 8% type 1 diabetes (T1DM) and 5% type 2 diabetes (T2DM).[2] Pre-existing diabetes (T1DM and T2DM) is associated with a number of risks to both mother and fetus including miscarriage, pre-eclampsia, preterm labour, malformations and stillbirth.[3-5] The risks of perinatal complications in T1DM pregnancies are quoted as two to five times greater than that of the general population,[6] even in the presence of good glycaemic control during pregnancy.[7] Inadequate glycaemic control is associated with a higher risk of recurrent miscarriage, stillbirth and congenital anomalies[8,9] and is the most important factor contributing to the increased risk of fetal and infant death in the absence of congenital malformations.[10]

It is well established that women with DM tend to have larger fetuses and babies (macrosomia) when compared to non-diabetic women.[5] Whilst the overall size of a fetus can be measured reliably ante-natally on ultrasonography, robust quantification of brain volume is considerably more difficult, if not impossible, with that technique. Surrogate measurements of fetal brain size in the literature are made by measuring the biparietal diameter (BPD) on ultrasound. It has been shown that BPD measurements are greater in those fetuses whose mothers have diabetes when compared to normal pregnancies.[11,12] The main problem is that there may be a disconnect between skull growth and brain growth; the BPD, as a subjective/operator dependant ultrasound assessment, is a poor indicator of ‘brain size’. By comparison, *in utero* magnetic resonance (*iu*MR) imaging provides a comprehensive cross-sectional evaluation which has been shown to be superior in the assessment of the

fetal brain and the detection of abnormalities.[13-16] Recent advances in *iu*MR imaging, in particular, rapid T2 weighted three-dimensional (3D) volume sequences, have allowed detailed assessment of the fetal brain,[17] facilitating estimation of brain volume (distinct from skull measurements) and the ability to assess brain maturity in terms of gyration/sulcation.

No data currently exists regarding brain volumes and the rate of fetal brain growth during third trimester pregnancy in DM. In this study, we assessed third trimester fetal brain growth (volume, as measured by *iu*MR) in women with DM to assess when, and if, differential brain growth occurs.

Materials and Methods

Participants and recruitment

The study population comprised of women with diabetes (T1DM, T2DM and GDM) who attended specialist antenatal clinics and workshops at our institution. Inclusion criteria were: maternal age >16 years at time of recruitment; normal anomaly ultrasound scan at 20 gestational weeks (GW); singleton pregnancy; between 20 and 28 GW at the time of recruitment. Exclusion criteria were: inability to speak fluent English (therefore unable to provide independent informed consent); contraindications to *iu*MR imaging. Potential participants were given an information leaflet on *iu*MR scanning, were contacted after 48 hours and offered three sequential MR examinations at GW 28±1 (visit 1), 31±1 (visit 2) and 34±1 (visit 3). Complete data sets were excluded if they fell outside these predefined timings. Recruitment occurred over a 20-month period from 2013 to 2015. Local institutional ethical approval was

obtained but did not allow for consecutive scanning of 'normal'/non-diabetic pregnant women. As such, pregnant women with GDM acted as a 'disease control' given that they are much less likely to have large babies compared to women with pre-exiting diabetes.[18-21] Informed consent was obtained during the first pre-scan discussion in addition to formal MR safety screening which was performed at least twice prior to scanning.

MR imaging

All *iu*MR imaging was performed on the same whole body 1.5T GE HDx (General Electric Healthcare, Milwaukee, WI) scanner using an eight-channel cardiac phased-array coil. No maternal sedation was used. Following routine imaging of the fetal brain, 3D volumetric data sets were acquired using the Fast Imaging Employing Steady-state Acquisition (FIESTA) sequence in the axial plane relative to the fetal brain.[17] Imaging parameters were: 4-5 ms minimum repetition time (TR); 2-3 ms minimum echo time (TE); refocusing flip angle of 60°; 0.75 number of excitations (NEX); field of view (FOV) 340 x 270 mm; matrix size of 320 x 256 mm. Partition thickness was 1.8-2.2 mm with 28-32 scan locations per slab dependent on fetal brain size. In order to allow full coverage of the fetal brain with maximal resolution, the section thickness or number of scan locations was adjusted and achieved in a timeframe conducive to a maternal breath-hold (20-23 s).

