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Original Article

Estimate of fetal brain temperature using proton resonance frequency thermometry during 3 Tesla fetal magnetic resonance imaging

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Background: T2-weighted Single Shot Fast Spin Echo (SSFSE) scans at 3 Tesla (3T) are increasingly used to image fetal pathology due to their excellent tissue contrast resolution and signal-to-noise ratio (SNR). Temperature changes that may occur in response to radio frequency (RF) pulses used for these sequences at 3T have not been studied in human fetal brains. To evaluate the safety of T2-weighted SSFSE for fetal brains at 3T, magnetic resonance (MR) thermometry was used to measure relative temperature changes in a typical clinical fetal brain MR exam.

Methods: Relative temperature was estimated using sets of gradient recalled echo (GRE) images acquired before and after T2-weighted SSFSE images which lasted 27.47±8.19 minutes. Thirty-one fetuses with cardiac abnormalities, and 20 healthy controls were included in this study. Fetal brain temperature was estimated by proton resonance frequency (PRF) thermometry and compared to the estimated temperature in the gluteal muscle of the mother. Seven scans with excessive motion were excluded. Local outlier factor (LOF) was performed to remove 12 additional scans with spurious phase measurements due to motion degradation and potential field drift. Linear regression was performed to determine if temperature changes are dependent on the rate of energy deposition during the scan.

Results: For the 32 participants used in the analysis, 17 with cardiac abnormalities and 15 healthy controls, the average relative fetal temperate change was 0.19±0.73 ℃ higher than the mother, with no correlation between relative temperature change and the rate of images acquired during the scans (regression coefficient =–0.05, R-squared =0.05, P=0.22, F-statistic =1.60). The difference in the relative temperature changes between the fetal brain and mother's gluteal tissue in the healthy controls was on average 0.08 ℃ lower and found not to be statistically different (P=0.76) to the group with cardiac abnormalities.

Conclusions: Our results indicate that the estimated relative temperature changes of the fetal brain compared to the mother's gluteal tissue from RF pulses during the course of the T2-weighted SSFSE fetal MR exam are minimal. The differences in acquired phase between these regions through the exam were found not to be statistically different. These findings support that fetal brain imaging at 3T is within FDA limits and safe.

Keywords: Thermometry; fetal; brain; magnetic; resonance

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Introduction

Magnetic resonance imaging (MRI) has been shown to aid diagnosis of fetal neurological abnormalities beyond the capabilities of ultrasound (1) and is commonly performed to evaluate fetal brain pathology due to high tissue contrast of cerebral anatomy (2), and no exposure to potentially harmful ionizing radiation. As the use for MRI in pregnant women increases, and scanning occurs in higher magnetic fields [3 Tesla (3T)], there is a need for continued evaluation of safety with regards to potential temperature increases in the fetal brain. The fetal brain is sensitive to increases in temperature since the surrounding amniotic fluid is conductive and has poor thermal regulation (3), the mother has weak perception of local increases in temperature, and the developing fetus has an unknown ability for sensing and regulating heat (3-5). Fetal neurodevelopment models in the pregnant Guinea pig show that increases in temperature during critical periods of development result in reduction in brain weight which persists into maturity resulting in impaired learning performance (6). The current regulations suggest preventing temperature increases in the pregnant woman by 0.5 ℃ [whole body Specific Absorption Rate (wbSAR) of 2 W/kg] (7) and fetal temperatures are expected to be 0.3–0.5 ℃ higher than the mother's whole-body temperature under normal environmental conditions (7,8). Additionally, fetal brain temperature is tightly regulated during development and expected to be highly coupled to temperature changes in the mother (9). The signal-to-noise ratio (SNR) gain at 3T offers potential improved diagnostic value which has led to more institutions performing fetal scans at 3T. Since radio frequency (RF) energy deposition is higher with greater magnetic field strength, evaluation of temperature changes at 3T is needed to ensure fetal safety. Temperature estimates have been used to evaluate fetal temperature with MRI in simulation (3,10,11) and in pregnant animal models (6,12) but not measured directly in humans at 3T. Specific energy dose (SED) and specific absorption rate (SAR) estimates have been previously compared at 1.5T and 3T (13,14), however a direct estimate of fetal temperature changes has not been examined. Since increases in temperature are of greater concern at higher field strength, we focus on fetal brain imaging at 3T. Proton resonance frequency (PRF) thermometry is an established method to measure temperature changes *in vivo* with MRI (15-17). We use PRF thermometry to evaluate 3T imaging safety by measuring temperature changes in the fetal brain after T2-weighted SSFSE scans and expect temperature changes to be within safety guidelines. While a clinical fetal exam may include other sequences besides SSFSE, these are the most SAR intensive sequences, which are the focus of this study. Temperature measurements via phase imaging are prone to artifacts which we aim to address by using an unsupervised machine learning technique, local outlier factor (LOF) (18), to remove cases that were motion degraded or corrupted from field effects.