A report was issued for all scans by a neuroradiologist (PDG, over 15 years of fetal neuroradiology experience) stating that the procedure was performed for research purposes. If no brain abnormality was shown, 'no unexpected abnormalities' was reported. If there was a further intracranial abnormality, a full clinical report was

provided directly to the patient's obstetrician. Each participant was invited back for further scan(s) according to the predefined time limits above, however they were under no obligation to do so. A complete data set comprised of three consecutive *iu*MR scans.

Post-processing and statistical analysis

All imaging was anonymised, reformatted, transferred onto a desktop personal computer and loaded into three-dimensional (3D) reconstruction software (www.slicer.org). As shown in Fig. 1a-1d, the ventricles, cerebral hemispheres, cerebellum and extracranial cerebrospinal fluid volume were delineated by hand on every axial slice in the volumetric MR acquisition by trained operators involved in the study (DAJ, experienced operator {operator 1}; RA, newly trained {operator 2}). The volumetric data for qualitative analysis were generated from surface rendered 3D models for each area of delineated anatomical interest, as shown in Fig. 1e and 1f. This method is based on previously published work from our institution.[22]

Fourteen data sets from visit 1 were measured separately by the two operators for inter-rater analysis (all seven T1DM and seven randomly selected GDM cases). Independent *t*-tests were used to compare percentage differences and intraclass correlation coefficient (ICC) was calculated to assess correlation. A Bland-Altman plot was constructed to assess agreement, variability and bias.

Total parenchymal brain volume (TPBV) was derived from the difference between the total brain volume (both cerebral hemispheres and cerebellum) and the internal (ventricular) cerebrospinal fluid volume: the TPBV 3D model is shown in Fig. 1f. Independent *t*-tests were employed to evaluate any differences in fetal brain growth

between both groups. The difference between individual fetal brain volumes were calculated between visits 1 and 3 and divided by the number of weeks (6 weeks) to calculate rates of brain growth. $p<0.05$ was considered statistically significant and the *p* values were 1-sided to provide more power to detect an effect. Statistical analysis was performed using SPSS 22 (SPSS, Chicago, IL).

Results

Over the 20-month recruitment period, 157 pregnant women with DM were approached for potential recruitment (106 with GDM, 22 with T1DM and 29 with T2DM). Of those, 48 gave consent for participation (age range 21 to 45 years). 12 incomplete data sets were excluded leaving 36 complete data sets available for analysis: n=29, GDM (age range 21 to 44 years); n=7, T1DM (age range 23 to 37 years); n=0, T2DM. The recruitment and attrition rates are outlined in Fig. 2.

One fetus from a pregnant woman with T1DM had unilateral mild ventriculomegaly (defined by trigone measurements ≥10mm) diagnosed on visit 1 *iu*MR imaging: the trigone of the left lateral ventricle measured 11mm and the right trigone measured 6mm. The ventriculomegaly persisted throughout the study period measuring 11mm on visit 2 and 10mm on visit 3 *iu*MR imaging. No other structural brain abnormalities were shown.

Inter-rater analysis is shown in Table 1. No statistically significant difference was found: $t(26)=0.88$, $p=0.194$ (95% confidence interval (CI), -5.52 to 13.78). The average measure ICC was 0.93, $p<0.001$ (95% CI, 0.643 to 0.981). The corresponding Bland-Altman plot (Fig. 3) illustrates that all values lie within the 95% confidence limits

with a degree of bias towards the results of the more experienced operator 1 (10 data points lie above zero).

Fig. 4 illustrates the distribution of TPBV at each visit. The visit 1 GDM TPBV was statistically significantly higher than T1DM (p=0.020). The possible relevance of this apparently spurious result is described below. There was no statistically significant difference between GDM and T1DM brain volumes at visit 2 (p=0.456) and visit 3 (p=0.053). The growth rates (cm^3/week ± standard deviation) between visit 1 and 3 were not statistically significantly different (GDM, 17.39 ± 0.64; T1DM, 18.24 ± 3.15; t(33.8)=1.34, p=0.095).

Discussion

This study highlights the difficulty in recruiting pregnant women with DM into *iu*MR studies, relevant when attempting to perform a study from a single centre. We found that it was easier to recruit women from workshops that were less time-pressured when compared with busy clinics. Over the 20-month recruitment period, 157 potential participants were approached. After formal discussion and allowing sufficient time for consideration, the rate of consented participants was low (n=48/157, 30.6%). Once consented, the retention rate was relatively high (n=36/48, 75%); reasons for incomplete data sets are provided in Fig. 2. The overall attrition rate from approach to completion was far lower than expected (n=36/157, 77.1%) and only 36 complete data sets were acquired, i.e. less than 2 per month.

Participants were not asked about their reasons for withdrawing/not attending/not wanting to book further scans but some offered reasons without prompting: childcare issues; previous miscarriage, worried about the long term effects

of MR; claustrophobic, could not tolerate further scans; time commitments as still working; too many other appointments. Some commented that a significant attraction of this study was direct funding/reimbursement of all travel expenses. Given that recruitment and retention from this patient group is difficult, the research design of any larger study would need to be dynamic and flexible. Furthermore, formal qualitative assessment should be undertaken through formal patient and public information (PPI) engagement with specific reference to the acceptability of consecutive *iu*MR scanning in third trimester pregnancies to address the practicality and viability of a larger scale study.

The high proportion of pregnant women with GDM who were approached, consented and retained for final analysis is similar to the reported prevalence in the general population.[1] The difficulties of recruiting pregnant women into research studies is well documented,[23-26] particularly during the third trimester with high attrition rates also reported.[27] This was the first study from our unit attempting to recruit pregnant women for consecutive third trimester *iu*MR scanning, which to our knowledge no reported study has previously attempted. It is clear that future studies attempting to recruit women for consecutive *iu*MR third trimester scanning would need to employ multicentre recruitment to allow for potentially suboptimal participation and high attrition, in addition to funding travel expenses. The links forged from previous multicentre work co-ordinated at our institution would facilitate this process.[28]

Inter-rater analysis allows us to assess the reliability (inherent repeatability) and precision of the 3D volumetric measurements between operators so that our results have external validity (generalisability). All inter-rater percentage differences between both operators varied by less than ±10%, with half varying by less than ±5% and there was excellent correlation (ICC 0.93, $p<0.001$). The Bland-Altman plot (Fig. 3)

demonstrated that the mean differences became slightly larger as the mean volume increased. However, given the small sample size (n=14) and with all results within the narrow limits of agreement, any bias or variability demonstrated by Operator 1 is very unlikely to be clinically or practically significant which is important when considering the generalisability of this technique. Furthermore, we demonstrated no statistically significant difference between the volume data measurements between both operators (p=0.194).

Factors contributing to variability or bias centred around the segmentation process and accurate delineation of structures at 'true' interfaces, i.e. parenchymal-cerebrospinal fluid interface, noted to be most difficult at the trigonal ventricular choroid plexus-periventricular white matter interface. Other factors included: fetal and/or maternal movement artefact resulting in poor image quality; subjective differences in contrast and brightness settings which can be altered at any time during segmentation; changes in ambient lighting; visual and muscular fatigue when segmenting older gestational fetal brains because of the more complex sulcation pattern.

Previous studies have demonstrated that neonates born to diabetic mothers have larger head circumferences when compared to those born to non-diabetic mothers,[29] interpreted to indicate that they would have larger brains. Our assumption before this study commenced was that T1DM fetuses would have larger brain volumes when compared to GDM/normal brains, although we did not know at what gestational age this difference would become apparent. In spite of the lack of supporting data from antenatal ultrasound, we predicted that any statistically significant differences in brain volume would be apparent by visit 3 (34±1 GW) given that maximal neural growth and development occurs during this period.[30] Brain volumes in fetuses of women with T1DM however were not significantly larger than those with GDM and there was no

200 significant difference in the rate of growth between 28 to 34 GW. It is likely therefore
201 that the divergence in brain growth could be found beyond 35 weeks given the larger
202 head size in T1DM neonates at birth.[11,29] Contrary to our expectation, the T1DM mean
203 TPBV at visit 1 (28±1 GW) was statistically significantly smaller than that of GDM
204 (p=0.020). There is no supporting evidence in the literature that BPD measurements
205 on ultrasound are smaller in fetuses of mothers with T1DM than their GDM
206 counterparts, and given the small sample size (n=7 in the T1DM group), this is
207 probably a spurious result. This time point (28±1 GW) could be further re-examined in
208 a larger study to determine the time point at which differential brain growth occurs.
209 Recent literature has debated the impact of endothelial dysfunction on umbilical
210 arteries in pre-existing DM.[31,32] Blood flow is more critical for organ development
211 earlier in pregnancy and the subsequent dysregulation in umbilical blood flow may
212 result in underdevelopment of the fetal brain. It is possible that this is more pronounced
213 in brains of fetuses whose mothers have T1DM, such that from a metabolic
214 perspective there is more physiological 'catching up' to do *in utero* which is
215 compensated for in later pregnancy (≥36 GW). This may explain why those born to
216 mothers with DM have bigger heads and are larger than their non-diabetic
217 counterparts. Evidently, the underlying physiological mechanism warrants further
218 investigation in addition to an assessment of fetal brain growth not captured in this
219 study.