Methods

Study sample

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of University of California San Francisco. Pregnant women were recruited from the UCSF Clinics, and they provided written informed consent. Fifty-one participants were recruited and imaged between June 2017 and January 2022 in this prospective study. The average gestational age at scan is 33.90±0.85 weeks. Statistics on gestational age for all participants is shown in *Table 1*. SAR and temperature estimates in simulation have been shown to increase during scans in this later stage of pregnancy (19). Volunteers were determined to be eligible based on willingness to participate and if there were no abnormal genetic or ultrasound findings. In addition to healthy volunteers, some participants are part of an ongoing brain maturation study of fetuses with congenital heart defects, seen at the UCSF Fetal Cardiovascular Program. There were no expected differences in relative fetal temperature changes during the course of the examination between groups.

Order of MRI acquisition

The imaging protocol follows the outline in *Figure 1* using a GE MR750 3T scanner and a 32-channel cardiac coil. Two 2D gradient recalled echo (GRE) images are acquired within the span of 30 seconds to establish a baseline phase evolution [echo time (TE) =12 ms, repetition time (TR) =100 ms]. Then T2-weighted SSFSE images are acquired for anatomic evaluation. Due to fetal motion, there are a variable number of images and scan durations for each participant; 328.29±85.41 images, and 27.47±8.19 minutes. Following the SSFSE, another set of two 2D GRE images are acquired to measure phase evolution after the stacks of SSFSE. All imaging occurs between the hours of 8 am

Table 1 Gestational age for all participants

Groups of participants	Number of participants	Gestational age (weeks)
Total	51	33.90±0.85
Total healthy controls scanned	20	33.91±1.02[a]
Total cardiac brain maturation group participants scanned	31	33.89±0.73[b]
Healthy controls used in analysis	15	33.77±0.96[c]
Participants in cardiac brain maturation group used in analysis	17	33.92±0.60[d]
Total used in analysis	32	33.85±0.78

Superscripts [a] and [b] denote groups that were compared for statistical differences. Groups [c] and [d] were also compared. There were no statistically significant differences between [a] and [b] (P=0.94), and no statistically significant differences between [c] and [d] (P=0.60). Data are shown as mean ± standard deviation.