220 As previously discussed, initial recruitment proved difficult and many data sets
221 remained incomplete due to patient withdrawal. In order to recruit sufficient numbers,
222 the list of possible participants was discussed with the specialist diabetes midwifery
223 team at the start of each specialist clinic or workshop. Given the time and expense
224 involved in performing 3 *iu*MR scans, we sought to recruit patients invested in

completing all 3 scans in order to obtain complete data sets. As such, those known to the local service with a history of non-compliance, who frequently missed appointments and with complex social issues were deemed not appropriate to approach. However, even in spite of this, some of the latter recruited participants still did not attend all three scans or withdrew.

The sample size (n=36) was not large enough to capture any results that were likely to be that clinically meaningful however this data can be used to power a larger study. As described above, an assessment of late third trimester diabetic pregnancies (>35 GW) may elucidate the point at which differential brain growth occurs. A larger study should encompass the influence of maternal factors on brain growth and maturation including: weight (body mass index); type and/or combination of management of diabetes in pregnancy (diet controlled, oral hypoglycaemics, insulin); quality of glycaemic control, particularly considering that even in the presence of an overall good level of glycaemic control the frequency of macrosomia remains high.[33,34]

Alongside the 3D *iu*MR data sets, the 3D surface rendering of the fetal brain[22] could be used to estimate the gestational age of the fetus based on its sulcation pattern, comparing to standard atlases and actual gestational age. An assessment of brain maturation rate between the different types of diabetes could also be performed which would allow further development of a fetal brain maturation database and subsequent validation of a fetal brain maturation scoring system building upon previously published work in this area.[35]

The novel techniques described could be expanded to assess the effect of conditions known to affect fetal growth during pregnancy: placental insufficiency; intra-uterine growth restriction in both singleton and multiple pregnancies; baseline growth differences in twin pregnancy; twin-to-twin transfusion syndrome.

Conclusion

We have shown that 3D volumetric modelling from manually segmented 3D *iu*MR acquisition is a reliable and reproducible technique. Users with no prior knowledge of the software or technique can be trained to use the programme to produce reliable results. The method does not require specialist computer software (3D slicer is freely available) or specialist knowledge to operate. This technique can be implemented in the clinical environment with wide-range applicability for use by any healthcare professional. With regard to fetal brain growth and maturation, it is clear that more work in this area is needed and that larger studies would need to employ multicentre recruitment and encompass a flexible research design.

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Figures Legends

Figure 1. An example of the manual segmentation and construction of brain models from which the total parenchymal brain volume (TPBV) was calculated. Figures 1a – 1d are the same axial slice from a 3D FIESTA acquisition of a 29 week fetus from a woman with gestational diabetes. (a) Delineation of the internal cerebrospinal fluid (ventricular) volume (blue), (b) right hemisphere (gold), (c) left hemisphere (cream) and (d) external cerebrospinal fluid (extracranial) volume (red). The cerebellum is also segmented (green, not shown in these images). Segmentation is performed on all slices in the volume acquisition and models of the ventricles (e) and whole brain (f) are created. The models generate quantitative volumetric data for each area. The TPBV is derived from the difference between the total brain volume (both cerebral hemispheres and cerebellum) and the internal (ventricular) cerebrospinal fluid volume.

Figure 2. Flowchart outlining recruitment and attrition. GDM=gestational diabetes mellitus. T1DM=type 1 diabetes mellitus. T2DM=type 2 diabetes mellitus.

Figure 3. Bland-Altman plot of differences between operator 1 (DAJ, experienced) and 2 (RA, newly trained). Solid black line=mean. Dashed lines=95% limits of agreement.

Figure 4. Box-and-whisker plot illustrating the total brain parenchymal volume (TPBV) over the course of the third trimester at each visit by type of diabetes mellitus. Visit 1 (gestational weeks)=28±1. Visit 2=31±1. Visit 3=34±1. The visit 1 GDM TPBV was significantly higher than T1DM ($t(34)=2.15$, $p=0.020$, 95% confidence interval (CI) -22.52 to -0.62). There was no significant difference between GDM and T1DM brain volumes at visit 2 ($t(34)=0.11$, $p=0.456$, 95% CI -17.96 to 16.09) and visit 3 ($t(34)=1.17$, $p=0.053$, 95% CI -17.34 to 1.71).

Table Legend

Table 1. Percentage differences for 14 selected volumes (seven T1DM and seven randomly selected GDM cases) from visit 1 (28±1 gestational weeks) between two operators involved in the study. Operator 1=DAJ. Operator 2=RA.

Figure 1

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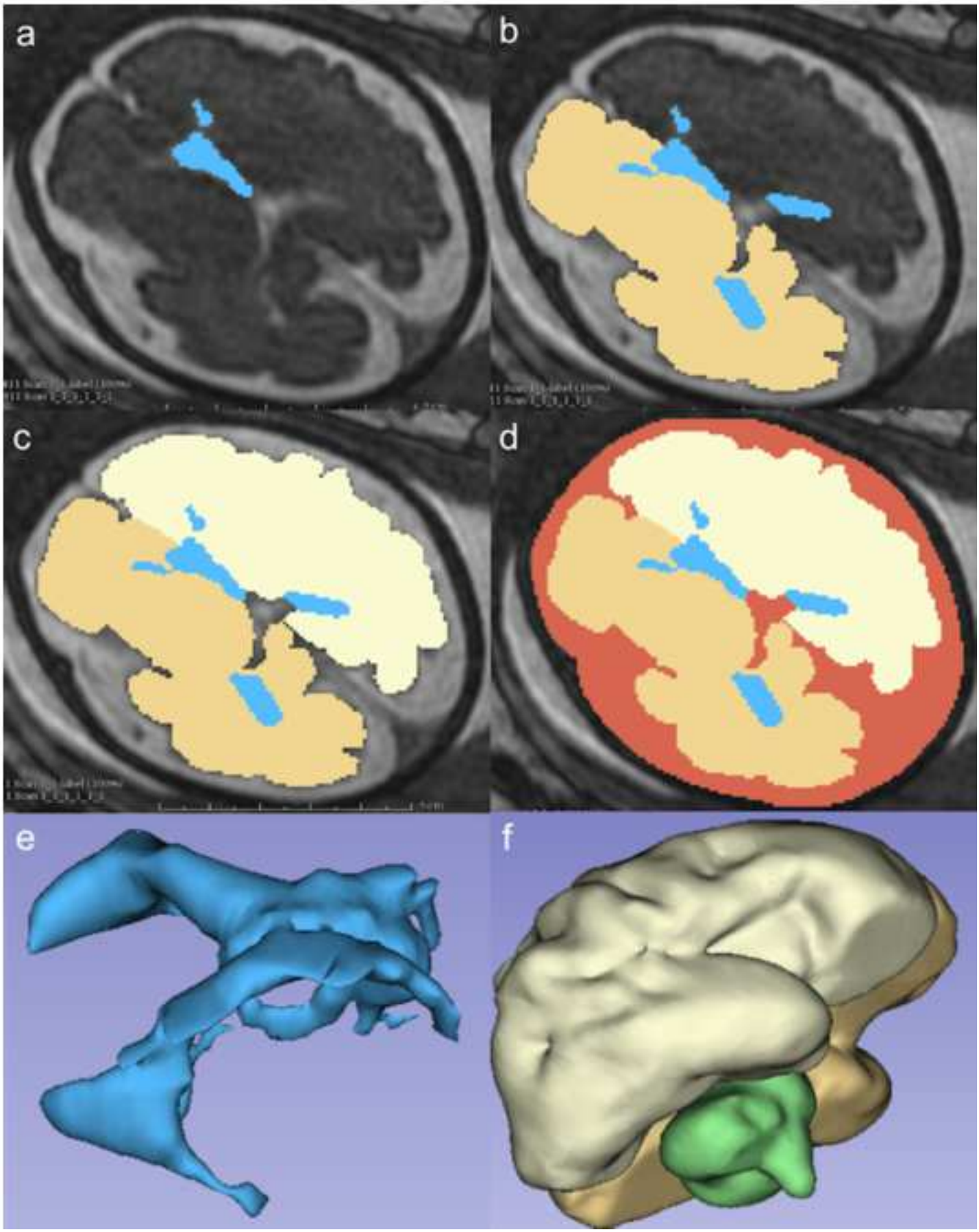