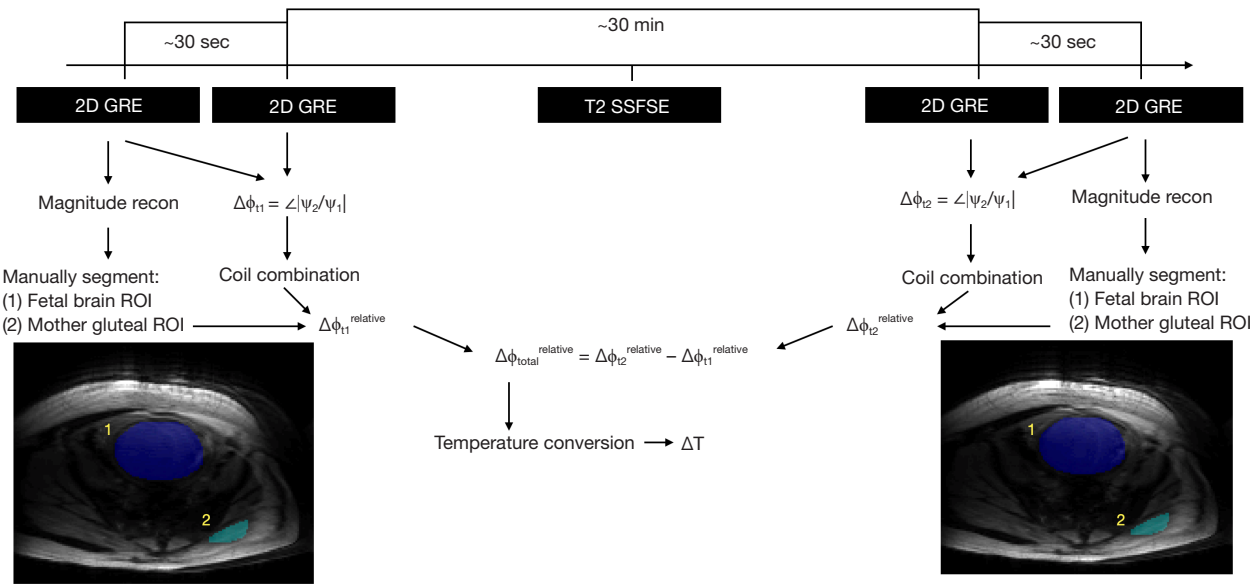

Figure 1 Total imaging acquisition and processing schematic. Relative phase differences are measured pre- and post-SSFSE and then subtracted and converted to temperature through the PRF method (15). T1-weighted 2-dimensional GRE images without contrast in the axial plane with corresponding fetal brain (dark blue) and mother gluteal (cyan) ROIs are shown. 2D, 2-dimensional; GRE, gradient recalled echo; SSFSE, Single Shot Fast Spin Echo; ROI, region of interest; PRF, proton resonance frequency.

and 11 am, which would prevent any effect of potential temperate oscillations in the fetal brain from influencing the derived temperature shifts.

Phase evolution and relative phase

Since phase evolution is calculated throughout the long duration SSFSE, there is potential B_0 field shift and motion that may corrupt the calculation of phase evolution directly. In order to measure increases in temperature from the SSFSE, phase change is compared between sets of GRE images pre- and post-SSFSE. Only the absolute values of phase changes are considered in this stage of operation to track the total extent of phase evolution before and after the SSFSEs. Phase evolution before the SSFSE is expected to be small due to limited RF energy deposition in the beginning of the scan. The phase evolution after the SSFSE sequence measures cooldown from increases in temperatures that

occurred during the SSFSE, and its extent is proportional to any increase in temperature that occurred during that time. B_0 drift during the exam can be reduced by subtracting the two phase differences.

In order to additionally mitigate inaccurate measurements from B_0 field shift while calculating the phase evolution within the fetal brain, we assume a homogeneous global B_0 field and calculate relative phase change within the fetal brain to a control region.

Regions of interest (ROIs) selection

ROIs of the fetal brain and control region were hand drawn then reviewed by board-certified radiologist YL (11 years of experience). The mother's gluteal tissue was selected as a control region to provide a comparison of tissue that is not expected to undergo large changes in temperature during clinical SSFSE. This is due to the comparatively less motion (less phase accrual) and better thermal regulation of the gluteal tissue than the fetus. This tissue is expected to experience a small increase in temperature but expected to stay within safe temperature ranges during the scan and dissipate heat absorbed during standard SSFSE safely, resulting in minimal phase change during the second set of GREs. ROIs were drawn for each GRE, and only the resulting intersection of ROIs were used in order to limit calculated phase changes to corresponding anatomical locations that experience little change throughout scanning. The ROI selection of the gluteal tissue was selected on one side to avoid selection of tissues involved in other structures. The resulting phase calculations within each ROI were averaged before relative phase calculations.

Unsupervised anomalous phase detection

After removal of the scans flagged for visibly high degrees of motion, there was still large variability in phase measurements indicating potential additional artifacts arising due to undetected movement or heterogeneity of the field shift. An unsupervised anomaly detection technique that identifies outliers based on density relative to their neighbors, LOF (18), was applied to all 51 participants in order to identify spurious relative temperature measurements resulting from these artifacts in phase calculations. Euclidean distance was used as the measure of distance between local samples. LOF was implemented with SciKit-Learn 1.0.2 using the default of 20 nearest neighbors and the contamination threshold determined by the method described in the paper (18). LOF was applied along three dimensions of the data; the total phase evolution within the control region and fetal brain, as well as the total relative phase evolution, to reduce the impact of artifacts in phase calculation resulting from field effects or movement that would either impact the intra-ROI phase evolution or total phase evolution between time points. These features were standardized before LOF was applied.