Figure 2

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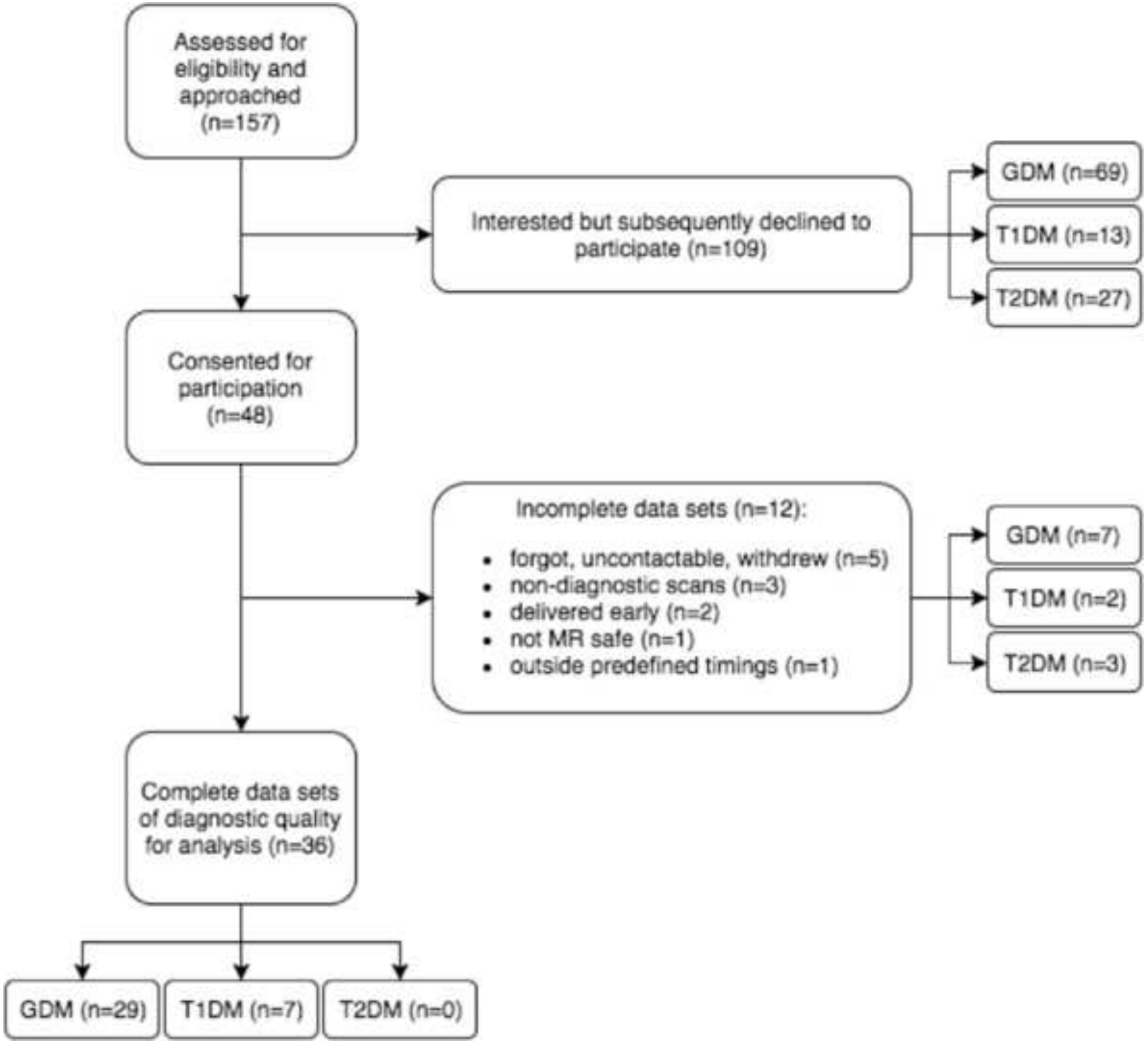

Figure 3

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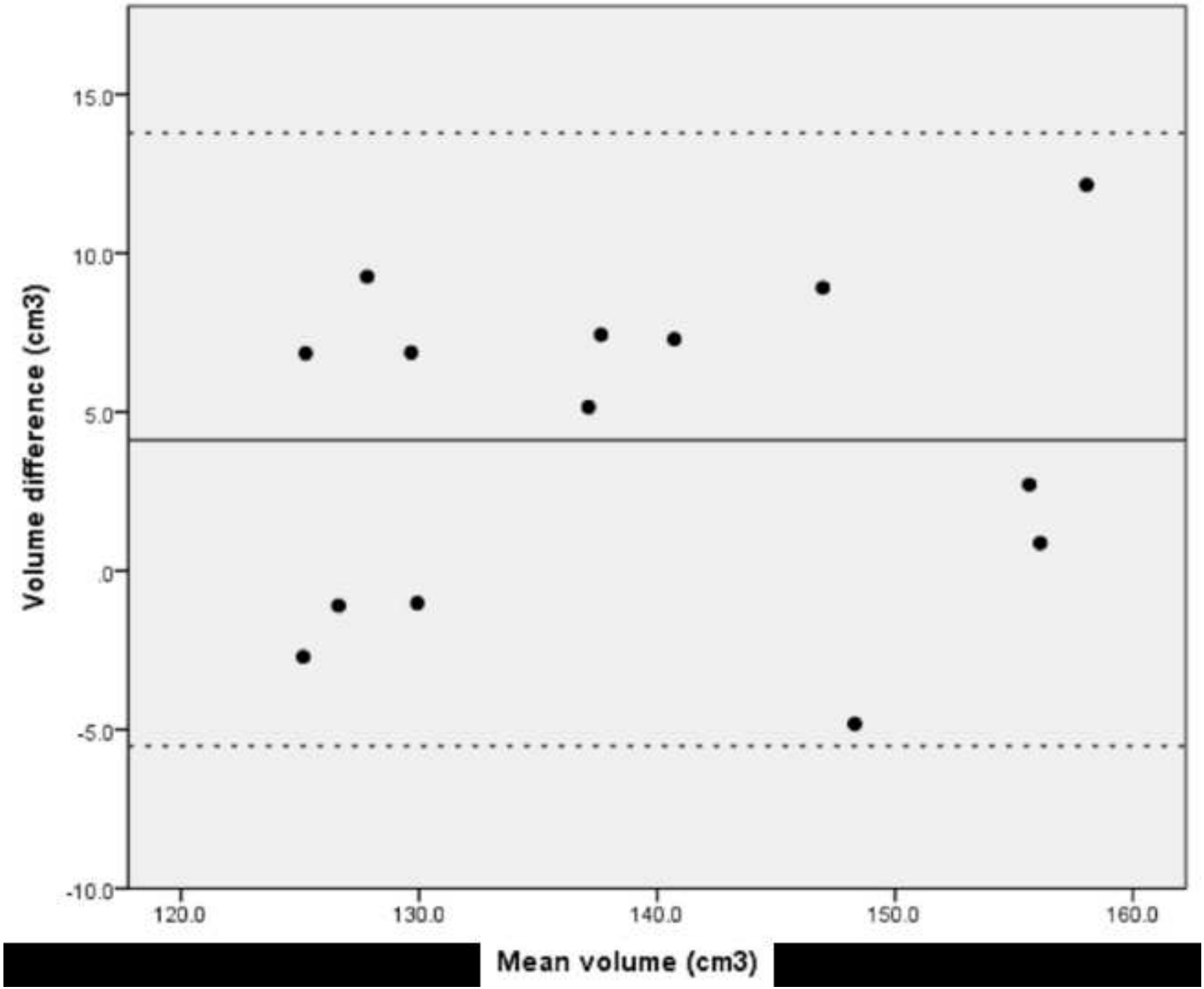