Temperature calculation

Relative phase changes between the fetal brain and control region that evolve through the course of the SSFSE sequence are converted to temperature shifts following the PRF method (15). Details on how relative temperature calculations are obtained are shown in the Supplementary file (Appendix 1). Additionally, absolute temperature changes were obtained by subtracting the temperature measurements for each ROI independently between the two timepoints.

Linear regression analysis

In order to determine if there was any relationship between RF energy deposition during the SSFSE scans and relative changes in the fetal brain temperature, we performed linear regression between relative temperature change and the image rate. Image rate was calculated as the number of T2-weighted SSFSE images acquired divided by the scan duration in minutes. This measure is a proxy for energy deposited into the mother during the SSFSE sequence. Linear regression was also performed for the healthy controls and participants with cardiac abnormalities followed for brain maturation separately in Figure S1.

Statistical methods

Two tailed Welch's *t*-test implemented with Scipy 1.6.2 is used to determine statistical significance between gestational age and temperature changes between the group with cardiac abnormalities and healthy controls. Single tailed Welch's *t*-test implemented with Scipy 1.6.2 is used to determine statistical significance between absolute temperature shifts in the mother and fetal ROIs. P values for linear regression analysis are determined with an *F*-test implemented with Statsmodels 0.13.2. Code and data used for the analysis are available at https://github.com/jacob-ellison/fetal_prf_thermometry. Raw data is available upon request.

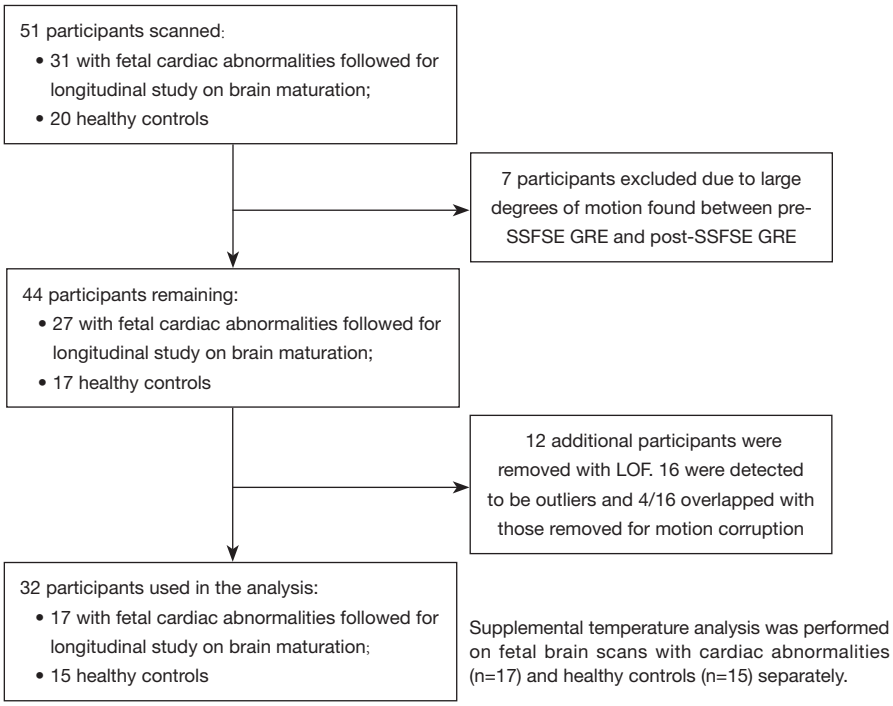

Figure 2 Flow diagram of overall participant removal from the analysis. 32 participants after motion corruption and LOF removal were used for analysis. SSFSE, Single Shot Fast Spin Echo; GRE, gradient recalled echo; LOF, local outlier factor.

Results

Of the 51 participants, average gestational age 33.90± 0.85 weeks [interquartile range (IQR) =0.79 weeks], 32 were used in the final analysis (33.85±0.78 weeks). A flow diagram illustrating the exclusion of participants from analysis is shown in *Figure 2*. Scans with high movement resulting in high or complete misalignment of fetal brain ROIs between time points (7/51) were discarded in the analysis. A visual representation of excluded participants from LOF and motion corruption (gray) are shown in reduced dimensionality (principal component space) of the standardized original 14 features in *Figure 3*. LOF was performed on all 51 participants, and 16 were identified as outliers, 4 of which overlapped with those identified by visual inspection to contain high degrees of motion. In total, 19 participants were excluded from the dataset, 12 participants were excluded using LOF, and 7 from visual inspection of motion corruption. The minimal overlap between the LOF exclusion and motion exclusion could be due to the fact that the motion exclusion was performed solely on the basis of visual inspection. This may not account for elements of motion that are not easily visibly perceptible such as sweeping motions that arrive in the starting position when the second set of GREs is acquired, or jitters during the scan that do not result in visually perceptible misalignment between timepoints. The statistics on gestational age for all participants in this study are shown in *Table 1*.

Temperature calculation

For the remaining 32 participants, we found that the average relative temperature change of the fetal brain to the mother's gluteus was 0.19±0.73 ℃, with a median change of 0.05 ℃. Sixteen fetal brains experienced positive relative temperature changes, and 16 fetal brains experienced negative relative temperature changes. The differences between mean absolute temperature between fetal (0.06±1.00 ℃) and mother (−0.13±0.69 ℃) gluteal ROIs was determined to be statistically insignificant (P=0.20). These results indicate that the fetal brain temperature change after the SSFSEs relative to the mother was low, and there was no statistical difference in temperature change between the mothers' gluteal tissue and fetal brains. However, the variance of the relative temperature change is high with five participants above 1 ℃, and one participant below −1 ℃. This may indicate that the method described above is sensitive to movement,

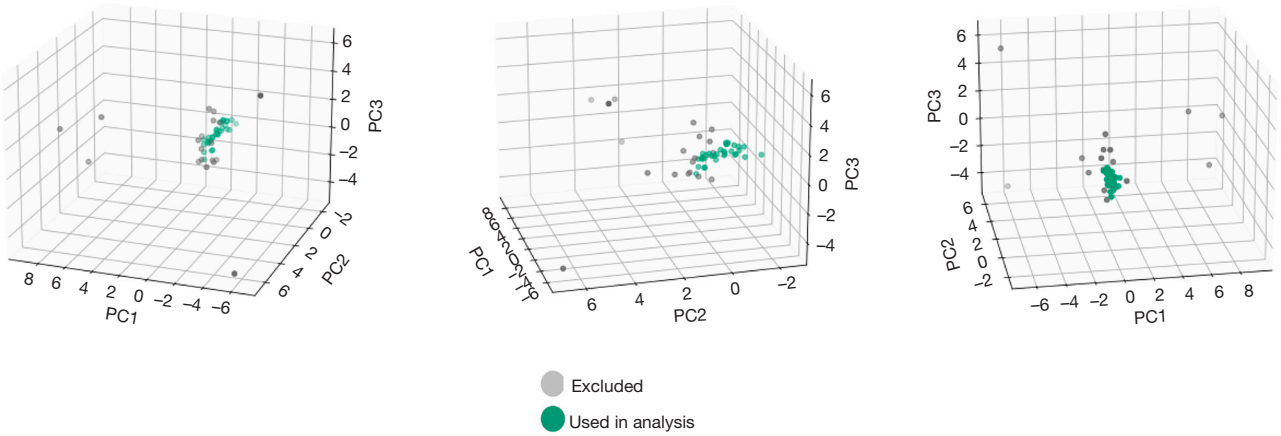

Figure 3 Outlier removal visualization (qualitative performance of LOF) and motion corrupted scan removal). Participants excluded are shown in gray. LOF was performed on all participants before motion removal resulting in classification of 16 participants as outliers. 4/16 overlapped with those removed by motion removal, thus 12 additional participants were removed with LOF. Participants used for the analysis 32/51 are shown in teal. Data is visualized in principal component space of the standardized original 14 imaging features. PC, principal component; LOF, local outlier factor.