Figure 4

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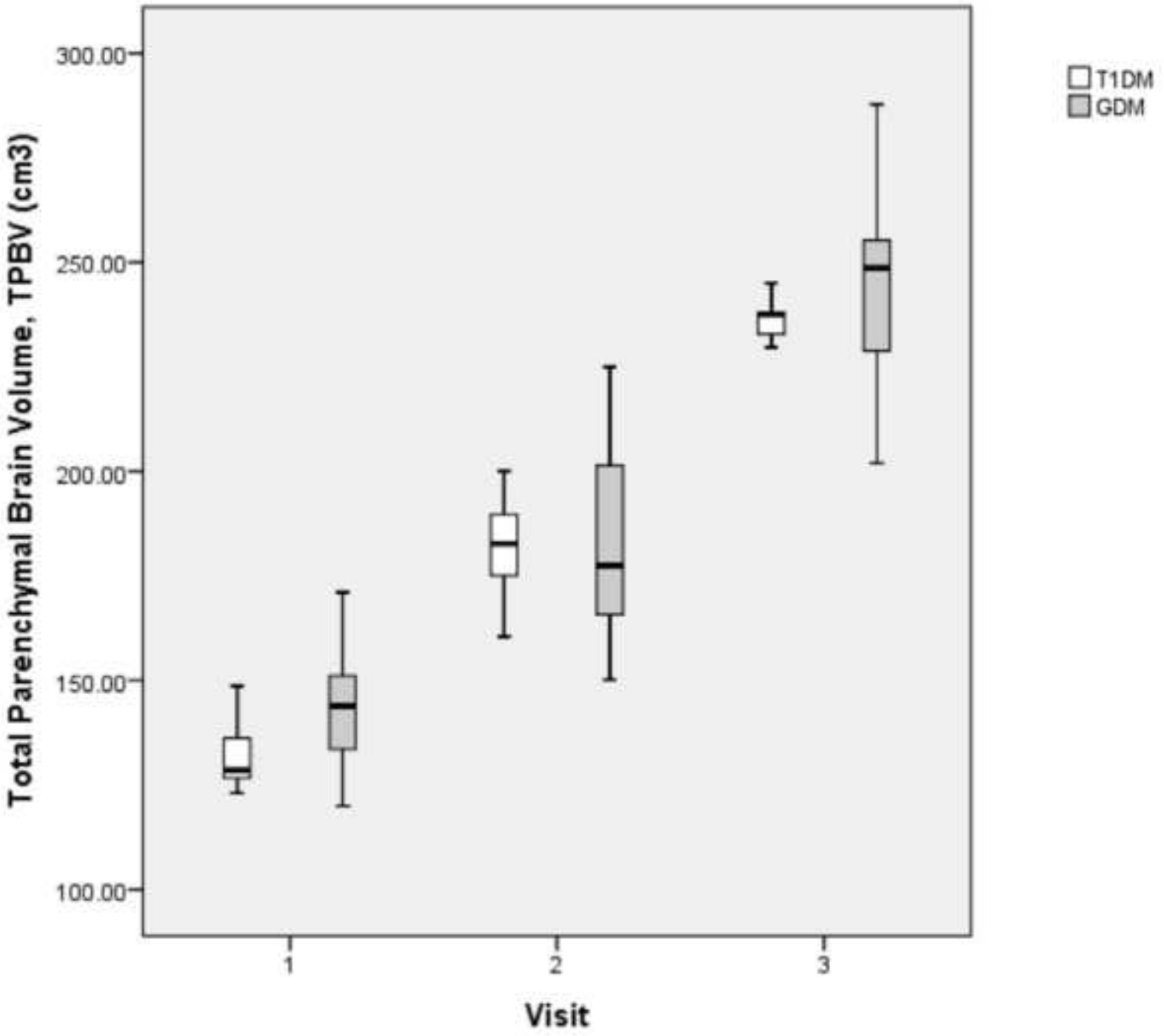

Table 1

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Participant number	Operator 1 volumes (cm^3)	Operator 2 volumes (cm^3)	% difference (cm^3)
1	134.55	139.70	3.83
11	127.17	126.07	-0.86
14	130.44	129.42	-0.78
17	123.19	132.45	7.52
22	137.08	144.37	5.32
24	151.97	164.12	7.99
25	133.93	141.36	5.55
32	121.81	128.66	5.62
35	142.51	151.42	6.25
36	126.49	123.78	-2.14
37	126.23	133.10	5.44
39	155.66	156.53	0.56
44	154.28	156.99	1.76
45	150.72	145.90	-3.20
Mean	136.86	140.99	3.06

HIGHLIGHTS

- No differential brain growth occurs over the third trimester of diabetic pregnancy
- Manual segmentation of 3D *iu*MR acquisitions requires no specialist knowledge
- 3D volume modelling of the fetal brain is a reliable and reproducible technique