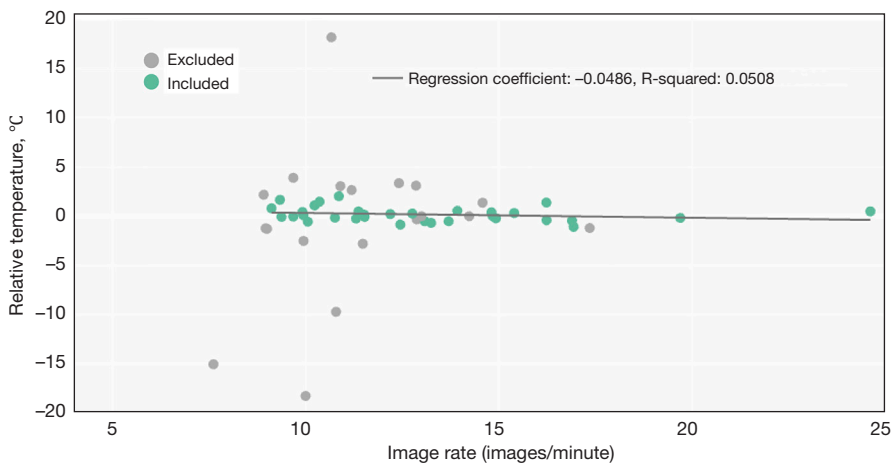

Figure 4 Image rate and relative temperature change. Participants in gray are excluded from the analysis through LOF and motion removal. Participants in teal (32/51) are used for linear regression analysis. The coefficient of regression was found to be –0.05, with an R-squared value of 0.05, and P value of the F-statistic of 0.22. LOF, local outlier factor.

field shift, or other artifacts in phase measurements with four participants representing very large relative temperature changes. Values for temperature measurements for all groups are shown in the Table S1.

Relative temperature changes were compared for healthy controls and those with cardiac abnormalities separately and showed no statistical significance between groups (P=0.76). The results of this analysis are described in additional detail in Appendix 1.

Linear regression analysis

From the linear regression analysis, we found that there was no linear relationship between the image rate and relative temperature changes in the fetal brain. The data can be seen in *Figure 4*, with participants excluded (by LOF and motion removal) from the regression shown in gray. We found the coefficient of regression to be –0.05, with an R-squared value of 0.05, P=0.22. This indicates that there is

not a significant linear relationship between image rate and relative temperature and that the relative fetal temperature change to the gluteus of the mother is not influenced by the number of images acquired during the T2-weighted SSFSE sequence.

Linear regression analysis between image rate and relative temperature was also performed for healthy control participants, and those with cardiac abnormalities separately which both showed no linear relationship between image rate and relative temperature. The results of this analysis are described in additional detail in Appendix 1.

Discussion

Over the last decade, MRI has been increasingly utilized to evaluate fetal abnormalities suspected on prenatal ultrasound and abnormalities that may be occult on prenatal ultrasound (1,2). With the wide adoption of 3T MRI scanners, the SAR concerns of fetal imaging have not been well studied. This study leveraged PRF thermometry to study the potential increase in temperature in the fetal brain during 3T MRI.

As our results show, the fetal temperature increase, relative to the gluteal muscle of the mother, did not change with the number of SSFSE images acquired (coefficient of regression =−0.05, R-squared =0.05, P=0.22). This indicates that the heat dissipation within the fetal brain is comparable to that of maternal muscle and that the stacks of T2-weighted SSFSEs are not elevating fetal brain temperature. Since half of the measured relative temperature changes of the fetus were positive and half were negative compared to the mother, this demonstrates that the variability in measured relative temperature shifts is reflective of variability in the measurement method and not substantial temperature increases.

Under normal environmental conditions, the difference in fetal temperature to the mother is expected to be 0.3–0.5 ℃ (7,8). Our findings show that the temperature change experienced by the fetus, 0.19 ℃, is on average greater than the mother, but of an extent that would remain within the variability of the expected range. Simulation of fetal temperature during MRI has shown that with constant SAR exposure of 2 and 4 W/kg, fetal temperatures are expected to be in excess of 0.2 and 0.4 ℃ after 10 minutes, and 0.3 and 0.6 ℃ after 1 hour (20). Although not a direct measure of fetal brain temperature changes, our results appear to validate these findings. If the absolute temperature change in the mother is assumed to be low (between 0.01 and 0.41 ℃), the 0.19 ℃ change within 27.47±8.19 minutes will fall between the simulated values of 0.2 ℃ and 0.6 ℃ after 10 minutes of constant exposure at 2 W/kg or one hour at 4 W/kg. This appears to be a reasonable assumption since the recommendation for clinical fetal brain MRI require limiting SAR exposure that would raise the mother's body temperature above 0.5 ℃. Differences may be explained by the fact that the total SAR exposure time during the scans may be less than 27 minutes, the simulation was performed using physiological values from sheep fetuses, and the simulation does not account for intrasubject variability in the rate of heat transfer from the fetus to the mother. Differences in the absolute measurement may be explained by the fact that the absolute measurements do not account for field effects. Additionally, our results may differ since fetal brain temperature was compared to a single region of tissue rather than a core temperature measurement. Since skeletal muscle may experience a difference in temperature to the core temperature measurements which are assumed to stay within the expected range of 0.3–0.5 ℃ and below the maximum of 0.6 ℃, it cannot be assumed that the derived relative temperature changes equate to safety. In addition to the relative measurements, when examined on an absolute scale between ROIs, there were no significant differences in temperature change between the mother and fetus. While the absolute measurements do not account for field effects like the relative measurement, they further support that differences in the dissipation of heat due to RF absorption during the T2-weighted SSFSE were not statistically significant for the fetal brain compared to the mother's gluteal tissue. Our results indicate that the temperature change in the fetal brain compared to the mother's gluteal tissue during the stack of T2-weighted SSFSEs for evaluation of anatomy is relatively minimal and statistically insignificant; and that the temperature change is not correlated with number of SSFSE images (RF excitations). The range of relative temperature change is fairly large due to the technique's sensitivity to motion and field effects. The variance in the observed relative temperatures could also be explained by physiological differences between the mothers in the perfusion of the gluteus muscle and the adiposity of the surrounding tissue which could both affect the rate of heat transfer in the control regions and would vary by each mother. It is unlikely that the observed variance is due to scan duration since the regression analysis conducted shows no statistical significance or correlation to image rate which was defined as the number of scans acquired divided by the scan duration. Additionally, we do not believe that

sex differences or any other physiological factors would explain the variance of the measurements, since fetal brain temperature is so tightly controlled under normal environmental conditions and is unlikely to change because of these factors during the scan (9). By including late term gestational fetuses in the study, the fetal head is generally down with relatively much less motion in comparison to earlier gestational fetuses.

The largest limitation of this study is that MR thermometry depends on the phase of the acquisitions. The standard deviation of 0.73 ℃, shows that some participants exhibited large relative temperature changes. With the current analysis, it is difficult to discern exactly whether this is related to the variability of phase measurement caused by motion or field shift, or if this reflects a fetal brain temperature rising above the expected relative difference to the mother due to RF energy deposition.

Typically, the PRF thermometry method is used to measure temperature through changes in phase between two images directly instead of comparing differences in phase changes between sets of images. Further work is needed to account for motion and field shifts such that direct measurement of temperature changes in the fetal brain throughout the duration of a 30-minute SSFSE sequence at 3T can be obtained. Additional studies could further validate this approach by finding the optimal time frame for comparing phase changes with sets of GRE images surrounding the heating protocol since 30 seconds may not be a the optimal duration for temperature differential to accumulate following the T2-weighted SSFSE stack. Similarly, there are often small delays in GRE acquisition after the SSFSE due to repositioning which should be investigated as they relate to the robustness of phase change and temperature measurements.

MR spectroscopy thermometry (MRST) is an alternative approach for measuring temperature noninvasively using MR. This technique allows the measurements of absolute temperatures and may potentially be used in further studies. In this study we chose to use PRF since it is the predominant MR thermometry method with the highest spatial and temporal resolution. Additionally, MRST suffers from inability to sample larger volumes which would make comparing the two regions (fetal brain and mother gluteus) difficult (21). Furthermore, PRF lends itself most to further development of the temperature shift measurement method presented which may be of interest to monitor and adjust clinical scans in real time.

Additionally, after the removal of outliers, only 32 participants were included and acquiring additional data may strengthen the analysis. Finally, this study was performed at a single institution, thus the generalizability of this method and results to different vendors, and imaging environments is unknown at this stage. Despite the challenges of this approach, our results support similar heat dissipation in the fetal brain relative to the gluteal tissue of the mother during the 3T clinical scan in first level-controlled mode of T2-weighted SSFSE imaging.

Conclusions

Our results indicate that the estimated relative temperature changes of the fetal brain compared to the mother's gluteal tissue from RF pulses during the course of the T2-weighted SSFSE fetal MR exam are minimal. The differences in acquired phase between these regions through the exam were found not to be statistically different. These findings support that fetal brain imaging at 3T is within FDA limits and safe.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-708/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of University of California San Francisco, written informed consent was provided by the pregnant women.

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